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Special Program and Abstract Issue

Getting Connected with Women in Science

Lisa M. Harrison-Bernard
Louisiana State University Health Sciences Center School of Medicine, New Orleans, Louisiana

Lisa M. Harrison-Bernard

We all know that professional networking is an important part of climbing the ladder to success. What might you gain from building a network of colleagues? You may develop comradery, friendships, confidants, and mentors to help guide you in your career. Networks may expose you to new ideas, provide scientific collaborations, expand your influence, and alert you to opportunities. But how do you build this network? Networking can be awkward and time-consuming, and conflict with your struggle to maintain a healthy work-life balance. Don't let this push networking to the back burner. If you sit back and wait for the network to come to you, it might not come knocking on your door. You must be willing to devote time and energy to building your network. What if you are shy or introverted? Do you really need to get out there and get to know people in your scientific field? The answer is a big fat, YES! The best way to have a strong professional network is to build it yourself. Look for successful women in science, introduce yourself, and ask them questions about their path to success. Build a mentoring and professional network to help you navigate the next step in your career. Dismiss the myth that asking for help means that you are weak or incompetent. It is important to recognize your strengths and weaknesses; to capitalize on your strengths and find ways to improve your weaknesses. In fact, knowing who and when to ask for help could provide you with the "leg up" that you need to navigate the path to success. Asking for help communicates to others that, although you may not have all of the answers, you are willing to find out strategies

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A Matter of Opinion

Sci-Hub: Piracy Across the Open (Access) Seas

Background

In 2011, a graduate student, Alexandra Elbakyan from Kazakhstan, made freely available what has now grown to 50 million articles illegally downloaded from copyrighted materials, primarily from the scientific literature. The copyrighted materials are collected into a repository known as Sci-Hub. An injunction filed in the U.S. in October 2015 ordering Sci-Hub to desist drove the website domain name out of the reach of the U.S. legal system behind Russian firewalls, where the servers were already based. Sci-Hub continued to thrive. Legally, this action by Elbakyan constituted theft, or piracy, in the *lingua franca* of intellectual

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Headquarters phone: 301-634-7118
Fax: 301-634-7241
Email: webmaster@the-aps.org
http://www.the-aps.org
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Report

Sci-Hub Downloads of APS Papers

Phil M. Davis, *Publishing Consultant*

Sci-Hub is an illegal repository of scientific articles operating in Russia, with several mirror sites located around the world. Founded in 2011 by a graduate student from Kazakhstan, use of the service has grown steadily, despite repeated legal attempts by Elsevier to shut down the service. New content is added to Sci-Hub's repository using donated or compromised subscriber authentication credentials. Free and open access content is also found in the repository.

As part of a feature article in *Science Magazine* (1), Sci-Hub article requests were made public in the Dryad data repository. These data represent nearly 30 million user requests made from September 2015 through February 2016. Since these data were made public, Sci-Hub has received widespread attention in the media such as *The New York Times* (3) and *The Washington Post* (4). It is assumed that Sci-Hub usage has increased as a result.

Although most publishers are not supportive of illegal and covert systems to redistribute content, the Sci-Hub dataset provides a unique opportunity to study what content was requested and where requests were being made. Studying patterns in the data may provide publishers with insights into future content creation, marketing, advertisement, and access models.

Data and Methods

Monthly Sci-Hub files were joined to form a single dataset containing 27,819,966 separate download events from September 2015 through February 2016. Two weeks of Sci-Hub downloads were missing from November 2015. Matching the prefix of each Digital Object Identifier (DOI) with a list of publisher names from the CrossRef registry (CrossRef.org), we associated each document download with a publisher. We further identified the journal name and article identifier from the DOI suffix.

For example, in the DOI 10.1152/ajplung.00070.2014, the prefix (10.1152) identifies the publisher, The American Physiological Society, and ajplung identifies the journal. Following the period, the rest of the DOI denotes the specific article, with the first part (00070) identifying the manuscript number, and the second part (2014) specifying the year of submission. The journal *Physiological Reports* is registered under the publisher prefix for John Wiley and Sons and includes a manuscript number but no date of submission (e.g., 10.1002/phy2.5).

For highly downloaded papers, print and online details were retrieved from the PubMed biomedical literature database. For mapping purposes, country names from

Figure 1. Sci-Hub downloads to APS content by day, 09/2015 to 02/2016.

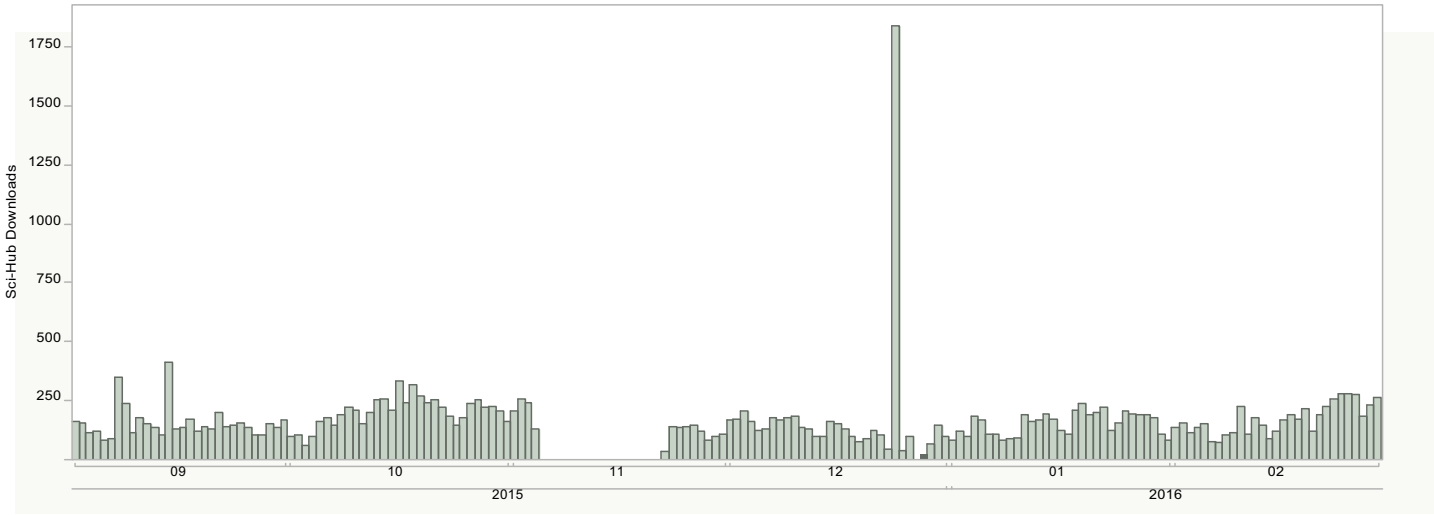
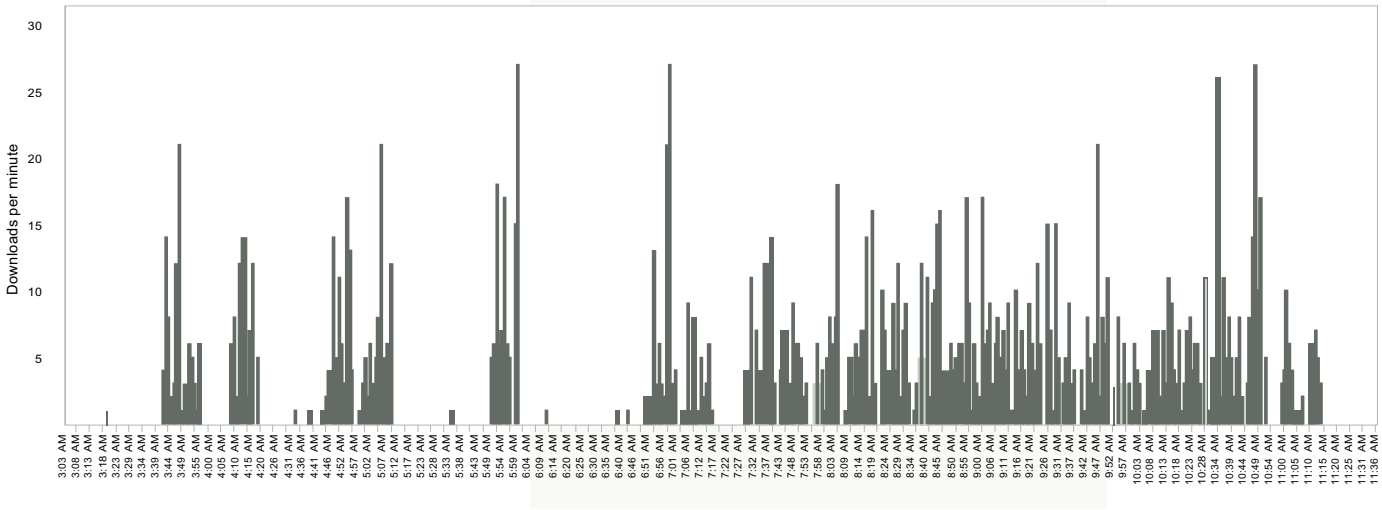


Figure 2. Sci-Hub downloads on December 24, 2015 between 3:00 and 11:30 AM. This activity was likely the result of a software robot.



the Sci-Hub dataset were matched with a geographical file specifying each country's average latitude and longitude. All statistical analysis was performed using JMP version 12 (SAS).

Results

The dataset includes 26,703 APS document downloads that took place between September 2015 and February 2016, peaking at 1,827 downloads on December 24, 2015 (see spike in Figure 1). Further investigation of this spike identified a single IP address registered in Iran that was responsible for more than 98% (1,798) of downloads for that day. Download activity began at 3:15 AM and continued until 11:15 AM (Figure 2). The download rate did not exceed 27 papers per minute, was spread over multiple APS titles, and did not trigger the online publishing platform to block the suspected IP address. In the full Sci-Hub dataset, a total of 88,202 article downloads across hundreds of scientific publishers were traced to the same IP address.

Although Sci-Hub users downloaded APS papers submitted as early as 1999, 42% of all downloads were to papers accepted for publication in 2014 or 2015 (Figure 3). Downloads from the suspected Iranian robot are highlighted.

Within the first 2 months of 2016, 46% of all requests were to content submitted in 2014 or 2015, with 23% of all downloads focused on papers submitted in 2015 (Figure 4). With the exception of the suspected software robot, these results suggest that Sci-Hub is used primarily as a tool to access recently published papers.

Figure 3. Sci-Hub downloads by year of manuscript submission. Download by suspected Iranian robot are highlighted.

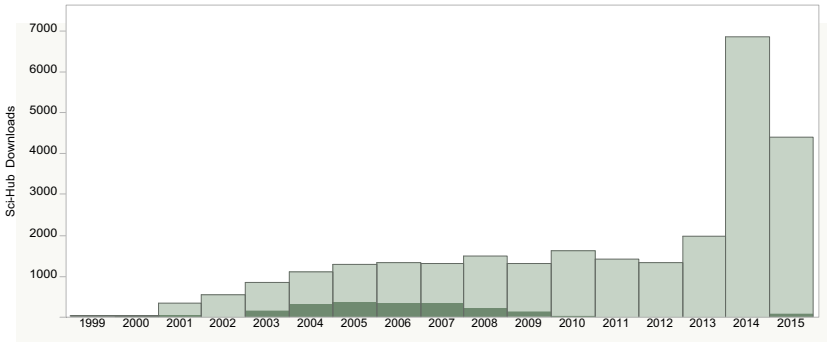
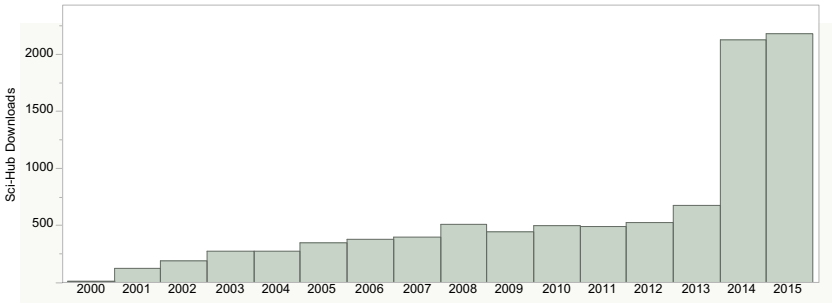


Figure 4. Sci-Hub downloads in the first 2 months of 2016.

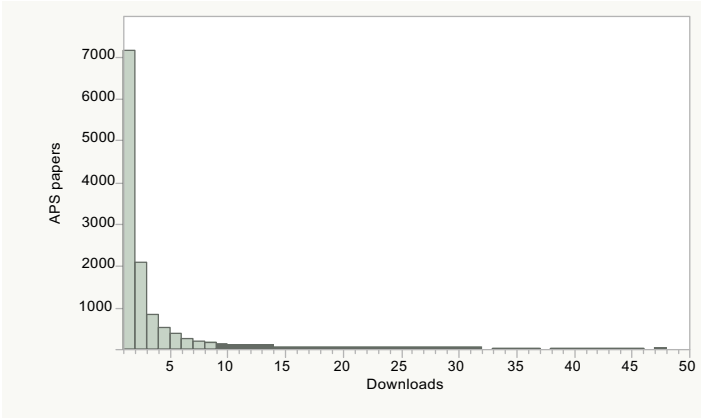


For those APS papers downloaded during the observation period, 61% were requested just once, and 93% were requested five or fewer times (Figure 5). The most frequently downloaded paper (2) was requested 372 times. Lists of frequently downloaded papers are found in Table 3. Twenty-two of the top 30 downloaded papers were published in *Physiological Reviews*.

Similarly, 72% of all Sci-Hub users (as identified by their unique IP address) downloaded just one paper, and 96% of users downloaded five or fewer papers (Figure 7). The most frequent user, from Iran, downloaded 1,798 papers on December 24, 2015 (see spike in Figure 1). Heavy users (not suspected to be the result of robot activity) were from Japan (289 downloads), and China (127 downloads).

With the exception of *Physiological Reports*, all APS journals follow a subscription-access model that makes all content freely available from its website 12 months after print (issue) publication. Full-text (HTML) access is also available from PubMed 12 months after print publication for authors who have identified as being funded by governmental organizations and private charities that require free access from PubMed (see details at *http://www.the-aps.org/mm/Publications/Info-For-Authors/Depositing-Articles-in-PMC*). Open access papers are freely accessible immediately

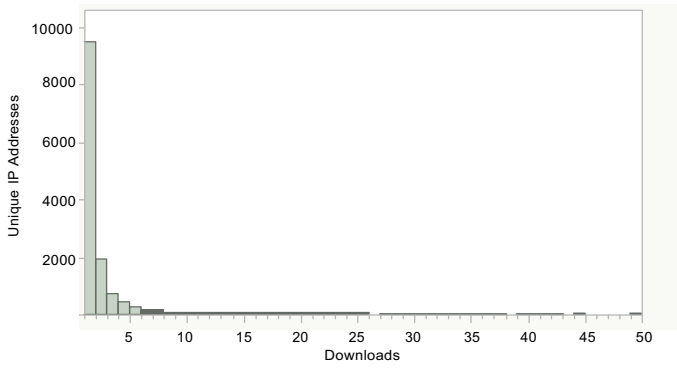
Figure 5. Frequency of Sci-Hub downloads to APS papers. The vast majority of papers were downloaded just once (median = 1, IRQ: 1-2 downloads), although some papers were frequently downloaded (max = 372). Table 3 lists frequently downloaded papers.



Quantiles		
100.0%	maximun	372
99.5%		21
97.5%		10
90.0%		5
75.0%	quartile	2
50.0%	median	1
25.0%	quartile	1
10.0%		1
2.5%		1
0.5%		1
0.0%	minimum	1

Summary Statistics	
Mean	2.295058
Std Dev	4.7807712
Std Err Mean	0.0443215
Upper 95% Mean	2.3819357
Lower 95% Mean	2.2081804
N	11635

Figure 6. Frequency of Sci-Hub downloads by user (as measured by unique IP address). The vast majority of users downloaded just one APS paper (median = 1, IQR: 1-2 documents). One user (the suspected Iranian robot) downloaded a maximum of 1,798 papers.



Quantiles		
100.0%	maximum	1798
99.5%		19
97.5%		7
90.0%		3
75.0%	quartile	2
50.0%	median	1
25.0%	quartile	1
10.0%		1
2.5%		1
0.5%		1
0.0%	minimum	1

Summary Statistics	
Mean	2.025256
Std Dev	16.218385
Std Err Mean	0.1412432
Upper 95% Mean	2.302113
Lower 95% Mean	1.748399
N	13185

Table 1. Sci-Hub downloads and unique papers by journal title.

Journal	Total Downloads	Unique Papers – All	Unique Papers – Iranian Robot
Advances in Physiology Education	209	126	16
AJP-Cell Physiology	1979	957	91
AJP-Endocrinology and Metabolism	2826	1212	129
AJP-Gastrointestinal and Liver Physiology	2195	1011	161
AJP-Heart	3342	1728	442
AJP-Lung Cellular and Molecular Physiology	1852	932	305
AJP-Regulatory, Integrative and Comparative Physiology	2357	1316	409
AJP-Renal Physiology	2312	1147	192
Journal of Applied Physiology	3264	1287	47
Journal of Neurophysiology	1950	981	4
Physiological Genomics	789	343	2
Physiological Reviews	2852	371	0
Physiological Reports	45	28	0
Physiology	731	196	0
Total	26703	11635	1798

Figure 7. World distribution of Sci-Hub downloads for APS papers.

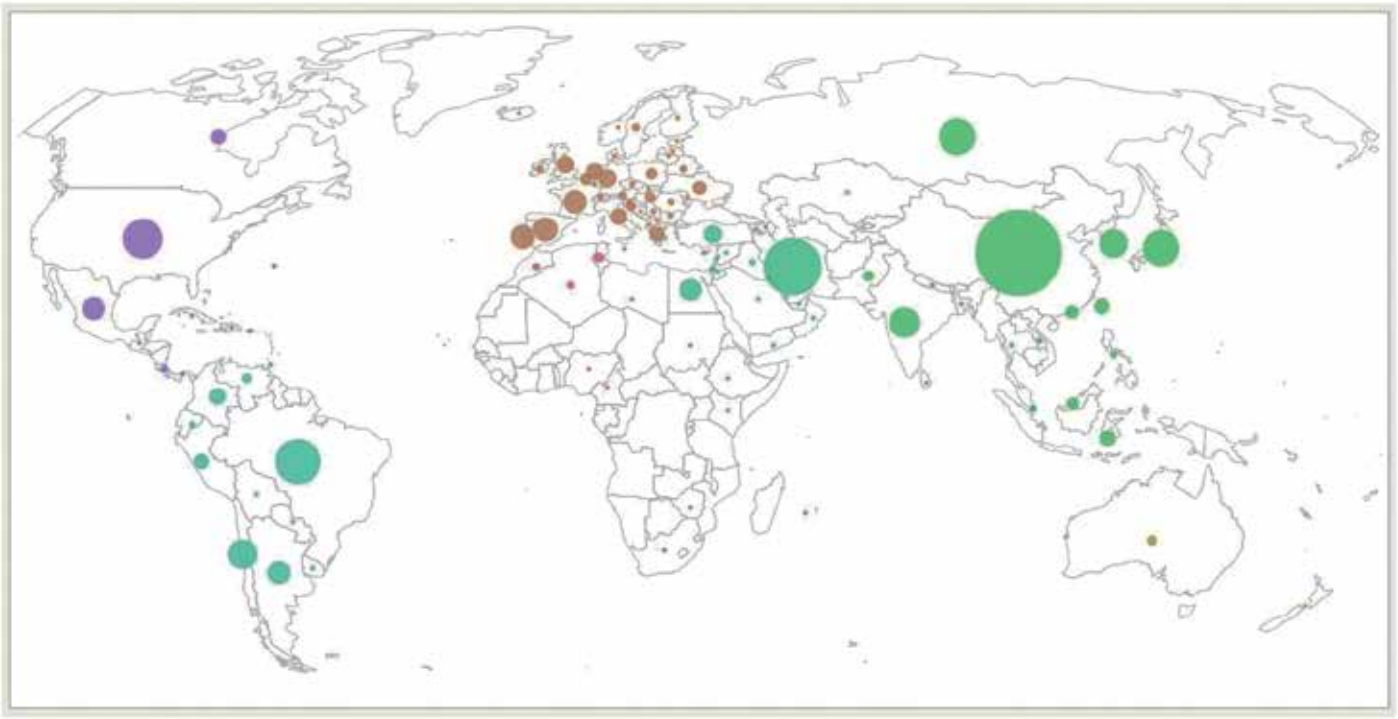


Table 2. Sci-Hub downloads by country (≥ 1% total).

Country	Downloads	% Total
China	6990	26.2%
Iran	3070	11.5%
Brazil	1886	7.1%
United States	1466	5.5%
Japan	1214	4.6%
Russia	1199	4.5%
India	844	3.2%
Chile	769	2.9%
South Korea	728	2.7%
Portugal	553	2.1%
Spain	544	2.0%
France	515	1.9%
Mexico	492	1.8%
Argentina	461	1.7%
Egypt	437	1.6%
Germany	321	1.2%
Turkey	284	1.1%
United Kingdom	284	1.1%
Unidentified	268	1.0%
Italy	267	1.0%
Netherlands	256	1.0%

upon publication from the journal website and from PubMed Central.

Although no level of illegal downloading is acceptable, Sci-Hub's use of APS content was very small, representing just 0.6% of total PDF downloads from the journal website, as measured over the same period. [In 2015, there were 9.6 million PDF and 20.0 million full-text (HTML) downloads from the journal websites and 1.5 million HTML downloads from PMC. We adjust for 5.5 months to arrive at a similar observation period. Data from Karie Kirkpatrick, Digital Publications Manager at the APS.] In contrast, full-text (HTML) views of APS content from PubMed Central (PMC) represented 16% of traffic compared with the journal website. Users from China accounted for more than one-quarter (26.2%) of all APS article requests, followed by Iran (11.5%), Brazil (7.1%), and the U.S. (5.5%) (Table 2).

Discussion

For APS content, Sci-Hub is used primarily as a tool for gaining access to recently published papers that are available only by subscription. Although most individuals used Sci-Hub infrequently, there were some individuals who have adopted Sci-Hub as a method for accessing open access papers and older literature, both of which are freely available from the

Table 3. Frequently downloaded APS papers.

Title. Publication. DOI	Downloads
Mechanisms underlying enhancements in muscle force and power output during maximal cycle ergometer exercise induced by chronic β2-adrenergic stimulation in men. 2015 Sep 1;119(5):475-86. doi:10.1152/japplphysiol.00319.2015	372
Aquaporins in Plants. 2015 Oct;95(4):1321-58. doi:10.1152/physrev.00008.2015 70 mTOR in Brain Physiology and Pathologies. 2015 Oct;95(4):1157-87. doi:10.1152/physrev.00038.2014	66
Cardiac Regeneration and Stem Cells. 2015 Oct;95(4):1189-204. doi:10.1152/physrev.00021.2014	63
The Mitochondrial Permeability Transition Pore: Channel Formation by F-ATP Synthase, Integration in Signal Transduction, and Role in Pathophysiology. 2015 Oct;95(4):1111-55. doi:10.1152/physrev.00001.2015	58
Store-Operated Calcium Channels. 2015 Oct;95(4):1383-436. doi:10.1152/physrev.00020.2014	55
Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. 2016 Jan;96(1):365-408. doi:10.1152/physrev.00014.2015	53
Neuroglial Transmission. 2015 Jul;95(3):695-726. doi:10.1152/physrev.00024.2014	53
Renal autoregulation in health and disease. 2015 Apr;95(2):405-511. doi:10.1152/physrev.00042.2012	53
Gut microbiota in health and disease. 2010 Jul;90(3):859-904. doi:10.1152/physrev.00045.2009	47
Membrane Repair: Mechanisms and Pathophysiology. 2015 Oct;95(4):1205-40. doi:10.1152/physrev.00037.2014	45

Histone Deacetylases in Bone Development and Skeletal Disorders. 2015 Oct;95(4):1359-81. doi:10.1152/physrev.00004.2015	44
Spermatogenesis: The Commitment to Meiosis. 2016 Jan;96(1):1-17. doi:10.1152/physrev.00013.2015	44
Are There Deleterious Cardiac Effects of Acute and Chronic Endurance Exercise? 2016 Jan;96(1):99-125. doi:10.1152/physrev.00029.2014	44
Extracellular and Intracellular Signaling for Neuronal Polarity. 2015 Jul;95(3):995-1024. doi:10.1152/physrev.00025.2014	43
Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. 2015 Oct 15;309(8):E691-714. doi:10.1152/ajpendo.00297.2015	42
The gastrointestinal microbiota and colorectal cancer. 2015 Mar 1;308(5):G351-63. doi:10.1152/ajpgi.00360.2012	41
Paradoxical Roles of Antioxidant Enzymes: Basic Mechanisms and Health Implications. 2016 Jan;96(1):307-64. doi:10.1152/physrev.00010.2014	40
Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality. 2015 Jul;95(3):727-48. doi:10.1152/physrev.00030.2014	40
Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. 2015 Apr;95(2):513-48. doi:10.1152/physrev.00013.2014	39
Mechanisms Regulating Neuromuscular Junction Development and Function and Causes of Muscle Wasting. 2015 Jul;95(3):809-52. doi:10.1152/physrev.00033.2014	39
Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. 2014 Jul;94(3):909-50. doi:10.1152/physrev.00026.2013	38
The role of sirtuins in cardiac disease. 2015 Nov;309(9):H1375-89. doi:10.1152/ajpheart.00053.2015	36
The anabolic response to a meal containing different amounts of protein is not limited by the maximal stimulation of protein synthesis in healthy young adults. 2016 Jan 1;310(1):E73-80. doi:10.1152/ajpendo.00365.2015	35
Effects of inhibitory gain and conductance fluctuations in a simple model for contrast-invariant orientation tuning in cat V1. 2007 Jul;98(1):63-78. doi:10.1152/jn.00152.2007	35
The Physiological, Biochemical, and Molecular Roles of Zinc Transporters in Zinc Homeostasis and Metabolism. 2015 Jul;95(3):749-84. doi:10.1152/physrev.00035.2014	35
The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. 2015 Jul;95(3):1025-109. doi:10.1152/physrev.00028.2014	34
Aerobic exercise training promotes physiological cardiac remodeling involving a set of microRNAs. 2015 Aug 15;309(4):H543-52. doi:10.1152/ajpheart.00899.2014	33
Maternal infection and fever during late gestation are associated with altered synaptic transmission in the hippocampus of juvenile offspring rats. 2008 Nov;295(5):R1563-71. doi:10.1152/ajpregu.90350.2008	31
Spreading Depression, Spreading Depolarizations, and the Cerebral Vasculature. 2015 Jul;95(3):953-93. doi:10.1152/physrev.00027.2014	31
ApoA-IV: current and emerging roles in intestinal lipid metabolism, glucose homeostasis, and satiety. 2015 Mar 15;308(6):G472-81. doi:10.1152/ajpgi.00098.2014	30
Myocardial autophagic energy stress responses – macroautophagy, mitophagy, and glycophagy. 2015 May 15;308(10):H1194-204. doi:10.1152/ajpheart.00002.2015	30
Hippo and TGF-β interplay in the lung field. 2015 Oct 15;309(8):L756-67. doi:10.1152/ajplung.00238.2015	30
Performance Enhancement: What Are the Physiological Limits? 2015 Jul;30(4):282-92. doi:10.1152/physiol.00052.2014	30

journal website and PubMed Central. These findings suggest that some users have adopted Sci-Hub as a general tool for accessing the scientific literature.

Sci-Hub is not easy to use, however. It requires users to have previously searched and identified a paper's URL, DOI, or PubMed ID (PMID) number. No general keyword, author, or title search is available currently from the Sci-Hub website. In addition, users are required to pass a CAPTCHA security test. Papers cannot be browsed in full-text (HTML) format and are available one at a time. Popular web search engines (e.g., Google) do not index Sci-Hub, meaning that direct Sci-Hub links will not appear to the web searcher. Free copies of papers may be more easily attained through the author's website or a commercial repository (e.g., ResearchGate and Academia.edu). In sum, there are many easier alternatives to users circumventing subscription access barriers. Sci-Hub may be a viable alternative for individuals without institutional access and where general search engines may be blocked or censured (e.g., China).

Iran represents a unique situation of a country that has suffered from decades of international sanctions that has left its researchers with poor access to the scientific literature. Informal conversations with publishers with sales experience in developing nations suggest that Iran may be in the process of "hording" digital copies of scientific papers as a solution to ineffective access. This is claim is backed by the observed behavior of the Iranian software robot downloading papers from the APS and other scientific publishers.

Last, although no level of illegal downloading is acceptable, Sci-Hub's use of APS content was very small relative to article downloads from the publisher's websites or PubMed Central. The loss of potential readership to Sci-Hub was comparable to other publishers' journals with similar liberal access policies as the APS. At this time, we recommend simply monitoring the publisher's usage traffic for evidence of future widespread Sci-Hub adoption. ●

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About the Consultant

Phil Davis provides statistical analysis of citation, readership, publication, and survey data for editorial boards, scientific societies, and academic publishers. Davis has a PhD in science communication from Cornell University (2010), extensive experience as a science librarian (1995-2006), and was trained as a life scientist. His research focuses on the dissemination of scientific information, rewards, and incentives in academic publishing, and economic issues related to libraries, authors, and publishers. He is a prolific author of scientific and popular articles on science communication, speaks regularly at national conferences, and has received several awards for his work in bibliometrics. Details may be found at http://phildavis.org.

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Sci-Hub: Piracy Across the Open (Access) Seas

property. Elbakyan has been championed by some as a Robin Hood – taking from the rich what morally should be shared by all. How does she do it? Loopholes in some academic institutions' library access systems, stemming from lax authentication, as well as complicit institutional users, are understood to be the sources of the Sci-Hub repository. Content is updated through these methods when articles not yet included are requested. Currently, Sci-Hub reports nearly 60 million downloads by users.

Those who condemn and those who condone Sci-Hub and the actions leading to its creation cut across all sectors of the scholarly communications community – authors, researchers, librarians, publishers. Users are not isolated to poorer countries without legitimate access, despite the repository being difficult to search and navigate, and the PDFs being offered in a rudimentary format. Rather, users are also based in the U.S. and Europe, and concentrated in university-rich cities. Downloads include content from open access as well as subscription sources. A list of Sci-Hub's 10 most downloaded papers from October 2015 can be found at http://www.sciencemag.org/news/2016/04/whos-downloading-pirated-papers-everyone (2). Although papers are downloaded in all scientific disciplines, these top papers seem to be skewed toward those with an implication for industry.

APS Commissions Report on Sci-Hub

Although articles of the journals of the American Physiological Society were not listed among the top 10 downloaded published papers, APS considered it in the interest of its journals and members to identify to what extent and which APS journal articles are being affected by Sci-Hub, and the circumstances of their downloads. Therefore, in July 2016, APS commissioned a report from Phil Davis Consulting to address just that.

The Report

The commissioned report, "Sci-Hub Downloads of APS Papers," is presented beginning on page 3. It analyzes the sources and frequency of 26,703 downloads in Sci-Hub of APS published papers during the period September 2015 through February 2016. The majority of downloads (46%) was to content published within the past 2 years (see Figure 3 of report). Downloads were distributed across all APS titles (see Table 1 of report), with most papers (61%) being downloaded only once, and the majority of users (72%) downloading only one paper. The majority of downloads are from China (26.2%) and Iran (11.5%) (see Table 2 of report). The single-most popular downloaded paper was from *Journal of Applied Physiology,* and the greatest number of downloaded papers was from *Physiological Reviews* (see Table 3 of report). Although readers may feel a rueful twinge in noting that APS papers were not downloaded in large numbers (Sci-Hub downloads of APS papers represent 0.06% of all downloads during the period), this usage is not unique among peer journals. The report notes that, "The loss of potential readership to Sci-Hub was comparable to other publishers' journals with similar liberal access policies as the APS."

What to Make of All This?

Given the small amount of usage of APS journals in Sci-Hub, the recommendation of the report is to monitor the situation, which is what APS will do. Nevertheless, Sci-Hub's broad use in rich and poor countries for reasons both of convenience and need raises broader questions about the sustainability of current models, as well as the perennial question: Who pays? Results of a survey (4) embedded in a *Science* feature article (2) analyzing 28 million downloads in Sci-Hub found that, of 11,000 respondents, "nearly 60% . . . report having used Sci-Hub" and "88% overall said it was not wrong to download pirated papers." As Sci-Hub users, respondents were inclined to be biased toward it, as noted in the results.

The real danger to the community of pirated content, made freely available in repositories like Sci-Hub, is that it will become a norm, threatening the existence of the vetted, curated content on which it depends. This conundrum is not entirely dissimilar to legally mandated, unrealistic embargoes for free public access of published research that have set a precedent. So this is perhaps not new, just illegal. Cogent discussions of costs and the value of the publishing process and measuring usage have been published (e.g., Refs. 1, 3) but have not carried a public news impact equivalent to other points of the conversation. And while there is increased awareness of these facts within the scholarly

community and of the tensions between end-user (institution) supported, author-supported, and no support of published research, even more stakeholders remain unaware or unimpressed. Global initiatives, such as research4life (http://www.research4life.org), which enable access to published research for countries that cannot afford it and in which all legitimate publishers participate, help a lot, but clearly not enough.

Commissioning a report to assess its own stake in Sci-Hub was a natural step for APS in keeping abreast of important issues affecting published scientific research. APS remains on the fore of developments in the scholarly publishing community and continues to participate and contribute on local and global levels to improve our own brand and that of all stakeholders – punching above our weight. ●

Rita Scheman

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Continued from page 1:

Getting Connected with Women in Science

to address these weaknesses. Use these relationships for exchange and promotion of ideas and information. Continue the networking conversation by following up with someone you've recently met at an event. For a network to be successful, the interactions should be continued over a suitable period of time and not just a one-time meeting. You might send them an e-mail when you return to work and make arrangements to meet during upcoming events. Say *yes* to serving on committees, and be an active and vocal member. Learn the names of the people on the committees and contact them outside of the committee service. You must be willing to do the work and ask for the type of help that you need, or you may be passed over when it really counts. Mentors may not know what you need as a mentee. Since your mentor may be your research advisor, a postdoctoral fellow in the next lab, a faculty member in the department, or a scientist you met at a national or international meeting, you may need to help each other figure out what type of mentoring relationship will provide the best outcomes. You want to feel connected, supported, and inspired as you build the professional network.

Advantages of Connecting with Women

For some female scientists, they may not perceive an advantage of gaining a mentoring relationship with female over male scientists. Male mentors might predominantly focus their efforts on your scientific goals, whereas female mentors are more likely to focus on guiding your life inside and outside of science. Many female scientists have experienced novel guidance from female mentors and role models. Female scientists are positioned to share their personal experiences with conscious or unconscious gender discrimination in science. By sharing their stories, female mentors may prepare their mentees to handle these types of encounters if they occur in the future or help mentees look in retrospect at discriminatory events. Female mentors may encourage you to be more direct in asking for what you need and in making your career goals clear to those around you. Women often need to be encouraged to value their knowledge, skills, and contributions to science, and not to underestimate their value and worth. Don't be afraid to ask successful women in science to share their secrets of how they have succeeded in a male-dominated career. Learning how the "good old boys" club works is not likely to be shared with you by male mentors; instead, women who have discovered how the system works can guide you into making strong connections and gaining experience. Don't wait to be invited as a scientific symposium speaker; propose a symposium and place yourself as a speaker. Don't patiently wait to be asked to give a research seminar within your institution or outside of your institution; chair a scientific session, serve as member of a committee, review abstracts, or serve as a judge. Volunteer your services and get in the middle of science instead of looking in from the outside. Many female mentees find that women mentors are able to share their experiences in maintaining a healthy life and work balance. Because these women have gone through the challenges of handling marriage, pregnancy, and child care with the demands of a scientific career, they may offer concrete suggestions on how to manage these many demands on your time. In fact, time management is very important, since it will focus your efforts on what needs to be accomplished in the laboratory in the upcoming week so that you'll have time for your personal life.

Connect Informally with Women at Your Institution

I have found that getting connected with women in science is important for guiding my career forward and providing me the forum to mentor junior women in science. I hope that you are inspired to take a closer look at the women in your institution that may serve as a part of your scientific network. I've been fortunate to have had the opportunity to be mentored by many successful women in science. I've found that it is worth the time and effort to seek out and serve on committees that are designed to serve women in science as well as committees to serve the department, university, societies, and organizations. My exposure to the benefits of meeting female colleagues, finding out the types of research that they conduct, and sharing difficulties and successes in science began as a first-year graduate student at Tulane University in New Orleans. At the time, there was one female faculty member in the department of physiology. She invited the female graduate students to lunch, and I was the only student who was available. I was amazed that a senior faculty member could take the time to get to know me. These lunches grew to include female postdoctoral fellows, technicians, and faculty. I looked forward to these times to get away from the campus and have a nice lunch in a

nearby restaurant. I had the opportunity to really get to know the graduate students, fellows, and female faculty in my department. Also during this time, she arranged for women faculty in the school to meet for lunch on a regular basis. At these networking events, I was able to learn from basic and clinical scientists about strategies to balance work and family, maintain resiliency, and become a successful woman in science. Maintaining a positive outlook and preventing burnout are important behaviors to learn in the highly competitive field of science. When the senior scientist left Tulane, I took over the role of continuing the physiology networking lunches until my departure. Now, I've begun a "Junior Women in Physiology Faculty Networking Luncheon" at LSUHSC and enjoy our time together. You may want to start your own networking luncheons at your institution. Also, I hope that you'll accept invitations from members of your department and institution to participate in social networking events. These meetings may provide a forum to discuss issues related to *1)* authorship order on manuscripts, *2)* strategies for grant proposals, *3)* collaborations on research projects, *4)* promotion and tenure, and *5)* work and life balance, to name a few. Be sure to start close to home and connect with women in your department and institution.

Connect Formally with Women at Your Institution

You might be surprised how serving on a committee at your institution may provide a unique perspective of success in academics. Serving on multiple committees for the school of medicine has fostered my interaction with basic scientists, clinicians, and university administrators. Working in these capacities has provided the forum for me to develop relationships with members of the school that I would not normally encounter if I focused all of my attention on my own department. Serving on committees may help you gain the bigger picture of what is going on at your institution. By sharing information, practices, education, and experiences, women can accelerate the advancement of women in science.

Connect with Women in Your Scientific Societies

It is never too early in your career to develop a supportive network. Be sure to develop friendships with fellow graduate students who share common research interests. Like you, they will become the scientists of the future. They may be able to help you find the right person to answer questions about methods, strategies for advancement, finding a fellowship, and how to gain teaching experience, to name a few examples. They can also be life-long friends with which you can share your successes and challenges during your entire career. As an assistant professor, I was appointed to the American Physiological Society Women in Physiology Committee. This was my first experience serving as a member of a scientific society committee. At the time, I thought that I was too junior to serve on a societal committee and almost declined the invitation. Many scientific organizations have trainee members on committees and may have an entire committee run by trainees and devoted to the specific challenges of graduate students and fellows. I learned a great deal from the women chairing and working on the committee. These successful female physiologists taught me how to positively impact the career success of women in physiology by implementing the symposia we hosted at the Experimental Biology meetings that were specifically designed to address issues related to being a successful female physiologist. I did not realize that my serving on one societal committee may lead to my serving on another committee in the same organization. Later, I was appointed to the American Physiological Society Membership Committee, for which I served as a member for 2 years and as the chair for 3 years. I worked closely with the members of the committee as well as the American Physiological Society staff. I gained confidence in leading a team, implementing new initiatives, and realizing that I could make a difference. During my time as chair of the committee, I had the opportunity to attend the annual summer council meetings, which broadened my circle of colleagues and my knowledge of their scientific area of expertise. At the time that I accepted the position of chair, I did not know that I would have the opportunity to attend the summer meeting with my fellow committee chairs, councilors, and presidents. Name and face recognition provided me with an extended scientific family. Looking back, I can see that saying *yes* the first time opened the door for my continued participation in the mission of the society. During this time, I was appointed to the American Society of Nephrology, Women in Nephrology Programming Committee, for which I served for 8 years. My major contribution to the mission of the committee was to organize scientific symposia topics that included female speakers for the annual American Society of Nephrology meetings. In addition to attending the business meetings held during the annual meetings, we also gathered each year for a group dinner. The conversations at the dinners were often the most informative for gaining strategies to optimize my career success while balancing the time that I needed to have a rewarding and fulfilling personal life. As a member

of this committee, I was able to connect with female nephrologists and renal physiologists. Continued service to the American Physiological Society as a member of the Education Committee cemented my relationships with the society staff members and physiologists with a commitment to further education initiatives in K-12. Without serving on these committees, I would not have developed long-lasting female scientist mentors who have assisted me with research ideas, strategies for career advancement, and invitations to give seminars and symposia, as well as provided letters of support for promotion. At the time that I said *yes* to serving on the committees, I did not realize the positive impact these women would have on my career trajectory. Be proactive in your volunteer service to societal organizations. Many committees would welcome a new member who is enthusiastic about contributing to the mission of the society. Trainees and junior faculty need to find a balance between the time commitment spent on research and service. Be careful that your time devoted to service does not hinder your career trajectory.

Connect with Women in Your Geographical Region

More recently, my time has been spent as a founding member, active participant, and secretary of the Southern Louisiana chapter of the Association for Women in Science. The chapter is dedicated to empowering women in science and technology by providing a platform for networking opportunities and career development programs, and to promoting an interest in science among girls and young women. In many ways, my service to this chapter is a compilation of my efforts honed while a member of societal committees. I'm in the position to gain mentoring from senior female faculty and to serve as a mentor for junior women in science in the geographical region. There is an intangible benefit to getting to know both the scientist and the person. Developing a working relationship with female scientists from basic and clinical science in the region has provided a larger and more diverse professional network. Contributing to education outreach and professional development programs offered by the chapter has provided me with a venue for me to reach out and mentor young women in science. It is rewarding to have a positive impact on the education and careers of young women in science. You may not have to look very far to find an established group of women in science in which to participate in your geographical region.

Summary

Networking expands opportunities within company walls and externally. It allows women to find role models and mentors inside the department, institution, region, nationally, and internationally. Of course, one can have many mentors, male and female, to help grow into the scientist, teacher, and person you want to be. Social connection and professional engagement can make your job more interesting, rewarding, and enduring. I hope that you will look for and engage in formal and informal gatherings that promote women professionals connecting with each other. Take a break from your desk or bench and get out to meet and learn from others. Invest more of your time building relationships instead of keeping your head to the grindstone. I hope that you find many new avenues for career development, advancement, and self-fulfillment by building and maintaining an effective professional network of mentors and colleagues. ●

Lisa is grateful for the assistance in the preparation of this article provided by Michael G. Levitzky, Kathleen H. McDonough, and the members of the Southern Louisiana Chapter of the Association of Women in Science.

Lisa M. Harrison-Bernard is a New Orleans native who graduated from the University of New Orleans in 1984. She graduated from Tulane University in 1990 with a doctorate in Physiology and continued with 4 years of postdoctoral training with Drs. Pamela Carmines and Gabriel Navar at Tulane Medical School. She joined the Tulane Physiology faculty in 1994 and rose through the ranks to associate professor in 2003. She joined the Physiology department at LSUHSC in New Orleans in 2004. Her research has been funded from the National Kidney Foundation, National Institutes of Health, and the American Heart Association.

Her research focuses on the prevention and reversal of diabetic kidney disease and the role of the renin-angiotensin system in the progression of renal disease in Type 2 diabetes.

She has published 58 scientific papers and is currently a member of the Editorial Review Board for the *American Journal of Physiology: Renal Physiology, Physiological Reports*, and three other scientific journals. She regularly serves on grant review committees of the American Heart Association and National Institutes of Health. Society memberships are held in American Physiological Society and the Association for Women in Science. She is active in community outreach and education, with an emphasis on increasing minorities and women in STEM fields.

APS News

ICPS 2016 – Beijing

The Chinese Association for Physiological Sciences (CAPS) welcomed physiologists to Beijing September 25-29, 2016 to participate in a quadrennial meeting to celebrate physiology. The ICPS 2016 meeting was the third in a series of international conferences held successfully in China. The first was held in 2008 in Beijing, and the second was held in 2012 in Suzhou. Each of the previous conferences represented the joint efforts of multiple national physiological societies. For ICPS 2016, 11 societies, including the American Physiological Society, Australian Physiological Society, Austrian Physiological Society, The Chinese Physiological Society in Taipei, The French Physiological Society, The Physiological Society of Japan, The Physiological Society, the Physiological Society of New Zealand, Psychoneuroimmunology Research Society, and The Scandinavian Physiological Society, contributed to the success of the conference. Support for ICPS 2016 was also provided by the International Union of Physiological Sciences (IUPS), the Federation of Asian and Oceania Physiological Societies (FAOPS), the China Association for Science and Technology (CAST), and the National Natural Sciences Foundation of China (NNSFC).

ICPS 2016 was held in the China National Convention Center located in the Olympic Village created when China hosted the 2008 Olympics (Figure 1). The meeting opened with a Welcome Reception on Sunday evening, September 25, and was followed on Monday, September 26, with an Opening Session highlighting the 90th Anniversary of the Chinese Association for Physiological Sciences. Professor Xiao-Min Wang, President of the Conference and of CAPS (Figure 2),

Figure 2. Professor Xiao-Min Wang, President of the Conference and of CAPS

Figure 1. The Bird's Nest Stadium in the Beijing Olympic Village

provided attendees with a historical review of CAPS and an overview of its prospects for the future (Figure 3), the latter of which includes the hosting of the 2021 IUPS Congress in Beijing. Professor Xiao-Min Wang hosted a dinner for many of the international attendees at a restaurant famous for its Peking duck (Figure 4). The Closing Banquet was held at the Grand Mansion Restaurant, which features excellent Chinese cuisine presented in conjunction with a floor show highlighting Chinese culture. It was an enjoyable evening that allowed attendees to interact with their colleagues from around the world.

ICPS 2016 was attended by 887 registrants, including 556 full delegates and 331 students. In addition, there were 40 exhibitors and 75 staff members in attendance. The staff members were the many graduate students who dressed in orange shirts and provided support and assistance to the conference attendees. Among the 887 meeting participants, there were representatives from 22 countries and regions, including Hong Kong and Taiwan. Although the vast majority of representatives were from Mainland China (747), there were 140 participants from overseas countries. Representation from the U.S. was the largest foreign delegation, with 52 participants (Table 1).

There were 38 symposia covering several aspects of physiological research included on the program for ICPS 2016. The participating societies served as sponsoring societies for a number of the symposia, as indicated in Table 2. The APS sponsored the following three symposia:

- **Intramyocardial Fibroblast, Myocyte and Extracellular Matrix in Heart,** organized by Jiang Chang, Texas A&M University Health Sciences Center, Houston
- **Sex-Specific Cardiac Regulation by Sex Hormones,** organized by Georgios Kararigas, Charite University, Berlin
- **The Neuronal Control of Breathing in Health and Disease,** organized by Jan-Marino Ramirez, University of Washington School of Medicine, Seattle

Figure 4. Dinner hosted by Xiao-min Wang for a number of international participants in ICPS 2016

Figure 3. Delegates at the Opening Session

Table 1. Information on ICPS 2016 participation

Regular Registration		Student	Total
Country	Count	Count	
Australia	8	0	8
Austria	3	0	3
Chinese Taipei	12	0	12
Mainland China	426	321	747
Denmark	2	0	2
Finland	2	1	3
Germany	1	0	1
Hong Kong-China	5	0	8
India	1	0	1
Iran	1	0	1
Japan	13	0	13
Korea	3	8	11
Malaysia	1	0	1
New Zealand	4	0	4
Norway	1	0	1
Pakistan	1	0	1
Saudi Arabia	1	0	1
Singapore	1	0	1
Sweden	2	0	2
UK	17	0	17
U.S.	51	1	52
Total	**556**	**331**	**887**
Exhibitors			**40**
Staff			**75**
Total participants			**1008**

To encourage and ensure the growth of young physiologists, the conference scheduled four early career physiologist speaker sessions. The conference also organized two workshops: one was jointly organized by American Physiological Society and The Physiological Society, the other was organized by Psychoneuroimmunology Research Society.

ICPS 2016 programmed 613 abstracts for the meeting. The abstracts were received from 7 Plenary Lecturers, 221 invited symposium speakers, 40 young physiologists' symposium speakers, and an additional 385 abstracts, which were presented as posters. The seven invited plenary lecturers were:

- **Shu Chien,** Y.C. Fung Professor of Bioengineering and Medicine & Director, Institute of Engineering in Medicine, University of California San Diego, San Diego, CA
- **Michael Hausser,** Wellcome Trust Principal Research Fellow and Professor of Neuroscience, University College London, UK
- **Peng Li,** Professor and Associate Dean of School of Life Sciences, Tsinghua University, China
- **Yoshinori Marunaka,** Professor and Chairman, Department of Molecular Cell Physiology, Kyoto Prefectural University of Medicine, Japan
- **Larry William Swanson,** University Professor and Appleman Professor of Biological Sciences, Neurology, and Psychology, University of Southern California, Los Angeles CA

Table 2. Summary of sessions and society sponsorship of symposia

Types of Presentation	Society Name	Count
Plenary Lecturers		**7**
Participating Physiological Society Symposia	American Physiological Society Symposium	3
	Australian Physiological Society Symposium	1
	Austrian Physiological Society Symposium	1
	Chinese Physiological Society in Taipei symposium	3
	Chinese Association for Physiological Sciences Symposium	21
	Physiological Society of Japan Symposium	2
	Physiological Society of New Zealand Symposium	1
	Psychoneuroimmunology Research Society Symposium	1
	The Physiological Society Symposium	3
	The Scandinavian Physiological Society Symposium	2
Young Physiologist Symposia		**4**
Workshops	The American Physiological Society and The Physiological Society	1
	The Psychoneuroimmunology Research Society(PNIRS)	1
Posters		385

- **Ruiping Xiao,** Professor and Director of Institute of Molecular Medicine, Peking University, China
- **Xu Zhang,** Professor and Associate Dean of Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, China

There were 12 exhibitions during the conference provided by the 40 exhibitors and 75 dedicated staff. Awards were given to young physiologists based on their poster or oral presentations. A total of 35 poster awards and 6 Young Physiologist Symposium speakers were selected as award recipients.

During the closing session, representatives from the partnering societies expressed their appreciation of the efforts of the Chinese Association for Physiological Sciences to organize and coordinate the meeting. APS President Jane Reckelhoff (Figure 5) commented on behalf of the APS: "I speak for all of the APS members that you made us feel very welcome, and we very much enjoyed the excellent scientific presentations and interactions that we have had while here. This meeting is a wonderful example of the internationality of our discipline that is unimpeded by national borders. The meetings in 2008, 2012, and now this one in 2016 set the stage for a larger international conference, the 2021 IUPS Congress, that will be organized by CAPS and will be held here in Beijing. The APS looks forward to participating in that Congress, and we look forward to experiencing the same high level of scientific excellence that we experienced here this week." At the close of the meeting, the organizers took a group picture with a number of the orange-shirted graduate students who were so influential in helping to make ICPS 2016 a success (Figure 6). ●

Figure 5. APS President Jane Reckelhoff addressing the audience during the Closing Ceremony

Figure 6. Group picture from the closing ceremony, with many of the international participants and the students in orange shirts who helped with the conference

Physiology 2016 – A Joint APS-TPS Meeting

Physiology flowed freely along the banks of the River Liffey as physiologists from APS and The Physiological Society (TPS) gathered July 29-31 in The Convention Centre Dublin (CCD) (Figure 1). Physiology 2016 represented a partnership between the two oldest and largest physiological societies in the world and marked the 140th anniversary of the founding of TPS and the 129th of the APS. Reflecting that partnership, the current Presidents of the two societies, Jane Reckelhoff and Richard Vaughan-Jones (Figure 2), welcomed meeting attendees to a celebration of physiology. The partnership between the APS and TPS was also evidenced by the branding found in the main lecture halls for the meeting (Figure 3).

Figure 1. The Convention Centre Dublin (CCD)

Figure 2. APS President Jane Reckelhoff and The Physiological Society President Richard Vaughan-Jones offering welcome to meeting attendees

As a joint meeting, Physiology 2016 attracted over 1,169 scientists from 69 countries to exchange information about their research and teaching (Table 1). Of the 1,169 attendees, 231 could be identified as APS members, and 504 could be identified as TPS members, although it is possible that some of the attendees had membership in both societies. Physiology 2016 represented a continuation of a program of strategic collaborations, including the joint publication of *Physiological Reports*, our joint open access journal.

In many ways, the format of the meeting was comparable to previous annual meetings of TPS. However, as a joint meeting, APS had input into the selection of the invited lecturers, and the APS membership was encouraged to submit symposium proposals for inclusion on the program. Overall, it was a positive collaboration that may lead to future joint meetings. Before this meeting, PhySoc had sponsored several symposia at APS's annual meeting at Experimental Biology, and APS had sponsored several symposia at the PhySoc annual meeting. The

Figure 3. Society branding in the large lecture halls for Physiology 2016

joint meeting was designed to integrate our interests in one meeting, even though APS had held its official annual meeting in San Diego in April 2016 as part of the Experimental Biology meeting.

Physiology 2016 consisted of 13 plenary and keynote lectures, of which 5 were presented by female scientists. In addition, the 32 symposia on the program included 128 speakers, of which 59 were female. The meeting also included nine workshops and general interest sessions. Participants in the meeting also submitted 834 abstracts for presentation at the meeting, in many cases as poster presentations (Figure 4). Table 2 indicates that the largest number of abstracts was submitted by physiologists in the United Kingdom, the U.S., and Ireland.

To encourage the participation of APS members in the meeting, the Society offered travel awards to interested individuals. APS made 39 travel awards to members from 8 countries. The majority of the awardees were from the U.S. (29), but awards were also given to members from Chile (3), Canada (2), and Argentina, Brazil, India, Nigeria, and the United Kingdom (1 each). When asked for their opinions about the meeting, the awardees rated the meeting a 7.9 out of 10. The awardees were asked to comment about their experiences at the meeting in Dublin, and they offered the following comments:

- "Personally, I was humbled to learn of the exciting research being done in countries outside the U.S., Asia, and Western Europe. I met scientists from the Middle East and Eastern Europe that do not typically attend large meetings in the U.S., and I am very grateful for that opportunity. Scientifically

Table 1. Country distribution of Physiology 2016 attendees

Country	Number of Registrants
United Kingdom	491
United States	183
Ireland	128
Turkey	42
Canada	32
Germany	32
Japan	23
Australia	16
France	16
Spain	15
Chile	12
Portugal	11
Nigeria	10
Ukraine	10
China	10
Brazil	8
Croatia	8
Denmark	8
Korea	7
New Zealand	7
Russia	7
Switzerland	7
Other	49
Total	**1,132**

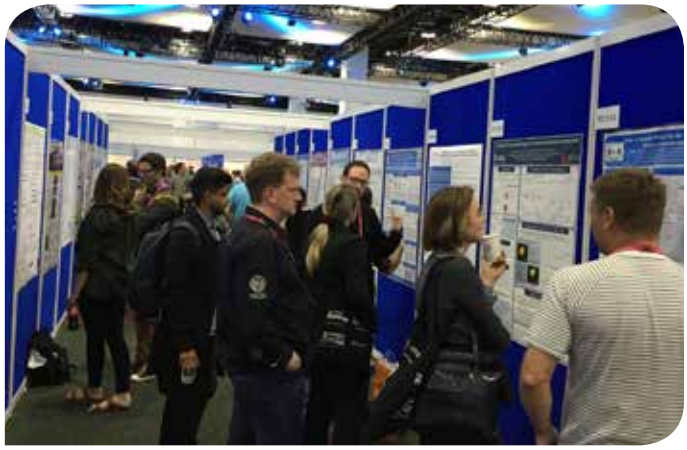


Figure 4. Poster session at the Physiology 2016 meeting

Figure 5. GI Distress performs at Physiology 2016

Table 2. Abstract submissions by country

Country	No. of Abstracts
United Kingdom	301
United States	105
Ireland	58
Turkey	42
Nigeria	31
Germany	18
Spain	18
Canada	17
Japan	17
Chile	14
France	13
Portugal	13
Ukraine	13
Brazil	12
Australia	11
China	8
Croatia	8
India	8
Poland	8
Russian Federation	7
Other	112
Total	**834**

and professionally, attending and presenting my work at this meeting was a tremendous opportunity, giving me the chance to share our research with a truly international community."

- "The award lectures, in particular John Cryan, Emma Hart, and Nobel Laureate John O'Keefe. All were outstanding and the highlight of my attendance."
- "As a new assistant professor who trained in labs that do not focus on physiology, this was my first general physiology meeting to learn broadly about current advances across different fields of physiology."
- "The APS support of the meeting was excellent, highly appreciated, and important for the viability of such joint meetings. In the absence of such support, attendance from the overseas partner would have been extremely low, especially among trainees."

Overall, attendees enjoyed the meeting and the ability to interact with international scientists. In addition, the attendees enjoyed a closing banquet that included Irish dancing and a performance by GI Distress (Figure 5). APS looks forward to future opportunities to collaborate with our colleagues in The Physiological Society. ●

Perkins Award Memories

Virginia Reverte Ribo

Mummy, what are we going to do this weekend? This is a very common question when you have a pair of kids like Pablo Jr. (6 years old) and Carlota (4 years old). Thanks to the John F. Perkins, Jr. Memorial Award for International Physiologists, our adventures grew in excitement and fun! My family and I are very grateful to the Perkins award; we have been able to enrich our family's cultural experience in the U.S. Thanks to my mentor and host Dr. Minolfa Prieto, I was able to transition my family as smoothly as possible to the U.S. lifestyle as well as integrate myself to her very diverse lab.

We are lucky to live in a city like New Orleans, where the climate is mild and culturally offers a wide variety of options, making our choice an arduous task. One of the first things we did after obtaining the award was acquire a membership for the Audubon Zoo and The Aquarium of the Americas. My family and I are very keen on animals and wildlife, so we made great memories at the zoo. In addition, we obtained a membership for the Audubon Butterfly Garden and Insectarium, where we enjoyed the Butterfly Garden, which is populated by hundreds of butterflies and where you can interact with them. During the summer, we enjoyed the funny splash park in the zoo and cinema sessions on Friday's nights.

To help my husband Pablo, who is an engineer working in building development and construction, while we were in Spain, to overcome the language barrier, he enrolled in a course of English as a Second Language (ESL) in the Delgado College in New Orleans. As a civil engineer, learning English will certainly open greater professional opportunities when we return back home to Cartagena, Spain.

We have also attended numerous cultural and gastronomic festivals organized in the city such as the French Market Creole Tomato Festival, New Orleans Oyster Festival, Louisiana Seafood Festival, and Theme Creole Gumbo Festival. Pablo Jr. and Carlota love going to festivals; they enjoy the ambience and the delicious food. I must say that the food in this city is exquisite! Speaking of food, Pablo had the opportunity to attend a couple of classes of Cajun cuisine because we want to take home some of the flavors of New Orleans.

Walt Disney World, September 2016

Bay St. Louis, Mississippi, July 2016

In New Orleans, even though there is not any special event, we always found something fun and interesting to do with the kids, like taking a horse carriage ride in the French quarter, cruising along the Mississippi River in the Natchez Steamboat, enjoying a dozen charbroiled oysters in Acme, and having a coffee and beignet in the Cafe du Monde for dessert.

Thanks to the support obtained from the John F. Perkins, Jr. Memorial Award, we have been able to explore places outside the

city. We have visited plantations such as Oak Alley, we took a tour through the swamp to see more closely the alligators and the way of Cajun lifestyle. We also visited a safari (and the kids had the best time feeding the giraffes) and the beach in Bay St. Louis in Mississippi.

Pablo, Pablo Jr., and Carlota

The best for last . . . in September of the present year, the Council of Hypertension took place in Orlando, FL, thus the whole family traveled to spend a week at Walt Disney World. There are no words to describe the emotion and excitement of my children's faces when they greeted Cinderella and saw the fireworks at Magic Kingdom! Unforgettable!

I am very grateful to the American Physiological Society, especially the committee for the John F. Perkins, Jr. Memorial Award, for giving me the opportunity to share with my family these amazing experiences, which we have enjoyed very much during our stay in the U.S., making this year an unforgettable experience.

Thank you so much! ●

Bylaw Amendment

The APS Council has authorized the placement of the following bylaw amendment on the agenda for the APS Business Meeting to be held on Tuesday, April 25, 2017. According to the Society's bylaws (Article XIII, Section 1), amendments to these bylaws may be proposed in writing, by any regular member, to Council at any time up to 3 months in advance of any Business Meeting of the Society. The proposed amendment (indicated by underlined text) is designed to make the bylaws consistent with how regular members are currently represented on the Publications Committee.

ARTICLE V. *Standing Committees*

SECTION 1. *Publications Committee.* A Publications Committee composed of <u>at least</u> five regular members of the Society appointed by Council shall be responsible for the management of all of the publications of the Society. The term of each member of the Publications Committee shall be three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairperson of the Committee who shall be an ex officio member of the Council, without vote. On the advice of the Publications Committee and consent of Council, the Executive Director shall be empowered to appoint and compensate the <u>Director of</u> Publications ~~Manager~~ who shall assist in carrying out the functions of the Publications Committee under the supervision of the Executive Director. The President, Executive Director, and the <u>Director of</u> Publications ~~Manager~~ shall be ex officio members of the Publications Committee without vote. The Committee shall have the power to appoint editorial boards for the Society's publications. The Committee shall present an annual report on publications and policies to the Council for approval and present an annual budget coordinated through the Executive Director, to the Finance Committee for its approval and recommendation to Council. ●

Education

APS Promotes Physiology to K-12 Teachers at Fall Meetings

The APS highlighted physiology for middle school science teachers and administrators at the annual Association for Middle Level Education (AMLE) Conference held in Austin, TX from October 9th to 12th. This was the seventh year for an APS presence at the AMLE Conference, which is attended by over 3,500 teachers, administrators, and counselors from across the country.

In a hands-on workshop led by Rebecca Evans, past Frontiers Teacher and mentor instructor, teachers were given a brief introduction to the *Next Generation Science Standards*. The newly released standards create a challenge for K-12 teachers and the way science will be taught in their classrooms. During this well attended workshop, sample resources and ideas for using the *Next Generation Science Standards* were presented, giving teachers the opportunity to actually try some of the hands-on engineering and modeling lab lessons that are currently available in the *LifeSciTRC*.

Teachers were as excited as ever for a science society's presence since so few opportunities are available for science-related materials at this meeting. The APS booth was extremely busy and well received, with many questions about the APS Life Science Teaching Resource Community, age appropriate careers materials such as the career trading cards, and the Online Six Star Science Professional Development Fellowship. Next year's conference will be held in Philadelphia, PA from November 5th to 8th.

APS also promoted physiology for K-12 biology teachers at the National Association of Biology Teachers (NABT) Conference in Denver, CO. The annual national conference, held the first week of November, attracts middle and high school teachers as well as 2- and 4-year college faculty from across the nation. APS sponsored an exhibit booth and featured speaker. The APS booth highlighted the Life Science Teaching Resource Community (*www.LifeSciTRC.org*), Frontiers in Physiology teacher professional development program, career materials, and K-12 outreach.

This year's sponsored speaker was APS member W. Larry Kenney, Penn State. Kenney presented "Aging in a Changing Climate: Physiology in Context." His presentation focused on the physiology of human aging in an ever-warming climate, how and why older men and women are at risk during episodic heat waves, and (potentially) what we can do about it. Teachers were engaged during this well attended session and had many follow-up questions for Kenney.

Interest in undergraduate programs was a highlight at the exhibit booth throughout the 3-day conference as resources and program materials were provided and discussed with community college attendees. Next year's conference will be held in St. Louis, MO from November 9th to 12th. For further information, please contact Margaret Shain Stieben, Program Manager, K-12 Education Programs (*mstieben@the-aps.org*). ●

Association for Middle Level Education (AMLE) Conference held in Austin, TX, and National Association of Biology Teachers (NABT) in Denver, CO

APS Minority Travel Fellows at 2016 APS Conferences

In 2016, APS held three conferences and provided Minority Travel Fellowship awards to seven underrepresented graduate students, postdoctoral fellows, and early career faculty (within 5 years of obtaining a PhD).

The APS Minority Travel Fellowship program seeks to increase active participation in and networking at scientific meetings among trainees and early career faculty who are from groups underrepresented in the physiological sciences. APS annually provides $125,000 in funding for travel fellowships for underrepresented minority physiologists to attend EB and APS conferences.

The 2016 Minority Travel Fellows, their Meeting Mentors, and conferences attended were:

Meeting	Travel Fellow, Fellow Institution and Abstract Title or Research Focus	Meeting Mentor
Inflammation, Immunity and Cardiovascular Disease	**Ruben Banuelos,** A.T. Still University *Research Focus:* Exercise intensity and insulin action response in diabetic populations	Melissa M. Markofski, PhD, University of Houston
	Shirley Dehn, Northwestern University *Abstract Title:* Ly6cHI Monocytic Clearance of Dying Cardiomyocytes by CD36 activates NR4a1 and is Required for Transition to Reparative Inflammation following Myocardial Infarction	Jennifer Sullivan, PhD, Augusta University
	Ijeoma Obi, University of Alabama at Birmingham *Abstract Title:* Renal and Splenic Cytokines are Altered in Early Life Stressed (ELS) Adult Male Rats	Keisa Mathis, PhD, University of North Texas Health Sciences Center
	Lia Taylor, Augusta University *Abstract Title:* A High Fat Diet Increases Blood Pressure and Leads to a Proinflammatory Immune Cell and Cytokine Profile in the Aortae of Female Dahl Salt-Sensitive Rats (DSS)	Alison Bloom Kohan, PhD, University of Connecticut
Institute on Teaching and Learning (ITL)	**Daniela Terson de Paleville,** University of Louisville *Research Focus:* Spinal cord injury rehabilitation, and, more precisely, how activity-based therapy has an impact in body composition, cardiovascular fitness, and metabolic function in individuals with chronic spinal cord injury	Nancy Aguilar-Roca, PhD, University of California, Irvine
Integrative Biology of Exercise VII	**Ashley Archer,** University of Kansas Medical Center *Abstract Title:* Heat Shock Protein 72 Activation in the Liver with Exercise	Esther E. Dupont-Versteegden, PhD, University of Kentucky
	Maria Torres, East Carolina University *Abstract Title:* Mechanistic Flexibility of Mitochondrial Complex I and its associated H_2O_2 Emitting Potential	Johana Vallejo, PhD, Midwestern University

Travel Fellows received up to $1,800 in travel-expense reimbursement to cover registration, travel, hotel, and meals. Fellows interacted with a meeting mentor, an APS member who volunteered to facilitate interactions among themselves, and others during the meeting.

This program encourages highly qualified racial/ethnic minorities and persons with disabilities to pursue professional careers in physiological/biomedical sciences. Applications will be available throughout 2017 to attend the three APS conferences (*www.the-aps.org/mm/Conferences/APS-Conferences/2017-Conferences*). To learn more, visit *www.the-aps.org/minoritytravel* or contact the Education Office at *education@the-aps.org*. ●

Travel Fellows at the Integrative Biology of Exercise VII meeting

Barb Goodman and Daniela Terson de Paleville at the ITL meeting

Travel Fellows at the 2016 Inflammation conference

Join the National Research Mentoring Network, a Nationwide Network of Mentorship Programming for Scientists

The National Research Mentoring Network (NRMN; NRMNet.net), funded by the National Institutes of Health (NIH), is a nationwide consortium of science professionals and institutions collaborating to provide students and scientists across all career stages of research in the biomedical, behavioral, clinical, and social sciences with enhanced networking, professional development, research resources, and mentorship experiences. APS is a proud partner and supporter of NRMN. APS encourages members to join today!

As a MENTEE with NRMN, you can:

- Navigate NRMNet, an online resource for mentoring, networking, and professional development.
- Participate in virtual mentoring with mentors recommended to you based on topics relevant to your field(s) of interest in the sciences and your interest to discuss the impact of cultural background on your scientific career.
- Stay up-to-date on NRMN's programming and nationwide diversity efforts through webinars, videos, news, and links to ongoing professional development opportunities.

As a MENTOR with NRMN, you can:

- Learn about mentoring best practices from other outstanding mentors.
- Participate in mentorship in your field that directly addresses diversity, inclusivity, and culture through NRMN's virtual mentoring platform.
- Stay up-to-date on diversity efforts and programs.

Visit *goo.gl/bx6wXf* to create your profile on the NRMN website today!

As you create your profile, please note:

- You will be prompted to create a password and answer a set of basic questions to create your profile.
- When asked, "From which organization did you hear about NRMN?" please select "APS - American Physiological Society" from the dropdown menu. You will be able to add other society memberships to your profile, but selecting APS will allow for more physiology matches.
- When you reach the end of the questions, you will be given the option of setting up your virtual mentoring profile. This will entail answering some additional questions, and so you may choose the option to log back in and complete this step later if you prefer.
- Once you've completed your registration, you will see a Confirmation page listing your responses. You must click the red button on the lower right-hand side of this page to finalize your registration.

Should you have any questions or concerns, please do not hesitate to contact *info@nrmnet.net* or contact the Education Office at *education@the-aps.org*. ●

Ring in the New Year with Award Opportunities from the Education Office!

To apply for any of these awards, go to *the-aps.org/awardapps*.

APS EB Undergraduate Research Awards

Application deadline: January 12, 2017

the-aps.org/eb-undergrad

The APS EB Undergraduate Research Awards are presented annually to undergraduate students who are first authors on an abstract submitted to an APS session for the Experimental Biology (EB) meeting and will be presenting their research at this meeting. There are two types of awards that students can apply for through a single application. See the website for more details.

Barbara A. Horwitz and John M. Horowitz Outstanding Undergraduate Abstract Awards

This award provides $100, an award certificate, and a 2-year complimentary membership with APS. The student must be enrolled as an undergraduate at the time of the abstract submission, be the first author on an abstract submitted to an APS session at the EB meeting, and be working with an APS member. Selection of awardees is based on the abstract, letter of application, and letter of support from the research host. Receipt of the award is contingent upon presenting the research at EB.

David S. Bruce Excellence in Undergraduate Research Awards

To be considered for this award, students must be a Barbara A. Horwitz and John M. Horowitz Outstanding Undergraduate Abstract Awardee and must attend and present a poster at the EB meeting. The recipients receive $400 and an award certificate. The highest-ranked awardee receives another $250, thanks to the generous contribution of an APS member. Selection of awardees is based on the quality of the poster and oral presentation of the poster to the Award Selection Committee.

Porter Physiology Development Fellowships

Application deadline: January 15, 2017

the-aps.org/porter

The goal of the Porter Physiology Development Program is to encourage diversity among students pursuing full-time studies toward the PhD in the physiological sciences and to encourage their participation in the Society.

The Porter program provides a full-time graduate fellowship ($28,300 during the academic year) to students in programs leading to the PhD in the physiological sciences at U.S. institutions. The program is open to underrepresented racial and ethnic minority applicants who are citizens or permanent residents of the U.S. or its territories and student members of the Society.

APPLICANTS AND THEIR ADVISOR/PI must be APS members or have submitted an application for APS membership at the time of submission of the application.

Dale J. Benos Early Career Professional Service Award

Application deadline: January 24, 2017

the-aps.org/benos

The Dale J. Benos Early Career Professional Service Award honors an early career stage (graduate student, postdoctoral fellow, assistant professor or equivalent position) member of APS who has made outstanding contributions to the physiology community and demonstrated dedication and commitment to furthering the broader goals of the physiology community. Awardees typically served on professional committees, participated in K-12 education outreach, participated in scientific advocacy and outreach programs, or otherwise strengthened and promoted the physiology community. See the website for more details.

Undergraduate Summer Research Fellowships

Application deadline: February 1, 2017

the-aps.org/summerresearch

APS is proud to offer four programs that allow undergraduate students to participate in research during the summer (IOSP, STRIDE, UGREF, and UGSRF). Recipients spend an average of 10 weeks in the laboratory of an established scientist and APS member. Each program recruits undergraduate students nationwide, two internationally. Some programs especially encourage applications from students from disadvantaged backgrounds, students from underrepresented racial and ethnic groups, or students with disabilities. Each Fellow receives a stipend plus additional funds for travel to present his or her research at a scientific meeting. Research hosts receive funds for student lab supplies. See the website for more details.

APS/NIDDK STEP-UP Undergraduate Summer Research Fellowships

Application deadline: February 15, 2017

the-aps.org/stepup

STEP-UP Fellows spend an average 8-12 weeks in the laboratory of an established scientist conducting research in the NIDDK mission areas. This program is open to students from disadvantaged backgrounds, students from underrepresented racial and ethnic groups, and students with disabilities. Each Fellow receives a stipend plus additional funds for travel to present his or her research at the STEP-UP summer research symposium. Research hosts receive funds for student lab supplies. See the website for more details and apply online at *http://1.usa.gov/1HyYspI*.


Missed Experimental Biology 2016? or
Attended EB 2016 but Missed APS Career/Trainee/Mentoring Sessions?
You can still attend them!
Listen to the talks and view the PowerPoint presentations for:
Career Symposium
Leadership and Management Skills: What You Might Not See in Your CV
the-aps.org/leadership
Trainee Symposium
Now Hiring PhDs: Post Doc Not Required
the-aps.org/hiring
Mentoring Symposium
Negotiating for Success!
the-aps.org/negotiating

Professional Skills Training

2017 Course Offerings

Manuscript Writing Skills

Writing and Reviewing for Scientific Journals • January 12-15 (Orlando, FL)
Work with leading experts in-person to improve your first-author draft manuscript while learning the essentials of scientific writing and reviewing.
www.the-aps.org/PST/WritingWorkshop

Writing and Reviewing for Scientific Journals • July 6-August 21 (Online)
Work with leading experts online to improve your first-author draft manuscript while learning the essentials of scientific writing and reviewing.
www.the-aps.org/PST/WritingSkills

Meeting and Presentation Skills

Creating a Poster for a Scientific Meeting • February 16-22 (Online)
Learn how to organize and create an effective and engaging scientific meeting poster.
www.the-aps.org/PST/MeetingSkills

Presenting a Scientific Poster • March 2-8 (Online)
Learn the essentials of presenting a poster to multiple audiences at a scientific meeting.
www.the-aps.org/PST/MeetingSkills

Networking at a Scientific Meeting • March 16-22 (Online)
Learn how to successfully network at a scientific meeting.
www.the-aps.org/PST/MeetingSkills

Abstract Writing for Scientific Meetings • October 19-26 (Online)
Receive feedback on your first-author abstract while improving your abstract writing skills.
www.the-aps.org/PST/MeetingSkills

For more information, deadlines, and application instructions, please visit www.the-aps.org/PST

Publications

Current Calls for Papers

Physiological Genomics

- Genetics of Metabolic Syndrome
- Single Cell Analysis
  Submission deadline:
  May 31, 2017

Journal of Neurophysiology

- Where Are You Going? The Neurobiology of Navigation.
  Submission deadline:
  June 30, 2017
- The Mouse Visual System
  Submission deadline:
  June 30, 2017
- Central Pattern Generators
  Submission deadline:
  June 30, 2017

Advances in Physiology Education

- Historical Perspectives and Living Histories

American Journal of Physiology – Endocrinology and Metabolism

- Role of Gut Microbiota and Gut-Brain and Gut-Liver Axes in Physiological Regulation of Inflammation, Energy Balance, and Metabolism
  Submission deadline:
  September 30, 2017
- Role of Fetal Programming and Epigenetic Regulation on the Development of Endocrine and Metabolic Alterations
  Submission deadline:
  September 30, 2017
- Browning and Beiging of Adipose Tissue, Its Role in the Regulation of Energy Homeostasis and as a Potential Target for Alleviating Metabolic Diseases
  Submission deadline:
  September 30, 2017
- Mechanisms of Effects on Sleep Disruption on Adipocyte/Obesity Metabolism and Their Relation to Other Metabolic Disease
  Submission deadline:
  September 30, 2017
- Metabolism and Signaling Functions of Amino Acids in the Regulation of Cell/Tissue Function in Health and Disease
  Submission deadline:
  September 30, 2017
- Role of Adipose Tissue Nutrient/Vitamin Metabolism in Physiological and Altered Metabolic Settings
  Submission deadline:
  September 30, 2017
- Endocannabinoids and Cannabinoid Receptors as Regulators of Endocrine Functions and Tissue Metabolism
  Submission deadline:
  September 30, 2017
- Role of Myokines and Adipokines and Other Cross-Talk Mechanisms of Regulation of Endocrine and Metabolic Functions
  Submission deadline:
  September 30, 2017
- Mitochondria Dysfunction in Aging and Metabolic Diseases
  Submission deadline:
  September 30, 2017

American Journal of Physiology – Gastrointestinal and Liver Physiology

- Gut-Brain Interactions and Brain Imaging
- Physiology of Gastrointestinal, Hepatic, and Pancreatic Cancer
- Metabolomics and Physiological Systems
- Systems Biology in Gastrointestinal Physiology and Diseases

American Journal of Physiology – Heart and Circulatory Physiology

- Advances in Cardiovascular Geroscience
  NEW DEADLINE: May 1, 2017
- Heart Failure – Novel Therapeutic Pathways Emerging from Basic Science
  Submission deadline:
  February 15, 2017

American Journal of Physiology – Lung Cellular and Molecular Physiology

- Electronic Cigarettes: Not All Good News?
  Submission deadline:
  October 1, 2017
- Ion Channels and Transporters in Lung Function and Disease
- Age-Related Dysfunction in Lung Barrier Function in Health and Disease
- Real-Time Visualization of Lung Function: from Micro to Macro
  Submission deadline:
  January 2017

- Biomarkers in Lung Diseases: from Pathogenesis to Prediction to New Therapies
  Submission deadline: January 2017
- Translational Research in Acute Lung Injury and Pulmonary Fibrosis
  Submission deadline: January 2017

American Journal of Physiology – Regulatory, Integrative and Comparative Physiology

- Exploiting Environmental Factors to Improve Health and Performance
  Submission deadline: March 31, 2017
- Model Systems for the Study of Integrative Physiology: The Rebirth of Translational Biology
  Submission deadline: May 1, 2017
- Oxygen Signaling
  Submission deadline: December 31, 2017

American Journal of Physiology – Renal Physiology

- Imaging Techniques in Renal (Patho)physiology Research
  Submission deadline: June 30, 2017
- Inflammation and Inflammatory Mediators in Kidney
  Submission deadline: June 30, 2017
- Mechanism and Treatment of Renal Fibrosis and Treatment
  Submission deadline: June 30, 2017
- Renal Hemodynamics
  Submission deadline: June 30, 2017
- Gender and Hormones in Lower Urinary Tract Function
  Submission deadline: June 30, 2017
- Transport Proteins as Regulators of Blood Pressure Homeostasis
  Submission deadline: June 30, 2017
- Endothelin in Renal Physiology and Disease
  Submission deadline: June 30, 2017

For a complete list of current Calls for Papers, visit the APS website.

Science Policy

ACE Committee Explores Ways to Reduce Regulatory Burden

At its fall 2016 meeting, the Animal Care and Experimentation (ACE) Committee tried to identify relatively simple ways to reduce burdensome practices associated with animal research oversight. As a starting point, the committee identified four actions IACUCs could take to decrease self-imposed regulatory burden:

- Use veterinary verification and consultation to streamline the process of amending animal protocols;
- Encourage designated member review over full committee review for protocol amendments;
- Avoid assigning pain categories to non-USDA-regulated species unless this is required by the funding agency
- Encourage investigators to use ranges of animal numbers and drug doses in protocols to reduce the need for amendments as the research progresses.

At Experimental Biology 2016, the ACE Committee organized a symposium (*http://www.the-aps.org/mm/SciencePolicy/AnimalResearch/Regulatory-Burden/Regulatory-Burden-Symposium*) on reducing burdensome institutional procedures associated with animal research oversight. Following the symposium, a website was developed to share the speakers' slides (*http://www.the-aps.org/mm/SciencePolicy/AnimalResearch/Regulatory-Burden/Regulatory-Burden-Symposium*), a summary of the session (*http://www.the-aps.org/mm/SciencePolicy/AnimalResearch/Regulatory-Burden/Regulatory-Burden-Symposium/ACE-Symposium-Seeks-Ways-to-Reduce-Regulatory-Burden.html*), and additional resources on alleviating regulatory burden (*http://www.the-aps.org/mm/SciencePolicy/AnimalResearch/Regulatory-Burden/Additional-Resources*). ●

USDA Inspections Find High Level of AWA Compliance

The vast majority of USDA inspections of registered research facilities during Fiscal Year (FY) 2015 did not uncover any Animal Welfare Act (AWA) violations. William Stokes, Assistant Director for Animal Welfare Operations with the USDA's Animal and Plant Health Inspection Service (APHIS), provided an overview of AWA inspection findings at research institutions on November 1, 2016. He spoke at the national meeting of American Association for Laboratory Animal Science (AALAS) in Charlotte, NC.

Some 1,045 research facilities were registered with the USDA in FY 2015, with a total of 1,187 inspection sites. During FY 2015, USDA inspectors conducted 1,350 unannounced inspections. In slightly more than 75% of those inspections, no Non-Compliant Items (NCIs) were found. ("NCI" is the USDA's term for alleged violations of the AWA.) Of the 330 or so inspections where inspectors found NCIs at research facilities, only 13 cases involved problems with a direct bearing on animal welfare, and those were concentrated in 6 institutions. (USDA conducts follow-up inspections when problems that may affect animal welfare are found.)

Almost 40% of USDA's noncompliance citations involved the responsibilities of the Institutional Animal Care and Use Committee (IACUC). The primary problem areas involved failures to conduct or document semi-annual program reviews and facility inspections; to ensure that alternatives to painful procedures were considered; and to review and approve significant changes to research protocols. Another 30% of the noncompliance citations involved failures to provide adequate veterinary care, including coverage outside of regular business hours.

Stokes underscored that an inspector's report of noncompliance is considered an alleged AWA violation because institutions are entitled to contest them. Institutions have 21 days to appeal an inspector's finding by presenting additional information about the alleged violation. If the institution is not satisfied with USDA's response, it can go before an Administrative Law Judge to challenge the inspector's report. Stokes said that, in most instances where serious AWA violations are alleged, institutions reach a settlement with USDA. This may involve a stipulation agreement and payment of a fine. The maximum fine under law is $10,000 per day for each animal and for each violation that has occurred. ●

Update on Overtime Rules for Postdocs

On December 1, 2016, revised rules on paid overtime under the Fair Labor Standards Act (FLSA) were scheduled to go into effect. However, implementation of the new rules was delayed by a preliminary injunction issued by a federal court on November 22nd.

The revised rules specify that workers who earn less than $47,476 per year are eligible for paid overtime. The National Institutes of Health (NIH) released a notice (NOT-OD-16-134) in August stating that postdoctoral fellows supported by National Research Service Awards (NRSA) will have their stipends raised above the threshold as of December 1. The NIH put out further guidance (NOT-OD-17-002) in November, outlining the process by which institutional training grants and individual NRSA fellows can request administrative supplements to cover the difference in salary level.

Many institutions that employ postdoctoral fellows use the NRSA salary levels as a guideline and, under the revised rules, would have the choice of either raising the salary levels above the threshold or tracking hours worked and paying overtime when appropriate. The NIH has signaled that it will go ahead with plans to raise NRSA stipends on December 1 despite the injunction, and many institutions are following suit. ●

Experimental Biology

Experimental Biology 2017 Distinguished Lectures

Physiology in Perspective: The Walter B. Cannon Memorial Award Lecture

Michael Welsh

Univ. of Iowa Roy J. and Lucille Carver Col. of Med.

Insights into the Pathogenesis of Cystic Fibrosis Lung Disease

Saturday, April 22, 2017, 5:30 PM

Sponsored by Sucampo AG

Claude Bernard Distinguished Lectureship of the APS Teaching of Physiology Section

Jeffrey D. Karpicke

Purdue Univ.

Retrieval-Based Learning: Simple Strategies for Helping Students Learn

Sunday, April 23, 2017, 10:30 AM

Sponsored by ADInstruments

Hugh Davson Distinguished Lectureship of the APS Cell and Molecular Physiology Section

Jennifer Lippincott-Schwartz

HHMI Janelia Research Campus

Emerging Fluorescence Technology to Study Cell Architecture and Dynamics

Sunday, April 23, 2017, 2:00 PM

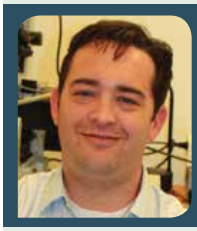
Ernest H. Starling Distinguished Lectureship of the APS Water and Electrolyte Homeostasis Section

Peter Bie

Univ. of Southern Denmark-Odense

Mechanisms of Sodium Balance

Sunday, April 23, 2017, 4:15 PM



Henry Pickering Bowditch Award Lecture

Brant Isakson

Univ. of Virginia

Coordinating Tissue Function Through Heterocellular Communication

Sunday, April 23, 2017, 5:45 PM

Carl Ludwig Distinguished Lectureship of the APS Neural Control and Autonomic Regulation Section

Robin McAllen

Florey Inst. of Neuroscience and Metal Health

Mapping the Diversity of Central Autonomic Control

Monday, April 24, 2017, 8:00 AM

Solomon Berson Distinguished Lectureship of the APS Endocrinology and Metabolism Section

Wolfgang Langhans

ETH Zurich

GLP-1 in Energy Homeostasis: There is More than Meets the *Eye*

Monday, April 24, 2017, 10:30 AM

Edward F. Adolph Distinguished Lectureship of the APS Environmental and Exercise Physiology Section

W. Larry Kenney

Penn State Univ.

Skin-Deep Insights into Vascular Aging

Monday, April 24, 2017, 2:00 PM

Carl W. Gottschalk Distinguished Lectureship of the APS Renal Section

Paul Welling

University of Maryland Med. Sch.

Protecting Potassium Balance at All Costs: Molecules to Man

Monday, April 24, 2017, 3:15 PM

Joseph Erlanger Distinguished Lectureship of the APS Central Nervous System Section

Jeff Lichtman

Harvard Univ.

Does Connectomics Make Sense?

Monday, April 24, 2017, 3:15 PM

Julius H. Comroe, Jr. Distinguished Lectureship of the APS Respiration Section

Peter D. Wagner

Univ. of California, San Diego

Lung and Muscle Heterogeneity: Consequences for Oxygen Transport Limitation

Tuesday, April 25, 2017, 10:30 AM

History of Physiology Lecture

Jack Rall

Ohio State Univ.

The XIIIth International Physiological Congress in Boston in 1929: American Physiology Comes of Age

Tuesday, April 25, 2017, 1:00 PM

Robert M. Berne Distinguished Lectureship of the APS Cardiovascular Section

Benjamin D. Levine

Texas Health Presbyterian Hospital Dallas

Astronauts, Athletes, and Aging. A TripTik Guide to the Cardiovascular Adaptation to Physical Activity

Tuesday, April 25, 2017, 2:00 PM

August Krogh Distinguished Lectureship of the APS Comparative and Evolutionary Physiology Section

Warren Burggren

Univ. of North Texas

Developmental Plasticity, Epigenetics and Evolution: A Comparative Physiologist's Od(d)yssey

Tuesday, April 25, 2017, 3:15 PM

Sponsored by Novo Nordisk Foundation

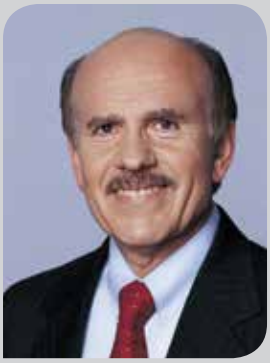
Horace W. Davenport Distinguished Lectureship of the APS Gastrointestinal and Liver Physiology Section

John L. Wallace

Antibe Therapeutics and Univ. of Calgary

Why the GI Tract Does Not Digest Itself: A Davenport-Inspired Journey

Tuesday, April 25, 2017, 3:15 PM



APS Nobel Prize Award Lecture

Louis Ignarro

UCLA Sch. of Med.

The Road to Stockholm: A Nobel Mission

Wednesday, April 26, 2017, 4:45 PM

Experimental Biology 2017

April 22–26, 2017, Chicago, IL

PHYSIOLOGY PLATFORM SESSIONS

Saturday, April 22, 2017

Room			
W375A			5:30 PM–6:30 PM *APS Lecture* Physiology in Perspective: The Walter B. Cannon Memorial Award Lecture **Welsh**
W190A	8:00 AM–12:00 PM *Education Committee Refresher Course* Curricular Innovation in Sex and Gender Based Medical Physiology Education **Scrogin/Sasser**	2:15 PM–5:15 PM *WEH Section Award Session* WEH Trainee Award Finalists and Data Diuresis	
W196B	9:30 AM–11:30 AM *MCS Symp* President's Symp: (Not) Lost in Translation: Bridging the Gaps Between Microcirculatory Basic Science and Clinical Science **Chillian**	1:00 PM–3:00 PM *MCS Symp* Depression and its Effects on Microvascular Function and Vascular Adaptation **Chantler/Olfert**	6:00 PM–8:00 PM MCS Poster Discussion amd Reception **Jackson**
W196C	9:00 AM–5:00 PM *ETG Group Special Session* Pre-EB Meeting of the ETG Group Young Investigators Symp		
W196A		1:00 PM–3:00 PM *Techniques Workshop Program Workshop* Choosing the Right Diet for Your Animal Model **Lund/Ney**	
W190B			3:15 PM–5:15 PM *Techniques Workshop Program Workshop* Using Ultrasound to Teach Cardiovascular Physiology and Anatomy **Silverthorn/Guttmann**
W192B	1:00 PM–3:00 PM *AFMR Symp* Small GTPases: Basic Science to Translational Research **Zhao/Birukova**	3:15 PM–5:15 PM *AFMR Symp* New Insights into Insulin Resistance-Molecular Mechanisms and Therapeutic Implications **Prabhakar/Hawkins**	3:30 PM–5:30 PM *Microcirculatory Society (MCS) Symp* Investigating Microvascular Physiology and Pathophysiology Using Novel Techniques **Stokes/Gavins**
W193			3:00 PM–5:00 PM *NCAR Section Award Session* DATA NCARnation

Saturday, April 22, 2017, *cont.*

Room			
W194B		1:00 PM–5:15 PM *Physiological Genomics Group Special Session* Fourth Annual Physiological Genomics Group Conference	
W192C		1:00 PM–3:00 PM *Science Policy Committee Symp* Why Scientific Rigor Matters and Ways to Improve It **Sutliff**	
W192A			3:00 PM–5:00 PM *Communications Committee Symp* Creative Science Communications Through Improv **Goodman/Crecelius**

Sunday, April 23, 2017

Room	8:00-10:00 AM	10:30 AM-12:30 PM	3:15-5:15 PM
W375A	*ACSM Symp* A Roadmap for the Future of Exercise Science: Key Research Directions **Bouchard**	*President's Symp Series* Sex Differences in Physiology and Pathophysiology **Prieto**	*Integrative Physiol Symp Series* Hypoglycemia: Neural Pathways of the Glucose Counter-Regulatory Response, Hypoglycemia Unawareness and Its Treatment **Verberne** 5:45 PM–6:45 PM Henry Pickering Bowditch Award Lecture **Isakson**
W190A	*GIL Section Special Session* John Forte Session of the GIL Session	10:30 AM–11:30 AM Teaching Section Bernard Lecture **Karpicke** 2:00 PM–3:00 PM Cell Section Davson Lecture **Lippincott-Schwartz**	3:15 PM–4:15 PM *WEH Section Lecture* WEH New Investigator Award Lecture 4:15 PM–5:15 PM WEH Section Lecture WEH Section Starling Lecture **Bie**
W196B	*CV Section FT* Sex Differences in Obesity and Cardiovascular Disease **Belin de Chantemele/Loria**	*EEP Section Symp* Cerebral Function of Permanent Residents of High Altitude: Problems and Solutions **West/Simonson**	3:15 PM–4:15 PM MCS Landis Award Lecture 4:30 PM–5:30 PM MCS Business Meeting **Chillian**
W196C	*NCAR Section Symp* Cardiac Sensory Afferents: The Cornerstone for Autonomic Reflex Processing in Health and Disease **Shivkumar/Wang**	NCAR Section Young Investigator Awards **Young/Sabharwal**	*CV Section FT* Immune Cells Involved in Cardiovascular Disease **Mitchell/Madhur**

Sunday, April 23, 2017, *cont.*

W196A	*Nutrition Group Symp* From Cancer-Causing Villain to Health-Promoting Hero: Taking a U-turn on Dietary Nitrite and Nitrate? **Keen/Hast**	*Resp Section Symp* Ventilatory Control and Function Following Perinatal Insults **Bailey/Revill**	*Resp Section FT* Epigenetic Regulation of Lung Development, Injury, and Repair **Rogers/Tipple**
W190B	*EEP Section Symp* SIRT1 in Muscle Health and Disease **Ljubicic**	*CV Section FT* Vascular-Mediated Mechanisms of Cognition and the Role of Exercise **Baynard**	*E&M Section Symp* Stressing the Beta Cell: The Good and The Bad **Corbett**
W192B	*CV Section Symp* Mathematical Modeling of Cardiac Excitability and Arrhythmias **Hund/Ripplinger**	*Physiol in Industry Committee Symp* Nitric Oxide Pathway Modulation for Therapeutic Intervention and Exercise Enhancement **Mattson**	*NCAR Section FT* Ion Channel Modulation: Contributions to Autonomic Dysfunction in Cardiovascular and Metabolic Diseases **Chen/Toney**
W193	*Teaching Section Symp* Inclusive Practices for Diverse Student Populations **Johnson**	*Muscle Biology Group Symp* The Role of Ribosome Biogenesis in Skeletal Muscle Hypertrophy **McCarthy**	*ETG Group Symp* MicroRNAs in Kidney and Epithelial Transport Physiology, Development and Disease **Loffing/Cai**
W194B	*Renal Section FT* Renal Section Young Investigator Award FT **Pochynyuk**	*Renal Section Symp* Mining Protein-Protein Interactions to Study Renal Transporter Regulation **Chen/Brown**	*PG Group Symp* Single Cell Analysis and Genomic Approaches **Coller**
W192C	*WEH Section FT* Stress and Physiological Responses Throughout Life **Pollock/Taylor**	*PG Group Award Session* Trainee Highlights in Physiological Genomics	*Cell Section FT* Cellular Mechanisms of Stress and Inflammation **Bomberger/White**
W192A	*TransPhys Group FT* Translation Physiology Showcase: Focus on Sex differences in Obesity and Blood Pressure, Developmental Programming, and Women's Health	*Women in Physiol Committee Symp* Choosing the Right Lab and Personnel for Your Career **Edelblum/Wynne**	CEPS Section Trainee-Driven FT

Monday, April 24, 2016

Room	8:00-10:00 AM	10:30 AM-12:30 PM	3:15-5:15 PM
W375A		*President's Symp Series* Women's Health Research **Brooks**	*Integrative Physiol Symp Series* Engineering for Health: Integrating Engineering and Physiology to Combat Disease **Yosten**
W190A	8:00 AM–9:00 AM NCAR Section Ludwig Lecture **McAllen** 9:00 AM–10:00 AM NCAR Section Ludwig MiniSymp	E&M Section Berson Lecture **Langhans**	2:00 PM–3:00 PM EEP Section Adolph Lecture **Kenney** 3:15 PM–4:15 PM Renal Section Gottschalk Lecture **Welling**

Monday, April 24, 2017, *cont.*

Room	8:00-10:00 AM	10:30 AM-12:30 PM	3:15-5:15 PM
W196B	*CV Section Symp* Vascular Autophagy and Endothelial Cell Nitric Oxide Generation **Symons/Gutterman**	*CV Section Symp* Adipose Tissue and the Cardiovascular System: Interactions with Sleep and Cardiometabolic Risk Factors **Covassin/Gollasch**	3:15 PM–4:15 PM CNS Section Erlanger Lecture **Lichtman** 4:15 PM–5:15 PM CNS Section Erlanger MiniSymp
W196C	*WEH Section FT* Hypertension and Sodium Homeostasis-Developing Concepts **Sandberg/Gohar**	*WEH Section FT* Neural and Hormonal Modulation of Fluid Balance and Ion Homeostasis in Health and Disease **Gao/Schiller**	*Teaching Section Symp* Examining the Changing Landscape of Course Delivery and Student Learning **Halpin/Gopalan**
W196A	*E&M Section FT* Brown Fat versus Skeletal Muscle as Metabolic Targets: Activation of Thermogenesis or Glucose Oxidation **Symonds**	*Resp Section FT* Respiratory Control: Beyond the Diaphragm **Fuller/Turner**	*Resp Section Symp* The Emerging Role of Lipids in Lung Physiology and Disease **Kuebler/Letsiou**
W190B	*Hypoxia Group FT* Phyisological Adaptation to Hypoxia and High Altitudes **Iturriaga**	*CV Section FT* Carl J. Wiggers Award FT **Heusch/Meininger**	*E&M Section Symp* Sleep, Circadian Clocks and Metabolism **Van Cauter/Samson**
W192B	*CV Section Symp* Ubiquitin and Ubiquitin-Like Proteins in Cardiovascular Physiology and Disease **Weisleder/Wang**	*CEP Section Symp* Consequences of Physiological Stressors on the Development and Function of the Cardiovascular System **Gillis**	*CV Section Symp* Emerging Concepts in the Local Regulation of Blood Flow **Freed/Duncker**
W193	*Teaching Section FT* Innovation in Teaching: Abstract Driven **Osborne**	*NCAR Section FT* Circumventricular Organs: A Blood-Brain Interface for Modulation of Cardiovascular and Immune Function and Fluid and Electrolyte Balance **Yao**	*WEH Section FT* New Animal Models and Their Utility for WEH Research **Palygin/Pochynyuk**
W194B	*GIL Section Symp* Posttranscriptional Regulation of Intestinal Homeostasis: Stem Cells to Cancer **Hamilton/Chatterji**	*GIL Section FT* Cytoskeletal Proteins in GI and Liver Diseases **Snider/Toivola**	*Cell Section Symp* Transport Proteins and Cellular Signaling in Choroid Plexus Epithelia **Blazer-Yost/Praetorius**
W192C	*Renal Section FT* Advances in Renal Physiology I **Ortiz**	*Careers Committee Symp* The Many Facets of a Teaching Career **Williams/Brandauer**	*PG Group FT* Novel Genetic Risk Factors and Early-Pregnancy Mechanisms Contributing to Preeclampsia **Grobe/Young**
W192A	*Pubs Committee Symp* Publishing 101: How to Get Your Work Published and Avoid Ethical Minefields **Sigmund/Scheman**	*ETG Group FT* Steve Hebert Lecture FT **Moeller**	*Hypoxia Group Symp* Intermittent Hypoxia: Molecular, Integrative, and Clinical Implications **Svatikova/Schreihofer**

Tuesday, April 25, 2017

Room	8:00-10:00 AM	10:30 AM-12:30 PM	3:15-5:15 PM
W375A		*President's Symp Series* Developmental Programming of Diseases **Alexander**	*Integrative Physio Symp Series* Exercise Intolerance in Metabolic, Pulmonary and Cardiovascular Diseases: Did We Forget the Brain? **Brassard/Bailey** 5:45 PM–7:30 PM APS Business Meeting
W190A	*PG Group and ASHG Symp* Atttaching Physiology to the Genome: Spotlight on Cardiovascular Genetics **Lettre/Joe**	10:30 AM–11:30 AM Resp Section Comroe Lecture **Wagner**	2:00 PM–3:00 PM CV Section Berne Lecture **Levine** 3:15 PM–4:15 PM GIL Section Davenport Lecture **Wallace**
W196B	*Resp Section Symp* Embracing the Heterogeneity of Lung Injury: A Bedside to Bench to Bedside Perspective **Dudek/Shaver**	*CV Section Symp* Mechanisms of Stiffening in Large and Small Vessels: From the Cytoskeleton to the Extracellular Matrix **Martinez-Lemus**	3:15 PM–4:15 PM CEP Section Krogh Lecture Supported by Novo Nordisk Foundation **Burggren**
W196C	*NCAR Section Symp* Brain Secrets Revealed by Optogenetics/Chemogenetics Approaches **Rahmouni/De Kloet**	*WEH Section Symp* Sodium Homeostasis in Metabolic Syndrome: Sorting out New and Old Players **Ecelbarger/Tiwari**	*Resp Section FT* Central Neuromodulation in the Control of Breathing **Garcia/Mitchell**
W196A	*CV Section FT* Novel Insights in Vascular Pathophysiology **Isakson/Bagher**	*CNS Section FT* New Insights Into the Role of Hypothalamic Peptides in the Control of Appetite and Energy Balance **Blevins**	*CNS Section Symp* Role of CNS Osmosensory Networks in the Regulation of Cardiovascular Function in Health and Disease **Stern/Pires da Silva**
W190B	*EEP Section Symp* Exercise Training versus Metformin for the Treatment of Cardiometabolic Diseases **Schrage/Jenkins**	*CV Section FT* Kaley Lecture FT: The Complications of Diabetes and the Role of Inflammation: Mechanisms and Therapeutic Opportunities **Schmidt**	*History Group Symp* Twenty Years of Physiological Genomics **Mattson**
W192B	*CEP Section Symp* Developmental Programming of Vertebrate Health and Disease by Hypoxia **Galli**	*EEP Section FT* Impact of Dairy Based Nutritional Interventions on Cardiometabolic Health **Alexander/Miller**	*E&M Section Symp* Central GLP-1 Receptors in the Regulation of Energy Homeostasis **Langhans**
W193	*CNS Section FT* Neuroglial Interactions in Health and Disease **Gulbransen**	*NCAR Section FT* Epigenetic Modifications and Autonomic Regulation **Sriramula**	*EEP Section FT* The Integrated Physiological Response to Heat Stress in Vulnerable Populations **Sawka**
W194B	*GIL Section FT* Autophagy: Driver of Microbiome Composition and Intestinal Homeostasis **Theiss**	*Cell Section FT* Mechanisms and Influences on Cell Signaling **Worrell**	*Cell Section Symp* Multi-omics to Study the Cellular Pathophysiology of Neurodegenerative Diseases **Pimplikar/Tsai**

Tuesday, April 25, 2017, *cont.*

Room	8:00-10:00 AM	10:30 AM-12:30 PM	3:15-5:15 PM
W192C	*Renal Section FT* Advances in Renal Physiology II **Inscho**	*Renal Section Symp* Regulation of Glomeruli Physiological Function: Podocytes and Beyond **Ilatovskaya/Reiser**	*Sex Group Symp* Sex Differences in Diabetes, Obesity and Blood Pressure Control **Brooks**
W192A	*Cell Section FT* Ion Channels and Transporters in Health and Disease **Hamilton/Rodrigues**	*Muscle Biology Group FT* The Hot Zone: Skeletal Muscle Changes Caused by Hyperthermia and Heat Stress **Selsby**	*ETG Group FT* Hans Ussing Lecture FT **Klein**
Location TBD		1:00 PM-3:00 PM 2014 Tang Prize in Biopharmaceutical Science **Charpentier**	1:00 PM–2:00 PM History of Physiology Group Lecture

Wednesday, April 26, 2017

Room	8:00-10:00 AM	10:30 AM-12:30 PM	2:30-4:30 PM
W375A	*Integrative Physiol Symp Series* The Impact of Exosomes on Muscle Atrophy, Hypertrophy and Myogenesis **Wang/Mitch**		4:45 PM–5:45 PM APS Nobel Prize Award Lecture **Ignarro**
W190A	*CV Section FT* Mitochondrial Physiology in Cardiovascular Disease **Calvert/Elrod**	*CV Section FT* Inflammation and Immunity and Heart Disease **Halade/Thorp**	*WEH Section Symp* Hydration and Vasopressin Beyond the Kidney **Armstrong**
W196B	*Physoc/APS Symp* The Modulation of Aging Through Altered Proteostasis **Miller**	*CV Section Symp* MiRNA Regulation of the Mitochondrion in Cardiovascular Disease **Hollander/Thapa**	*WEH Section Symp* Mechanisms of Hypertension Risk **De Miguel/Abais-Battad**
W196C	*Resp Section FT* Organelle Dysfunction in Pulmonary Vascular Disease: Mitochondria, Endoplasmic Reticulum, Lysosomes and Beyond **Shimoda/Ryan**	*EEP Section Symp* Blood Doping: Physiology, Pharmacology and Detection Challenges **Bowers**	*TransPhys Group Symp* Leptin Beyond Appetite Regulation **Singh/Cohen**
W196A	*Muscle Biology Group FT* Satellite Cells: External and Systemic Influences **Brooks/Dupont-Versteegden**	*Physoc Symp* Sexual Dimorphism, Plasticity and Genomic Diversity of the Paraventricular Nucleus **Samson/Yosten**	*TransPhys Group Symp* Vasodilation in Human Microvessels: From Bed to Bench and Back **Kleinbongard/Ait-Aissa**
W190B	*Resp Section Symp* Mechanisms Preserving Breathing Stability **Watters/Braegelmann**	*CEP Section FT* Comparative Perspectives on Hypoxia Signaling and Tolerance **Scott**	*EEP Section Symp* Patent Foramen Ovale: The Hole Story of Environmental and Exercise Physiology **Halliwill/Lovering**

Wednesday, April 26, 2017, *cont.*

Room	8:00-10:00 AM	10:30 AM-12:30 PM	2:30-4:30 PM
W192B	*Cell Section Symp* Glial Cell Development, Migration, and Pathophysiology **Gagnon/Sontheimer**	*CV Section FT* Cardiovascular Control after Spinal Cord Injury **Phillips/West**	*E&M Section Symp* Fighting the Fat: Lifestyle Approaches to Protect Against Adipose Tissue and Liver Dysfunction **Wright**
W193	*CNS Section Symp* Non-motor Dysfunctions in Parkinson's Disease **Travagli**	*NCAR Section FT* Neural Control of the Heart: New Tools, New Mechanisms **Chapleau**	*EEP Symp* Novel Imaging Technologies in Reproductive Physiology **Yamaleyeva/Lindsey**
W194B	*GIL Section Symp* Environmental, Microenvironmental and Nanoenvironmental Factors Which Drive Liver Disease Pathogenesis and Progression **Pritchard**	*Renal Section Symp* New Insights into the Regulation of Renal Blood Flow in Health and Disease **Polichnowski/Williams**	*Cell Section Flex Session* Omics Approaches to Understanding Muscle Biology **Burniston/Chen**
W192C	*E&M Section FT* Central and Peripheral Mechanisms Regulating Body Weight and Glucose Homeostasis **Zsombok**	*Trainee Committee Symp* Kick Start Your Funding: Looking Beyond NIH and NSF **Steiner/Streeter**	Pan-American Symp **TBD**
W192A	*EEP Section FT* Exploiting Environmental Stressors to Improve Health and Performance **Minson/Romero**	*TransPhys Group Symp* Peptides and Metabolites in Cardiovascular Disease **de Castro Brás/Halade**	*ETG Group FT* New Insights into Renal Transport: Application of Genetic Models **Rieg/Fenton**

Membership

New Regular Members

***transferred from student membership**

Celine Aguer
Institut De Recherche De L'Hôpital Montfort, Ottawa, ON, Canada

Mubbasheer Ahmed
Baylor College of Med./Texas Children's Hosp., Houston, TX

Arne Andreasen
Aarhus Univ. Aarhus Denmark

Sadia Ashraf
Univ. of Mississippi Med. Ctr., Jackson, MS

Tyler Basting
Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA

David Mark Burmeister
U.S. Army Inst. of Surgical Res. Fort Sam, Houston, TX

Timothy Burnett
Oregon State Univ. Cascades, Muncie, IN

April Carpenter
Ursinus College, Collegeville, PA

Melissa J. Coleman
Claremont McKenna College, Claremont, CA

Jennifer Maria Connolly
Ross Univ. Sch. of Med., Portsmoth, Dominica

Taylor Craig
Univ. of Missouri, Columbia, MO

Steven Crowley
Duke Univ. Med. Ctr., Durham, NC

Diana Cruz-Topete
LSU Hlth. Sci. Ctr.-Shreveport, Shreveport, LA

Mei-Zhen Cui
Univ. of Tennessee, Knoxville, TN

Huxing Cui
Univ. of Iowa, Iowa City, IA

Jeroen H. F. De Baaij
Radboud Univ. Med. Ctr., Nijmegen, The Netherlands

Robert K. Dearth
Univ. of Texas Rio Grande Valley, Edinburg, TX

Sonia Poonamjot Deol
Univ. of California, Riverside, CA

Rienzi A. Diaz
Univ. de Valparaiso, Vina Del Mar, Chile

R. Blair Dodson
Univ. of Colorado Denver Anschutz Med. Ctr., Aurora, CO

Mikaela Lee Drake
Butler Univ., Indianapolis, IN

Satoru Eguchi
Temple Univ., Philadelphia, PA

Mohammed Zubaerul Ferdaus
Oregon Hlth. & Sci. Univ., Portland, OR

Luzia Furukawa
Sch. of Med. of Univ. of Sao Paulo, Sao Paulo, Brazil

Ethan Goldberg
The Children's Hosp. of Philadelphia, Philadelphia, PA

Marilyn Helen Gordon
Univ. of Calgary, Calgary, AB, Canada

Eric R. Gross
Stanford Univ. Stanford CA

Lauren Haar
Loyola Univ. of Chicago, Maywood, IL

Bryan T. Hackfort
Univ. of Nebraska Med. Ctr., Omaha, NE

Corey Hart
Mayo Clinic, Rochester, MN

Mar Huertas
Texas State Univ., San Marcos, TX

Masumi Inoue
Univ. Occupational Environmental Hlth., Kitakyushu/Fukuoka, Japan

Dwayne N. Jackson
The Univ. of Western Ontario/Schulich Sch. of Med. & Dentistry, London, Canada

Ryan Jankord
Air Force Res. Lab., WPAFB, OH

Bruce R. Johnson
Cornell Univ., Ithaca, NY

Colleen Julian
Univ. of Colorado, Denver, CO

Justin Kavanagh
Griffith Univ., Gold Coast, Australia

Cetin Kocaefe
Hacettepe Univ. Faculty of Med., Ankara, Turkey

Hyun-Wook Lee
Univ. of Florida, Gainesville, FL

Christy Ludlow
James Madison Univ., Washington, VA

James Frederick Markworth
Univ. of Michigan, Ann Arbor, MI

Warren H. Meck
Duke Univ., Durham, NC

Corrinne Rose Meyer
Carrington College, Reno, NV

Gary Charles Mouradian
Med. College of Wisconsin, Milwaukee, WI

Gretchen Neigh
Virginia Commonwealth Univ., Richmond, VA

Sacha B. Nelson
Brandeis Univ., Waltham, MA

Samuel Neymotin
SUNY Downstate Med. Ctr., Brooklyn, NY

Thao P. Nguyen
UCLA David Geffen Sch. of Med., Los Angeles, CA

Shawn O'Connor
SDSU, San Diego, CA

Jeff Padberg
Univ. of Central Arkansas, Conway, AR

Se-Woong Park
Northeastern Univ., Boston, MA

Randall Keith Powers
Univ. of Washington, Seattle, WA

Nicole K. Rendos
Florida International Univ., Miami, FL

Nancy Rice
Western Kentucky Univ., Bowling Green, KY

Michael Charles Riddell
York Univ., Toronto, Canada

Brandon Roberts
Univ. of Alabama at Birmingham, Birmingham, AL

Corinna Ross
Texas A&M Univ.-San Antonio, San Antonio, TX

Ina Maria Schießl
Univ. of Regensburg, Regensburg, Germany

Julia A. Shanks
Unmc, Omaha, NE

Tetsuya Shiuchi
Tokushima Univ. Graduate Sch., Tokushima, Japan

Farida Sohrabji
Texas A&M Univ. College of Med., Bryan, TX

Nick John Spencer
Flinders Univ., Bedford Park, Australia

Kathryn Spitler
Univ. of Iowa, Iowa City, IA

Karthik Suresh
Johns Hopkins Univ., Baltimore, MD

Kristoffer Svensson
Univ. of California San Diego, La Jolla, CA

Gaurav Swarnkar
Washington Univ. in St Louis, Saint Louis, MO

Shingo Takada
Hokkaido Univ. Graduate Sch. of Med., Sapporo Hokkaido, Japan

Hisashi Takakura
Doshisha Univ., Kyotanabe-City, Japan

Dharendra Thapa
Univ. of Pittsburgh, Pittsburgh, PA

Edgar David Torres Fernandez
Univ. of Mississippi Med. Ctr., Jackson, MS

Dana K. Townsend
Wheaton College, Wheaton, IL

Wakako Tsuchida
Nihon Fukushi Univ., Handa, Aichi, Japan

Maria Velez
Texas A&M Univ.-Kingsville, Kingsville, TX

Ferdinand C. L. Von Walden
Karolinska Inst., Stockholm, Sweden

Mark Thomas Waddingham
VU Univeristy Med. Ctr., Amsterdam, The Netherlands

David L. Williamson
Penn State Harrisburg, Middletown, PA

Ayako Yamaguchi
Univ. of Utah, Salt Lake City, UT

Xiaoyuan Yang
Univ. of South Florida, Tampa, FL

Xiaohui Zhang
Lehigh Univ., Bethlehem, PA

Youhua Zhang
NYIT College of Osteopathic Med., Old Westbury, NY

New Graduate Student Members

Mohammed Anwaar Ahmed
Bhaskar Med. College, Hyderabad, India

Billie Katherine Alba
Pennsylvania State Univ., State College, PA

Andrew Alexander
Kansas State Univ., Manhattan, KS

Joselyn Natasha Allen
Pennsylvania State Univ., University Park, PA

Shenavia Balcom
Texas Woman's Univ., Carrollton, TX

Jade Marie Bearham
Infection and Immunity, London, United Kingdom

Sara Bisetto
Thomas Jefferson Univ., Philadelphia, PA

Alexandria Marie Bobe
The Univ. of Chicago, Chicago, IL

Josh Bock
Univ. of Iowa, Coralville, IA

Austin Boese
Tulane Univ., New Orleans, LA

Lauren Borkowski
Univesity of Missouri, Columbia, MO

Baylye Katelyn Boxall
College of Charleston, Charleston, SC

Alex Brodjeski
Univ. of Iowa, Coralville, IA

Eduardo Mazuco Cafarchio
Faculdade De Medicina Do ABC Santo André, São Paulo, Brazil

Jacob Troy Caldwell
Kansas State Univ., Norman, OK

JC C. Carr
The Univ. of Oklahoma, Norman, OK

Carla Carvalho
Uppsala Univ., Uppsala, Sweden

Todd Castleberry
Texas Woman's Univ., Fort Worth, TX

Chia Jung Chang
National Pingtung Univ. of Sci. and Tech., Taiwan Neipu Township, Taiwan

Priya Chatterji
Univ. of Pennsylvania, Philadelphia, PA

Nathan De Jong
Hope College, Denver, CO

Whitney Paige Deneen
NSU, Tulsa, OK

Janice M. Diaz-Otero
Michigan State Univ., East Lansing, MI

Jesse James Dicello
Monash Inst. of Pharmaceutical Sci., Melbourne, Australia

Kaylin Dix Didier
Kansas State Univ., Manhattan, KS

Savannah Jane Dunn
Dartmouth College, Lebanon, NH

Cody Durrer
Univ. of British Columbia, Okanagan Kelowna, Canada

Adrian Eddy
Univ. of Mississippi Med. Ctr., Flowood, MS

Monique Francois
Univ. of British Columbia, Kelowna, Canada

Jaime Freire
UPR Med. Sci. Campus, Carolina, PR

Adriana Maria Fresquez
Rosalind Franklin Univ., North Chicago, IL

Jordan Fuqua
Univ. of Iowa, Iowa City, IA

Vinicius Pacheco Garcia
Fluminense Federal Univ., Niterói, Brazil

Elizabeth Alejandra Garcia
Univ. of Texas at Austin, Austin, TX

Vincent P. Georgescu
Appalachian State Univ., Boone, NC

Trevor Gohl
Michigan State Univ., East Lansing, MI

Erika Ruth Ellen Guise
Univ. of Mississippi Med. Ctr., Flowood, MS

Dinesh Gyawali
Maharishi Univ. of Management, Fairfield, IA

Hesamedin HakimJavadi
Univ. of Cincinnati College of Med., Cincinnati, OH

Shane Hammer
Kansas State Univ., Manhattan, KS

Reem E. Hassan
Liberty Univ., Lynchburg, VA

Eman Helmy, Jr.
Alexandria Univ., Alexandria, Egypt

Carly Hennessey
Univ. of California-Davis, Davis, CA

Jessica Hersh
UNTHSC, Fort Worth, TX

Ryanne Hijmans
Univ. Med. Ctr. Groningen, Groningen, Netherlands

Yi Huang
Univ. of Connecticut, Mansfield Center, CT

Alyssa D. Huff
Univ. of Louisville Sch. of Med., Louisville, KY

Jordan Johnson
East Carolina Univ., Greenville, NC

Natalie Kathryn Jones
Univ. of Edinburgh, Edinburgh, United Kingdom

Kawamorita
Teikyo Univ. Sch., Tokyo, Japan

Bram Kilapong
Univ. of Indonesia, Batam, Indonesia

Marija Kuna
Univ. of Mississippi Med. Ctr., Jackson, MS

George H. Kunkel
Univ. of Louisville, Louisville, KY

Michael Bruno La Monica
Univ. of Central Florida, Orlando, FL

Sofien Laouafa
Centre de Recherche du CHU de Québec, Quebec, Canada

Harold Lee
Univ. of Memphis, Houston, TX

Wesley Lefferts
Syracuse Univ., Syracuse, NY

Monica Paige Louis
Univ. of California-Riverside, Riverside, CA

Yimin Lu
UNIL, Lausanne, Switzerland

Adam Alexander Lucero
Massey Univ., Riverside, CA

Tales Lyra De Oliveira
UNIFESP-EPM, São Paulo, Brazil

Jacqueline Morris Machi
Nova Southeastern Univ., Fort Lauderdale, FL

Hanumantha Rao Madala
Texas Tech Univ. Hlth. Sci. Ctr., Amarillo, TX

Karina Marshall-Goebel
German Aerospace Ctr., Cologne, Germany

Alexander Thomas May
Virginia Commonwealth Univ. Sch. of Med., Richmond, VA

Kelsey McLaughlin
East Carolina Univ., Greenville, NC

Manish Mishra
Univ. of Saskatchewan, Saskatoon, Canada

Nana Morita
Univ. of Fukui, Saitama, Japan

Dale Morrison
Deakin Univ., Burwood, Australia

Robert Morton
McMaster Univ., Hamilton, Canada

Robert Vincent Musci
Colorado State Univ., Fort Collins, CO

Anna Nichenko
Univ. of Georgia, Athens, GA

Grace Niemiro
Univ. of Illinois at Urbana-Champaign, Urbana, IL

Myles O'Brien
Dalhousie, Westville, Canada

Sara Oikawa
McMaster Univ., Hamilton, Canada

Marcelle Paula-Ribeiro
Federal Univ. of Sao Paulo, São Paulo, Brazil

Tiago Peçanha
De Oliveira Univ. of Sao Paulo, Sao Paulo, Brazil

Anna Pedrinolla
Univ. of Verona, Verona, Italy

Rubens Petit Homme
Univ. of Louisville, Louisville, KY

Andrej Roczkowsky
Univ. of Alberta, Edmonton, Canada

Steven Michael Romanelli
Univ. of Michigan, Ann Arbor, MI

Megan Rosa-Caldwell
Univ. of Arkansas, Fayetteville, AR

Juan Gabriel Santiago-Moreno
Univ. of Florida, Gainesville, FL

Anjali Saripalli
Univ. of Michigan, Ann Arbor, MI

Michael Wesley Schleh
Univ. of Montana, Missoula, MT

Elizabeth Cornellia Schroeder
Univ. of Illinois at Chicago, Chicago, IL

Fernando De Azevedo Cruz Seara
Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil

Corinna Serviente
Univ. of Massachusetts-Amherst, Sunderland, MA

Huanan Shi
Baylor College of Med., Houston, TX

Talita Miranda Silva
Universidade Federal de São Paulo, Santo André, Brazil

William Michael Southern
Univ. of Georgia, Athens, GA

Jordan Squair
Univ. of British Columbia, Vancouver, Canada

Shelbi Lorrae Sutterfield
Kansas State Univ., Manhattan, KS

Majid Mufaqam Syed Abdul
Univ. of Missouri, Columbia, MO

Ryo Takagi
Univ. of Tokyo, Kawasaki, Japan

Junya Takegaki
The Univ. of Tokyo, Tokyo, Japan

Jeremy Theisen
Colorado State Univ., Fort Collins, CO

Joshua C. Tremblay
Queen's Univ., Kingston, Canada

Nguyen Truong
Michigan State Univ., East Lansing, MI

Steve Vitti
Springfield College, East Granby, CT

Travis Wakeham
Michigan Technological Univ., Houghton, MI

Liana Wooten
George Mason Univ., Fairfax, VA

Jonathan Yde
Aarhus Univ., Aarhus, Denmark

Hong Yu
Univ. of Missouri, Columbia, MO

Undergraduate Student Members

Ashley Belbin
Univ. of New Hampshire, Concord, NH

Brooke Ashley Burgess
Texas Christian Univ., Helotes, TX

Nicholas Carlson
Michigan Technological Univ., Mohawk, MI

Christian Carr
Cornell College, Philadelphia, PA

Eric Cheung
Brigham Young Univ., Provo, UT

Hannah Elizabeth Clark
Univ. of Evansville, Evansville, IN

Catalina De La Pena
Univ. of Texas at El Paso, El Paso, TX

Feyisayo Omolola Edalere
Texas A&M Univ.-Kingsville, Kingsville, TX

Humberto Jay Garcia
Texas A&M Univ.-Kingsville, Benavides, TX

Amanda Joanna Gonzalez
Texas A&M-Kingsville, Kingsville, TX

Cecilia Gonzalez
Texas A&M Univ.-Kingsville, Kingsville, TX

Rebecca Harlow
Texas A&M Univ., College Station, TX

Natalia Henao
Texas A&M Univ. Kingsville, Corpus Christi, TX

Rachel Johnson
Texas A&M Univ.-Kingsville, Kingsville, TX

Audra M. Lewis
Texas A&M Univ.-Kingsville, Orange Grove, TX

Hector Lopez
Texas A&M Univ.-Kingsville, Corpus Christi, TX

Marc Matsumura
Brigham Young Univ., Provo, UT

Demi Mendoza
Texas A&M Univ.-Kingsville, Kingsville, TX

Stephanie Lydia
Njemanze Jackson State Univ., Jackson, MS

Victoria Ruth Posada
Texas A&M Univ.-Kingsville, Kingsville, TX

Judie Shang
Univ. of Calgary, Calgary, Canada

Ronald Williams
Texas A&M Univ.-Kingsville, Kingsville, TX

Affiliate Members

Miguel Angel Alejandre Alcazar
Univ. Hosp. of Cologne, Cologne, Germany

Hildebrando Candido Ferreira Neto
Augusta Univ., Augusta, GA

Young Charles Jang
Georgia Inst. of Tech., Atlanta, GA

Cecilia Edna Perez De Lara Rodriguez
Tulane Univ., New Orleans, LA

People and Places

APS Members Cone and Kibbe Elected to National Academy of Medicine

Roger Cone

Melina Rae Kibbe

In October, the National Academy of Medicine (NAM) announced its new 2016 class. APS members Roger Cone and Melina Rae Kibbe were among the 79 new members. Cone is a professor of molecular and integrative physiology and the Mary Sue Coleman Director of the Life Sciences Institute at University of Michigan. Kibbe is the Zach D. Owens Distinguished Professor and Chair of the Department of Surgery at University of North Carolina School of Medicine in Chapel Hill. Learn more on the NAM website: *nam.edu/national-academy-of-medicine-elects-79-new-members*. ●

Jean King Named Vice Provost for Biomedical Research

Jean King

APS member and past Porter Physiology Development Fellow Jean King was named Vice Provost for Biomedical Research of the University of Massachusetts Medical School. According to a university press release: "Dr. King successfully led the Office of Research to an impressive $280 million (FY16) in funding over the past two years, a figure that is worth noting particularly because it was achieved during a period of constrained federal funding." As part of her new role, King will continue on as Director of the Center for Comparative Neuroimaging and as Professor of Psychiatry, Radiology and Neurology. Read the full press release at *www.umassmed.edu/news/news-archives/2016/11/jean-king-named-vice-provost-for-biomedical-research*. ●

Mary Townsley Named Interim Senior Associate Dean

Mary Townsley

APS member Mary Townsley has been named interim senior associate dean of the College of Medicine at the University of South Alabama. Townsley, professor of physiology and cell biology, previously served as the associate dean of faculty affairs. Read the full press release at *http://ow.ly/Vifn306aAAQ*. ●

Milan K. Bagchi Named Deborah Paul Professor

Milan K. Bagchi

APS member Milan K. Bagchi has been named Deborah Paul Professor of Molecular and Cellular Biology at the University of Illinois. He received the honor in recognition of his work on the "the molecular genetic basis of steroid hormone action that controls cell proliferation, differentiation and immune response in female reproductive tissues." Bagchi is currently the head of the Department of Molecular and Integrative Physiology at Illinois. For more information, visit *http://www.las.illinois.edu/news/article/?id=19467&/news//news/2016/bagchiinvestiture16/*. ●

Meetings

2016 APS Intersociety Meeting: The Integrative Biology of Exercise VII

November 2-4, 2016, Phoenix, Arizona

The seventh APS Integrative Biology of Exercise meeting was held at the Hyatt Regency in downtown Phoenix. The Intersociety Meeting on Exercise Physiology is held every 4 years and offers concurrent symposia, plenary lectures, a career workshop, poster discussions, networking opportunities, and exhibits to the participants. This meeting was organized by P. Darrell Neufer (Chair; East Carolina University), Marcus Bamman (University of Alabama at Birmingham), Sue Bodine (University of California, Davis), Craig Emter (University of Missouri, Columbia), Roger Fielding (Tufts University), Monika Fleshner (University of Colorado, Boulder), Matthijs Hesselink (Maastricht University, The Netherlands), Jeff Horowitz (University of Michigan), William Kraus (Duke University), Mark Mattson (NIH, NIA), Deborah Muoio (Duke University), John Thyfault (Kansas University Medical Center), and Matt Watt (Monash University, Australia). The program for the 2016 meeting covered recent advancements in the exercise research area as well as emerging topics.

This exciting meeting attracted 350 total registrants, including a good presence of young investigators and students. The young investigators and students accounted for nearly half of the participants (47%). APS members made up 24% of the participants, whereas participants from the APS sister society and co-sponsor of the meeting, the American College of Sports Medicine (ACSM), made up 10% of attendees. Another 7% of participants registered as nonmembers. The invited speakers and chairs represented the remaining 12% of attendees. This meeting also had a large international presence, with participants coming to the U.S. from Australia, Belgium, Brazil, Canada, Denmark, France, Germany, Italy, Japan, Norway, Sweden, Switzerland, The Netherlands, and the United Kingdom. Out of the 350 registrants, 36% came from Japan, 16% represented Australia, 11% represented Canada, 36% came from countries within Europe, and 1% came from South America. Table 1 shows the breakdown of the different registration types.

Table 1. Registration statistics

Registrant Type	No. of Attendees (%)
APS member	85 (24%)
ACSM member	35 (10%)
Nonmember	26 (7%)
Postdoctoral	44 (13%)
Student	117 (34%)
Invited speaker	43 (12%)
Total	350 (100%)

The meeting kicked off with an Opening Reception, which gave participants the opportunity to network and catch-up with colleagues while watching the final game of the World Series between the Chicago Cubs and the Cleveland Indians, which was being shown live on a projector screen. The meeting program allowed for two concurrent symposia each morning and afternoon, with a total of nine symposia, and three plenary lectures, at which many interesting and exciting issues on exercise physiology were presented. In addition to the symposia, the APS Career Opportunities in Physiology Committee hosted a Career Development Session during the meeting on finding careers in industry.

The 2.5-day meeting also included two interactive poster sessions. During these sessions, established scientists and student attendees presented their abstract work to their colleagues and peers. There were a total of 236 programmed abstracts for the meeting and 32 invited presentations. Out of the abstracts that were submitted, 28% had a female first author; 11% of the submitted abstracts came from institutes in Japan. Countries in Europe also provided another 11% of the abstracts presented at the meeting, followed by Australia and New Zealand (7%), Canada (5%), and Brazil (1%) (see Figure 1).

Figure 1. Meeting participants present their abstracts during one of the poster sessions

Figure 2. Meeting Organizer and APS Member P. Darrell Neufer addresses the attendees during the Closing Banquet and Awards Ceremony

Figure 3. Recipients of the APS Research Recognition Award for Outstanding Abstract Presentation by a Graduate Student or Postdoctoral Fellow

The meeting closed with a Banquet and Awards Presentation, where the meeting organizer, P. Darrell Neufer, presented the winners of the Research Recognition Award for Outstanding Abstract Presentation by a Graduate Student or Postdoctoral Fellow with a certificate and a cash prize (Figure 2). The winners of the award are Laerke Bertholdt (University of Copenhagen, Denmark), Jessica Dent (University of Birmingham, UK), Bernard Duvivier (Maastricht University, The Netherlands), Megan Grace (Baker IDI Heart and Diabetes Institute, Melbourne, Australia), Amy Hector (McMaster University, Hamilton, Canada), Timothy Heden (East Carolina University), Jordan Johnson (East Carolina University), Kaleen Lavin (Ball State University), Alison Ludzki (University of Michigan), Paul Reidy (University of Utah), Gregory Ruegsegger (University of Missouri, Columbia), and Douglas Van Pelt (University of Michigan) (Figure 3).

In addition, Ashley Archer (University of Kansas Medical Center) and Maria Torres (East Carolina University) were awarded the APS Minority Travel Fellowship Award, which is provided to encourage participation of underrepresented minority individuals in the physiological sciences. The fellowship provides reimbursement of all expenses associated with travel and participation in the meeting.

The American Physiological Society and the Organizing Committee gratefully acknowledge the financial support provided through generous educational grants from NIH, NIAMSD, AdInstruments, Sable Systems International, and the Journal of Physiology. The American Physiological Society also wishes to thank our co-sponsor, the American College of Sports Medicine, for their support of this meeting.

Book Reviews

Respiratory Mechanics

Theodore A. Wilson

New York: Springer, 2016, 64 p., 29 illus., $39.99 (eBook)
ISBN 978-3-319-30508-0

Respiratory Mechanics thoroughly covers each subfield of respiratory mechanics: pulmonary mechanics, the respiratory pump, and flow. It presents the current understanding of the field and serves as a guide to the scientific literature from the golden age of respiratory mechanics, 1960-2010. Specific topics covered include the contributions of surface tension and tissue forces to lung recoil, the gravitational deformation of the lung, and the interdependence forces that act on pulmonary airways and blood vessels. The geometry and kinematics of the ribs are also covered in detail, as well as the respiratory action of the external and internal intercostal muscles, the mechanics of the diaphragm, and the quantitative compartmental models of the chest wall. Additionally, flow in the airways is covered thoroughly, including the wave speed and viscous expiratory flow-limiting mechanisms; convection, diffusion, and the stationary front; and the distribution of ventilation.

The 64-page monograph provides an in-depth review of a complex topic by one of the pioneers in the field. Wilson details concepts, ideas and mechanisms that have emerged from research mostly conducted during the latter part of the 20th Century but that remain relevant for biologists and health-care providers today. Although this is not a text for a casual reader, students and health-care providers in the fields of physiology, anesthesiology, critical care medicine, and pulmonology will appreciate that the effort to assimilate this knowledge will furbish them with essential tools for clinical problem solving. ●

Rolf D. Hubmayr
Mayo Clinic, Rochester, Minnesota

Positions Available

Assistant Professor: The Department of Biology in the College of Science and Health at the University of Wisconsin-La Crosse (UWL) invites applications for an academic year, tenure-track assistant professor position in physiology, with a specialization in mammalian cardiorespiratory physiology; expertise in respiratory physiology is strongly preferred. Our new colleague will participate in teaching the undergraduate level Human Anatomy and Physiology courses and the Advanced Human Physiology courses that serve MS students with focus in physiology or Nurse Anesthesia. Participation in the Mayo Clinic-Franciscan Healthcare Nurse Anesthesia program student oral examinations will be expected. There may be opportunities to teach other existing courses and/or to develop elective courses to complement existing curriculum. We seek an engaging teacher/scholar with a strong commitment to excellence in teaching and the potential to develop an externally funded research program involving undergraduate and graduate (MS) students. The Biology Department at UWL values diversity in its faculty, staff, and students. We are looking for a colleague who will be a dedicated teacher, active scholar, and inspirational mentor for students with varied backgrounds, preparation, and career goals. Our department's achievements in teaching and undergraduate research have been recognized through the 2013 UW System Regents Teaching Excellence Award as well as through national teaching awards to individuals. Additionally, the faculty members in our department have had strong success in obtaining extramural and internal funding to develop productive research programs that involve both undergraduate and graduate students. We work collaboratively with other departments, as well as local and regional agencies, including the Mayo Clinic and Gundersen Health Systems. Our highly productive and collegial faculty and staff create a stellar environment for professional and personal achievement. A doctoral degree in a life or biomedical science is required by the start date. Prior teaching experience is required. Academic year salary is competitive and commensurate with experience. Start date is August 28, 2017. A complete application will include *1)* a cover letter addressing your particular qualifications and interest in our position, *2)* curriculum vitae, *3)* a statement describing how your teaching experiences have enhanced student learning, *4)* a statement describing your research interests and how your research is amenable to undergraduate and MS students, *5)* unofficial undergraduate and graduate transcripts, and *6)* the names and contact information of three references (at least one reference should be able to comment on the candidate's teaching qualification). Electronic applications must be received by December 16, 2016 to ensure full consideration, although applications will be reviewed until the job is filled. *Note: Electronic submission of application materials is required.* For additional information about this position and to apply, please visit *https://employment.uwlax.edu/*. If you have a special need/accommodation to aid your participation in our hiring process, please contact the chair of the search committee, Dr. Sumei Liu (*sliu@uwlax.edu*), to make appropriate arrangements. The University of Wisconsin-La Crosse (UW-La Crosse) provides a challenging, dynamic, and diverse learning environment in which the entire university community is fully engaged in supporting student success. Grounded in the liberal arts, UW-La Crosse fosters curiosity and life-long learning through collaboration, innovation, and the discovery and dissemination of new knowledge. Acknowledging and respecting the contributions of all, UW-La Crosse is a regional academic and cultural center that prepares students to take their place in a constantly changing world community. UW-La Crosse's diversity and inclusion efforts are guided by our adherence to Inclusive Excellence. We define Inclusive Excellence as "our active, intentional and ongoing commitment to bridge differences with understanding and respect so all can thrive." The goals of Inclusive Excellence are to increase the retention of diverse faculty, staff and students while encouraging a campus climate that is inviting and welcoming to all. UW-La Crosse strives to promote acceptance of all facets of diversity from racial/ethnic diversity to diversity of thought and experience. UW-La Crosse is a 2014 recipient of the Higher Education Excellence in Diversity (HEED) award from INSIGHT Into Diversity magazine. UW-La Crosse is proud to be one of only 83 recipients of this national honor recognizing our commitment to diversity and inclusion. UW-La Crosse has appeared prominently on the *U.S. News & World Report* list of "America's Best Colleges" for more than a decade and is ranked consistently as one of the top institutions in the Midwest. With a student population of roughly

10,500, the university offers 91 undergraduate programs in at least 30 disciplines and 26 graduate programs in three colleges: Liberal Studies, Science and Health, and Business Administration, including the School of Arts & Communication and the School of Education. There are 502 full-time faculty and instructional academic staff, 76 percent of whom hold terminal degrees. UW-La Crosse boasts a retention rate (freshmen returning as sophomores) of 86%, graduation rate (degree within 6 years) of 70%, and is among only 12 institutions cited nationally by the American Association of State Colleges and Universities for its success in linking campus culture and university leadership to outstanding graduation rates. The UW-La Crosse campus is nestled in a residential area of the City of La Crosse (pop. 52,000), located in western Wisconsin. The area, known as the 7 Rivers Region, is famous for its exceptional natural beauty, which includes the Mississippi River on one side, majestic bluffs on the other, and views of rolling farmland and forested valleys in between. Ranked by *U.S. News & World Report* as one of the top 10 "Best Places to Live" in 2009, La Crosse is one of the most scenic places in mid-America. Abundant water, woodlands, and varying terrain provide ample opportunities for year-round outdoor recreation. Only a couple of hours from Minneapolis or Madison, La Crosse enjoys the affordability and charm of small town living with larger city benefits. Three colleges, two world-class medical institutions, the La Crosse Symphony Orchestra, a restored 19th century downtown business district, and a number of galleries and art centers have made La Crosse a regional center for culture, entertainment, medical care, shopping, sports and recreation. UW-La Crosse is proud to be an equal-opportunity employer. We strive to recruit, develop, and retain the most talented people from a diverse candidate pool, and we encourage applications from persons with varied backgrounds and perspectives. In support of the Wisconsin Veteran Employment Initiative, we encourage veterans and veterans with disabilities to explore employment opportunities at UW-La Crosse. As a prospective UW-La Crosse employee, you have a right to obtain a copy of campus safety and security information (Clery Act) for this institution. You may review this information at *http://www.uwlax.edu/Police/Annual-Security-Report/*. Employment will require a criminal background check. A pending criminal charge or conviction will not necessarily disqualify an applicant. In compliance with the Wisconsin Fair Employment Act, UW-La Crosse does not discriminate on the basis of arrest or conviction record.

Assistant Professor: Outstanding scientists are invited to apply for a tenure-track faculty position in the Department of Human Physiology at the University of Oregon. We are seeking individuals who have research interests that complement existing areas of excellence in biomedical and rehabilitation research. To be considered for a tenure-track position at the Assistant Professor level, applicants must hold a PhD and/or MD degree with appropriate (2-3 years) postdoctoral research experience. Successful candidates will have a strong background in neurophysiology, as evidenced by a strong publication record, and must either currently have or demonstrate potential to obtain significant extramural research funding such as NIH, NSF, or DoD. Previous university-level teaching experience is highly desirable. Special consideration will be given to candidates who are broadly trained and have experience with the neural principles underlying movement, neurorehabilitation, or other aspects of neuromuscular physiology. Applicants with a research program that aims to investigate central and/or peripheral nervous system disorders are strongly encouraged to apply. The successful candidate is expected to establish a vigorous research program supported by extramural funding, engage in collaborative research endeavors with existing faculty members, contribute to the mission of the department in undergraduate and graduate education, and engage in departmental and university service. The successful candidate will also have the ability to work effectively with faculty, staff, and students with diverse backgrounds. Competitive salary support and start-up funds will be provided. Applicants should prepare a curriculum vitae, a statement describing their research goals, a statement of their teaching philosophy, three representative publications, and three letters of reference, to apply online for our position at *https://academicjobsonline.org/ajo/jobs/7617*. Questions about the application process should be addressed to Dr. Michael Hahn (*mhahn@uoregon.edu*). To ensure consideration, please submit application materials by November 22, 2016. The position will remain open until filled.

Assistant Professor: Skidmore College invites applications for a full-time, 2-year faculty replacement position in health and exercise sciences for the academic years 2017-2018 and 2018-2019. We are particularly interested in candidates from underrepresented backgrounds who can contribute to the diversity and excellence of our academic community and have experience teaching and mentoring a diverse student body. *Qualifications:* a PhD is preferred (ABD considered); prior teaching experience is desired. The successful candidate will be able to teach several courses from among the following: human nutrition, exercise testing and prescription, introduction to exercise science, exercise physiology, and introduction to public health. Collaborative research opportunities will be available and encouraged. Additional responsibilities may include advising senior thesis projects. The successful candidate will join an energetic and collegial department that is passionate about teaching and deeply engaged with research. For full consideration, please submit online your faculty profile, curriculum vitae, a brief description of teaching experience, and graduate transcripts. Additionally, the application system will prompt you to submit three e-mail addresses for letters of recommendation addressed to Dr. T. H. Reynolds, Chair, Health and Exercise Sciences. All referees will be e-mailed once you've completed the application process. Skidmore is a liberal arts institution of approximately 2,450 students, with 22% students of color and 259 full-time faculty members, located in upstate New York. Enthusiasm for teaching a diverse population of students is essential. Review of applications begins March 2017 and will continue until the position is filled. To learn more about and apply for this position please visit us online at: *https://careers.skidmore.edu/applicants/Central?quickFind=57618*. Skidmore College is committed to being an inclusive campus community and, as an equal-opportunity employer, does not discriminate in its hiring or employment practices on the basis of race, color, creed, religion, gender, age, national or ethnic origin, physical or mental disability, military or veteran status, marital status, sex, sexual orientation, gender identity or expression, genetic information, predisposition or carrier status, domestic violence victim status, familial status, dating violence, or stalking, or any other category protected by applicable federal, state or local laws. Employment at Skidmore College is contingent upon an acceptable background check result. Creative thought matters.

Assistant Professor: The Department of Pharmacology at the University of Illinois at Chicago (UIC) is seeking applications for outstanding candidates for non-tenure-track research positions at the Assistant Professor rank in the field of Pharmacology. The department is one of the nation's leading Pharmacology departments, with extensive NIH funding in the areas of cell biology, vascular biology, regenerative biology, and immunology. Candidate will develop an independent research program with a focus on intravital microscopy as well as initiate collaborative research with Principal Investigators engaged in the above-mentioned areas of research. The candidate will also be required to design experiments, develop and implement cutting-edge imaging technologies, analyze research data, write scientific manuscripts, and present results of research at national and international scientific conferences. Selected faculty member is expected to write and submit grant proposals to obtain independent funding for research as well as instruct and train postdoctoral fellows, research technicians, and students. A PhD degree with 2 years postdoctoral experience in imaging of live small animals, e.g., mice, and image analysis using two-photon microscope is required. Experience in using two-photon microscopy in lungs is a plus. Highly attractive salary will be offered, commensurate with experience. For fullest consideration, candidates should send CV and references to *Ldevaney@uic.edu*. University of Illinois at Chicago is an affirmative-action/equal-opportunity employer. Minorities, women, veterans, and individuals with disabilities are encouraged to apply. The University of Illinois conducts background checks on all job candidates upon acceptance of contingent offer of employment. Background checks will be performed in compliance with the Fair Credit Reporting Act.

Assistant/Associate Professor: The Department of Physiology and Pharmacology at the University of Toledo College of Medicine and Life Sciences (UTCOMLS) is expanding its current research portfolio, with microbiome-related research being one of the priority areas for development. Along this line, the Department is invested in developing infrastructure in microbiome research and is leading

the University of Toledo-Microbiome Consortium (UT-MiCo), a research and academic multi-disciplinary collaborative effort of investigators within various Colleges (*http://www.utoledo.edu/med/depts/physpharm/hypertension_center/mico/*). UT-MiCo's mission aligns with the National Microbiome Initiative (NMI) and fosters and coordinates research and training efforts in a variety of aspects of the microbiome as it relates to cardiovascular and metabolic diseases and related morbidities, and includes basic and clinical scientists and a translational agenda. Applications are hereby solicited from candidates at the levels of Assistant to Full Professor. Candidates should have a PhD and/or MD degree, preferably with a past and current record of extramural research funding from the NIH or NSF and background in microbiome research. The Department has a superb environment for physiology and genomic sciences. Faculty have access to a variety of shared core facilities, including those for imaging and "omic" studies. Successful candidates will receive competitive salaries, start-up packages, and renovated laboratory space. In addition to highly competitive research incentive policies and retirement options, The University of Toledo offers tuition subsidies for graduate students and competitive per diem rates for housing and conducting experimental model organism research. Additional information about the Department can be found at *https://www.utoledo.edu/med/depts/physpharm/*. Applicants should submit curriculum vitae, names of at least three referees, and a statement of research interest as it applies to microbiome-related research to *https://jobs.utoledo.edu*. The University of Toledo is an equal-access, equal-opportunity, affirmative-action employer and educator.

Assistant/Associate/Full Professor: Michigan Technological University is seeking leaders for two endowed professorships – one in Preventive and Community Health, one in Medical Informatics. These endowed positions are being funded through the generous support of the Portage Health Foundation (PHFoundation). PHFoundation supports the regional health needs of the community through enhanced philanthropy and community collaboration. Candidates are expected to contribute to teaching, research, and scholarship within an academic unit aligned with human health education and research. Salary and start-up packages will be competitive and commensurate with credentials and experience. The "endowment" funds associated with this position are available for up to 4 years (potentially renewable beyond initial appointment), and provide an additional $40,000 per year toward activities that foster research, graduate education, and/or community health engagement. We seek two types of candidates for the positions. For *candidates with a PhD (1.0 full-time equivalent):* A successful candidate will have a record of federal, foundation, or industry funding oriented toward the selected position (i.e., preventative and community health or medical informatics). Preference will be given to investigators with active research awards and programs that can be successfully implemented in support of related research at Michigan Tech. For *candidates with an MD or DO (~0.5 full-time equivalent):* In partnership with two local healthcare providers, we seek MD or DO candidates who could be jointly hired by Michigan Tech and either UP Health System Portage (UPHS-Portage) or Upper Great Lakes Family Health Center (UGL). A successful candidate will be expected to work collaboratively and independently to secure federal, foundation, and/or industry funding oriented toward the selected position (i.e., preventative and community health or medical informatics). The following areas of expertise are sought since they align with local healthcare needs as identified by UPHS-Portage and UGL and existing or emerging research strengths of Michigan Tech: cardiology, emergency medicine, pediatrics, primary care, obstetrics and gynecology, sleep medicine. To view the full job description (including qualifications, essential duties, and requested materials) and apply, visit *https://www.jobs.mtu.edu/postings/4740* for the Preventive and Community Health position, or *https://www.jobs.mtu.edu/postings/4746* for the Medical Informatics position. Review of applications will begin November 1, 2016 and will continue until the positions are filled. Michigan Tech is an EOE, which includes protected veterans and individuals with disabilities. Michigan Tech is an ADVANCE Institution, one of a limited number of universities in receipt of NSF funds in support of our commitment to increase diversity and the participation and advancement of women in STEM. Michigan Tech acknowledges the importance of supporting dual-career partners in attracting and retaining a quality workforce.

Assistant/Associate/Full Professor: The Department of Physiology and Biophysics at Case Western Reserve University School of Medicine seeks a faculty member at the rank of Assistant, Associate, or Full Professor engaged in kidney research. Applicants must have a PhD, MD, or equivalent degree, and demonstrated academic excellence appropriate for career stage. Individuals seeking appointment at the Assistant Professor level must have at least 3 years of postdoctoral experience, a strong record of scholarly activity, and evidence of academic potential. Candidates for Associate Professor should have a considerable publication record, evidence of an international reputation, and a demonstrated ability to renew funding. For appointment at the Professor level, substantial evidence of leadership in the applicant's academic field, outstanding productivity, and a sustained funding history are required. Rank will be commensurate with experience. The successful applicant will be expected to develop and/or continue a robust, extramurally funded research program that compliments current programs within the Department. All areas will be considered; however, areas of particular interest are *1)* mechanisms of ion/water transport; *2)* regulation of transport; and *3)* renal control of blood pressure. The Department of Physiology and Biophysics includes 18 primary and 32 secondary faculty members. The Department has a strong record of renal research. Interested candidates should send an electronic application that includes a cover letter, complete curriculum vitae including funding history, a 1-page summary of research interests, and the names and contact information for 3 references to *RenaiSearch@case.edu*. Review of applications will begin November 1, 2016. "In employment, as in education, Case Western Reserve University is committed to Equal Opportunity and Diversity. Women, veterans, members of underrepresented minority groups, and individuals with disabilities are encouraged to apply." "Case Western Reserve University provides reasonable accommodations to applicants with disabilities. Applicants requiring a reasonable accommodation for any part of the application and hiring process should contact the Office of Inclusion, Diversity and Equal Opportunity at 216-368-8877 to request a reasonable accommodation. Determinations as to granting reasonable accommodations for any applicant will be made on a case-by-case basis."

Assistant/Associate/Full Professor: Franklin College invites applications for a tenure-track position in Biology to begin in August 2017. Located approximately 30 minutes from culturally rich downtown Indianapolis, Franklin College is a private, 4-year liberal arts and sciences college. Candidates who can demonstrate a dedication to teaching and a genuine interest in working with undergraduates in a small, collegial liberal arts setting that emphasizes close student-faculty interaction will be given preference. The successful candidate will possess a doctoral degree in some area of animal physiology and will be capable of teaching Human Anatomy and Physiology I & II, an advanced course in animal physiology, and an upper-level elective course that augments the disciplines taught by current faculty, depending on the needs of the department and the candidate's interest (possible electives include immunology or neurobiology). Candidates with broad training in biology and a demonstrated interest in teaching introductory majors and non-majors courses will be given preference. The successful candidate must be willing to develop an undergraduate research program that is complementary to a small liberal arts college environment. Broad service to and stewardship of the college, such as academic advising, new student recruitment, and committee work, are also required. PhD preferred and required for tenure consideration; ABD will be considered. Review of applications will begin November 15, 2016 and will continue until the position is filled. Applicants should send a single pdf file that contains only the following, in this order: *1)* letter of application; *2)* vita; *3)* statement of teaching philosophy; and *4)* undergraduate and graduate transcripts (unofficial copies accepted). Materials should be sent to (e-mail is preferred): Franklin College, Office of Human Resources, 101 Branigin Blvd, Franklin, IN 46131 (*humanresources@franklincollege.edu*). Three letters of reference, including at least one that can speak to the candidate's teaching effectiveness, should be sent separately to the same e-mail address. Applicants should have a teaching portfolio (sample syllabi and assignments plus teaching evaluations), and description of a potential undergraduate research project ready to provide immediately upon request. The College is committed to providing an inclusive and welcoming environment and to ensuring that educational and employment decisions are based on

individuals' abilities and qualifications. Consistent with these principles and applicable laws, it is therefore the College's policy not to discriminate on the basis of age, color, disability, gender, gender expression, gender identity, genetic information, national origin, marital status, race, religion, sex, sexual orientation, or veteran status as consistent with the Policy on Prohibited Discrimination. *Harassment and Related Misconduct.* No person, on the basis of protected status, shall be excluded from participation in, be denied the benefits of, or be subjected to unlawful discrimination, harassment, or retaliation under any College program or activity, including with respect to employment terms and conditions. Such a policy ensures that only relevant factors are considered and that equitable and consistent standards of conduct and performance are applied.

Assistant/Associate/Full Professor: American University of the Caribbean School of Medicine (AUC) is actively seeking experienced full-time Physiology Faculty to join a dynamic teaching group in the Department of Neuroscience and Physiology. The Physiology faculty members team-teach the Physiology I course, which is taught to first-year medical students three times a year. The successful candidate will have had significant experience teaching medical students cardiovascular physiology in a comprehensive, medical curriculum in accredited U.S., Canadian, or British medical education institutions, with demonstrated competence in course administration. American University of the Caribbean School of Medicine is where teaching and mentoring aspiring physicians on their journey to successful careers is the main focus of the faculty. Our dedicated faculty are part of a caring, collaborative educational community working toward one common goal: student success. *Responsibilities:* preparation and delivery of course materials such as course syllabus, lecture notes, and powerpoints; prepare and evaluate examinations to assess student academic competence; advise students in academic matters and exercise professional judgement in referring students to appropriate personnel; actively participate in relevant professional activities to improve teaching and subject matter competence; serve on institutional committees as appointed or elected. *Qualifications:* MD and/or PhD from an accredited U.S., United Kingdom, or Canadian medical school; academic teaching experience at the Assistant Professor rank or higher; experience teaching medical cardiovascular physiology to American, English, or Canadian medical students; skilled in cardiovascular physiology lecture delivery and designing learning assessments; ability to evaluate students' understanding of subject matter. American University of the Caribbean, founded in 1978 and located on the island of St. Maarten, is one of the highest ranked Caribbean medical schools and has placed nearly 6,000 physicians into U.S. residency programs. Our mission is to provide an excellent medical education to qualified students of diverse backgrounds. This is accomplished within an atmosphere of academic integrity and scholarship, which fosters the highest standards in professional ethics and competence. The majority of our students are from the U.S. and Canada. Students complete their first 2 years of medical sciences on our campus in St. Maarten before completing clinical rotations at our affiliated hospitals in the U.S. and United Kingdom. For a complete job description, go to *https://aucmed-devry.icims.com/jobs*. Discover AUC at *http://www.aucmed.edu*. A competitive salary, relocation assistance, and a comprehensive benefits package await the right candidate. Please send your CV with a cover letter explaining your interest in teaching cardiovascular physiology full time at AUC along with a list of cardiovascular physiology lectures you have taught and the number of years teaching those lectures to medical students. Interested candidates can apply online at *https://aucmed-devry.icims.com/jobs/search?ss=1&hashed=124496084* or contact Barbara Roberge, Senior Talent Acquisition Consultant, *BRoberge@devrygroup.com*.

Assistant/Associate/Full Professor: The School of Kinesiology at the University of Michigan, one of the highest ranked public universities in the nation and one of the world's preeminent research institutions, invites applications and nominations for a faculty position at the level of Assistant Professor, Associate Professor, or Professor. Candidates will be expected to maintain a robust, ongoing research program, teach undergraduate and graduate courses, and have research expertise appropriate for the effective mentoring of trainees at the undergraduate, doctoral, and postdoctoral levels in the area of exercise physiology. Successful candidates will be expected to maintain extramural funding for an active

research program at the University of Michigan. The School of Kinesiology (*www.kines.umich.edu*) is 1 of 19 independent academic units and 1 of 7 health science schools and colleges within the University of Michigan. The school is led by a dean, and has 28 tenure-line faculty and approximately 1,000 students. The school is home to one of the country's leading programs focusing on the interdisciplinary study of exercise and movement in humans and animal models. The University of Michigan is home to 260 degree programs, and Kinesiology is one of 103 graduate programs rated in the top 10 and provides unparalleled opportunity for collaboration. Collaborative opportunities exist both within the School of Kinesiology and with other units across campus. In addition to the many exciting achievements within the School of Kinesiology, the school has a strong record of successfully partnering with other academic units in the university – consistent with the culture of the University of Michigan that places significant value on innovation across disciplines. Faculty members are encouraged to collaborate with experts across campus to work on important, interdisciplinary, and ground-breaking projects. *Required qaualifications:* We have particular interest in candidates whose research program focuses on elucidating fundamental biological mechanisms and/or integrative physiological factors that underlie the health benefits of exercise. The successful candidate will have an outstanding record of performing cutting-edge research and producing high-quality/high-impact scientific publications. The successful candidate will have demonstrated the potential to secure extramural research funding, to mentor graduate students, and to teach in the area of exercise physiology. At the rank of Associate Professor or Professor, the successful candidate will also have demonstrated a consistent and ongoing record of securing extramural research funding and will have experience and skill in providing leadership that will advance the scholarly excellence of the Movement Science Program (*http://www.kines.umich.edu/academics*) and the School of Kinesiology. Candidates must possess an earned doctorate in exercise physiology or a related area of biological science. *How to apply:* Interested candidates must supply curriculum vitae, a letter of interest, and up to three examples of research publications (please provide each of these documents in PDF format). Please also include the names of three references (the reference letters need not be sent at this time). Please send this information to *kines-exercise-physiology-search@umich.edu*. Applicants will be considered on a rolling basis until the position is filled. For best consideration, candidates should apply by Monday, January 16, 2017. Applications will be reviewed upon receipt. For questions about the position, please contact Search Committee Chair Greg Cartee (*gcartee@umich.edu*). The School of Kinesiology seeks to recruit and retain a diverse workforce as a reflection of our commitment to maintain the excellence of the university and to offer our students richly varied disciplines, perspectives, and ways of knowing and learning. The University of Michigan is supportive of the needs of dual-career couples and is an equal-opportunity/affirmative-action employer.

Assistant/Associate/Full Professor: The Department of Biomedical Sciences at the West Virginia School of Osteopathic Medicine is seeking a full-time, tenure-track faculty position with emphasis in medical physiology. The successful applicant must have a PhD in Physiology or related field and should be able to teach multiple physiological systems with special interest in respiratory physiology. A commitment to excellence in teaching is required since this is the primary responsibility of this position. Completion of a postdoctoral fellowship is expected. An equivalent combination of relevant and recent experience, education, and/or training that provides the required knowledge, skills, and abilities may be considered. The successful candidate will also be expected to conduct research or scholarly activity. Research facilities and start-up funds are available. WVSOM utilizes a Patient Presentation-Based Curriculum in which disciplines are integrated. A variety of formats and modalities are utilized including lecture, lab, small group, and team-based learning. This position will be filled at the rank of assistant, associate, or full professor, commensurate with experience and accomplishments in both teaching and research. Salary and faculty rank will be commensurate with experience, and include an excellent benefits package including moving expenses. Research laboratory space and start-up funds can be provided to interested applicants. Teaching facilities at WVSOM include a cutting-edge lecture facility, multipurpose laboratory, and digital microscopy. Teaching duties will include delivery of lectures to medical students

as well as participation in and design of active learning sessions. The successful candidate will also be expected to conduct independent professional development activities. WVSOM has a rich diversity of faculty research interests and excellent facilities that accommodate laboratory animal research. WVSOM has been consistently recognized as "A Great College to Work For" by the Chronicle of Higher Education. WVSOM is a free-standing medical school nestled in the Allegheny Mountains. Located in "America's Coolest Small Town" (*Budget Magazine*, 2011), WVSOM is just minutes from the famed Greenbrier Resort, a Five-Diamond hotel and spa and host of the PGA's annual Greenbrier Classic. WVSOM brings over 40 years of history serving the health and wellness needs of the Greenbrier Valley, the state of West Virginia, and beyond. The school's small-town, rural community cherishes its connection with the college, and our students are actively engaged in service outreach and support for over 40 nonprofit organizations in this area. Additionally, WVSOM faculty and staff enjoy a vibrant cultural community, which features one of only four operating Carnegie Halls in the world, as well as the state professional theater of West Virginia. Throughout the year, employees enjoy live plays and musicals, a broad representation of visual artists, an annual chocolate festival, a flourishing literary series, and live music events within a historic preservation area featuring 19th century architecture, unique shops and dining, and limitless outdoor recreation. This one-of-a-kind environment brings together farmers and artists, lumbermen and world- renowned musicians, holistic physicians and thrill-seeking whitewater rafters in a diverse melting pot that is truly unique! *Application:* Interested applicants should apply online by visiting *http://www.wvsom.edu/employment*. The search committee will begin its review of applications upon receipt, and the search will remain open until the position is filled. Applications are considered confidential, and references will not be contacted without notification to the applicant. The West Virginia School of Osteopathic Medicine is an equal-opportunity employer and is committed to enhancing diversity among its faculty and staff.

Postdoctoral Fellowship: A postdoctoral position is immediately available in the Department of Pharmacology at University of Iowa. A highly motivated postdoctoral scholar will work on NIH-funded research projects to study the central regulation of energy homeostasis and cardiovascular function. To accomplish this, a combination of cutting-edge tools will be employed, including in vivo Cre-loxP technology, optogenetics and chemogenetics, functional neuroanatomy, neurophysiology, biochemistry, and molecular biology. Energetic and self-motivated individuals with strong background in system neuroscience and/or cardiovascular research are encouraged to apply. Applicants should have a PhD, a track record of productivity, and good writing and communication skills. Prior working experience with animal models is highly desirable. Preference will be given to those who have expertise in neuroanatomy, small animal surgery, metabolism, and cardiovascular research. *To apply:* Interested candidates should submit their current curriculum vitae, letter of interest, and contact information for 3 references to Dr. Huxing Cui by e-mail at *huxing-cui@uiowa.edu*. The University of Iowa is an equal-opportunity/affirmative-action employer. All qualified applicants are encouraged to apply and will receive consideration for employment free from discrimination on the basis of race, creed, color, national origin, age, sex, pregnancy, sexual orientation, gender identity, genetic information, religion, associational preference, status as a qualified individual with a disability, or status as a protected veteran.

Postdoctoral Fellowship: The Department of Pharmacology at the University of Virginia seeks a motivated postdoctoral Research Associate to conduct research in the laboratory of Drs. Patrice Guyenet and Ruth Stornetta. The project focuses on the role of the brain stem in respiratory, cardiovascular, and other (e.g., immune) autonomic responses to stress. An overview of our research interests can be found on the departmental website (*https://pharm.virginia.edu/faculty/by-research-area/cardio/?id=25681*) and publications from the lab (*http://www.ncbi.nlm.nih.gov/pubmed/?term=guyenet±P*). Candidates must have an MD or PhD in biological sciences by appointment start date. Candidates must have 4 years of experience of laboratory research (may include graduate studies) and expertise in two or more of the following areas: optogenetics, sleep or stress research, molecular and cellular biology, or patch-clamp electrophysiology. Experience in integrative

neuroscience and/or whole animal physiology is highly desirable. Candidates should be able to design, conduct, and troubleshoot experiments, as well as be proficient in English and have good communication skills. The incumbent should be comfortable with all the basic aspects of using computer hardware, software, and peripheral instruments. To apply, visit *https://jobs.virginia.edu* and search on posting no. 0619175. Complete a Candidate Profile online; attach a CV, cover letter, contact information for three references, and a statement of Research Interest. This position will remain open until filled. The University of Virginia is an equal-opportunity and affirmative-action employer. Women, minorities, veterans, and persons with disabilities are encouraged to apply.

Postdoctoral Fellowship: A 2-year A. O. Smith Postdoctoral Fellowship (with the possibility of a 3rd year of support) is available in the Medical College of Wisconsin Cardiovascular Center, Milwaukee, Wisconsin, in five major areas of research: Atherosclerosis & Thrombosis, Cardiac Biology & Heart Failure, Hypertension, Precision Cardiovascular Medicine, and Vascular Biology. The A. O. Smith postdoctoral fellow will receive personalized training within multidisciplinary mentoring teams led by exceptional faculty mentors (*http://tinyurl.com/CVCpostdoc-Mentors*). Fellows will create and follow an individualized development plan, conduct research studies, attend required courses/seminars, write grants, publish manuscripts, present oral presentations locally and nationally, and learn other skills necessary for a successful career in cardiovascular research or a closely related field. Clinical scholars will have protected time for research. We are especially eager to recruit women, persons with disabilities, and underrepresented minorities. Per NIH guidelines, the postdoctoral fellow must be a U.S. citizen or permanent resident. Applicants should be highly motivated, ambitious, productive, and have (or anticipate having) a PhD, PharmD, MD, or DO in a relevant research area such as biology, molecular biology, genetics, immunology, biochemistry, pharmacology, or physiology with a strong track record of, and a keen interest in, at least one of the five research areas. The stipend/salary is $50,000 and up, depending on prior experience. *Instructions:* To apply, go online to MCW Human Resources at *www.mcw.edu/Human-Resources.htm*, Job Requisition ID 20965, and submit your *1)* current curriculum vitae, *2)* statement of research interests, including preference for one of the five major research areas, *3)* contact information for at least three references, and *4)* mention of where you learned about the fellowship. For more information, visit our Facebook page (*http://tinyurl.com/CVCpostdoc*). For questions specific to the fellowship, contact Allison DeVan, PhD, at *adevan@mcw.edu*. *About the center:* The Cardiovascular Center is directed by Ivor Benjamin, MD. Last year, members of the Cardiovascular Center published more than 340 scientific articles in peer-reviewed journals, were awarded more than $43.5 million in total funding, with $21.3 million being funded by the National Heart, Lung and Blood Institute, and mentored more than 50 trainees. The mission of the Cardiovascular Center is to improve cardiovascular health in Southeast Wisconsin and beyond through cutting-edge research, cost-efficient and high-quality healthcare delivery, rigorous training of the next generation of cardiovascular scientists, and engaging the community to eliminate disparities in health outcomes. *About the institution:* The Medical College of Wisconsin is one of the largest healthcare employers in Wisconsin. It has a long-standing reputation of providing outstanding medical and graduate education, conducting cutting-edge biomedical research, providing innovative and compassionate patient care, and improving the health of the communities it serves. MCW is an equal-opportunity employer and does not discriminate against any employee or applicant for employment because of race, color, sex, age, national origin, religion, sexual orientation, gender identity, status as a veteran, and basis of disability or any other federal, state, or local protected class. ●

Meetings & Congresses

2017

February 11-15

Biophysical Society 61st Annual Meeting, New Orleans, LA. *Information:* Internet: *http://www.biophysics.org/2017meeting/Home/tabid/6672/Default.aspx*

April 1-4

28th International Symposium on Cerebral Blood Flow, Metabolism and Function and the 13th International Conference on Quantification of Brain Function with PET, Berlin, Germany. *Information:* Internet: *http://www.brain2017.net*

April 22-26

2017 Experimental Biology, Chicago, IL. *Information:* Internet: *http://apsebmeeting.org/*

May 13-14

50 Years of Comparative Biochemistry: The Legacy of Peter Hochachka, Winnipeg, Canada. *Information:* Internet: *https://www.csz-scz.ca/storage/app/media/PWH%20Symposium%20Webpage%20second%20announcement.pdf*

May 27-June 1

International Neuromodulation Society 13th World Congress, Edinburgh, Scotland. *Information:* internet: *http://www.neuromodulation.com/ins-congress*

June 27-29

Measuring Animal Welfare and Applying Scientific Advances – Why is it still so difficult? Surrey, United Kingdom. *Information:* Internet: *http://www.ufaw.org.uk/symposium2017*

August 1-5

IUPS 38th World Congress: Rhythms of Life, Rio de Janeiro, Brazil. *Information:* Internet: *http://iups2017.com/*

August 11-14

APS Conference: Cardiovascular Aging, New Frontiers and Old Friends, Westminster, CO. *Information:* Internet: *http://www.the-aps.org/mm/Conferences/APS-Conferences/2017-Conferences/CV-Aging*

August 30-September 2, 2017

APS Conference: Physiological Bioenergetics: Mitochondria from Bench to Bedside, San Diego, CA. *Information:* Internet: *http://www.the-aps.org/mm/Conferences/APS-Conferences/2017-Conferences/Bioenergetics; #Bioenergetics17*

Meetings and Conferences

Experimental Biology 2017
April 22-26, 2017 • Chicago, Illinois

APS Conference: Cardiovascular Aging, New Frontiers and Old Friends
August 11–14, 2017 • Westminster, Colorado

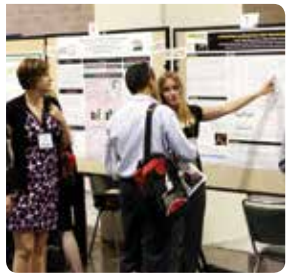
APS Conference: Physiological Bioenergetics: Mitochondria from Bench to Bedside
August 27–30, 2017 • San Diego, California

APS Conference: Physiological and Pathophysiological Consequences of Sickle Cell Disease
November 6–8, 2017 • Washington, DC

APS is also participating in the following meeting

IUPS 38th World Congress: Rhythms of Life
August 1–5, 2017 • Rio de Janeiro, Brazil





For more information on APS meetings, please visit:
the-aps.org/conferences

APS Members receive discounted registration to EB and APS Conferences!
The American Physiological Society usually holds one or more specialty conferences each year. In addition, APS joins with other societies to sponsor Intersociety Meetings as interest warrants. Please send an email to meetings@the-aps.org for questions or to propose APS Conference ideas.

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Intersociety Meeting:
The Integrative Biology of Exercise VII

November 2–4, 2016 • Phoenix, Arizona

Conference Program & Abstracts

Guest Society

the-aps.org/exercise

#IBExercise7

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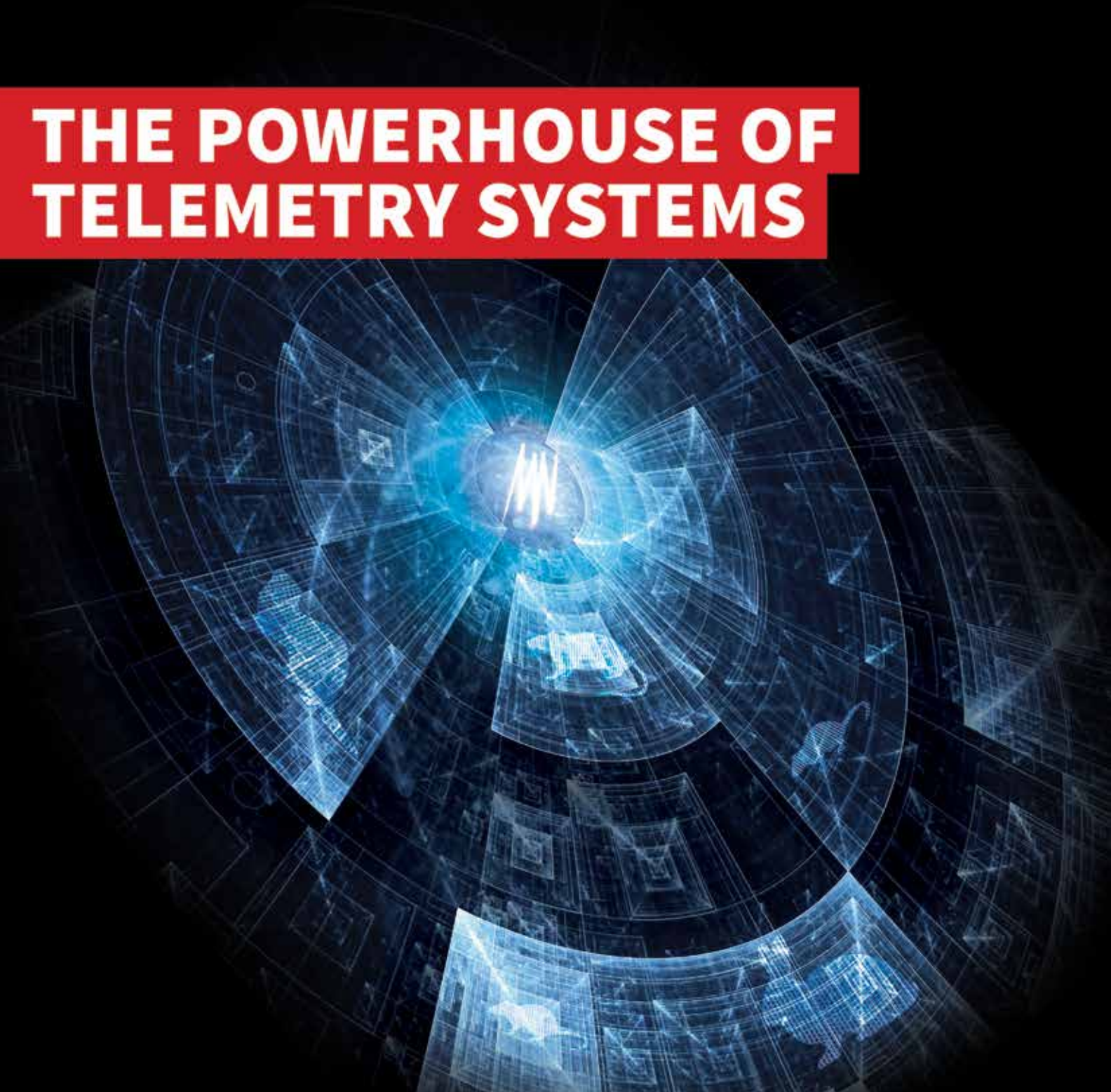

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2016 APS Intersociety Meeting
The Integrative Biology of Exercise VII

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Deborah Muoio *Duke Univ.*	**John Thyfault** *Kansas Univ. Med. Ctr.*	**Matt Watt** *Monash Univ., Australia*

Acknowledgements

The Conference Organizers and The American Physiological Society gratefully recognize the generous financial support from the following:

ADInstruments
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NIH, National Institute of Arthritis and Musculoskeletal and Skin Diseases*

*Funding for this meeting was made possible (in part) by R13AR070619 from the National Institutes of Health. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the National Institutes of Health and the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

2016 APS Intersociety Meeting: The Integrative Biology of Exercise VII
Week-at-a-Glance Schedule

Wednesday, November 2, 2016	Thursday, November 3, 2016	Friday, November 4, 2016	Saturday, November 5, 2016
2:00-8:00 PM: **Registration**	7:00 AM-6:30 PM: **Registration**	8:00 AM-5:30 PM: **Registration**	**Depart**
4:00-6:15 PM: Symposia I: **Toward Deciphering the Exercise Responsome** Chair: P. Darrell Neufer	8:30-10:45 AM: Concurrent Symposia II: **Exercise Triggers Adaptive Brain Cell Stress Responses** Chairs: Mark Mattson, and Monika Fleshner	8:30-10:45 AM: Concurrent Symposia VI: **Activity/Exercise During Pregnancy and Early Development: Implications for Long-term Health** Chair: John Thyfault	
6:15-8:00 PM: **Welcome and Opening Reception**	8:30-10:45 AM: Concurrent Symposia III: **Substrate Control During Exercise: Novel Insights for Halting the Pathogenesis of Metabolic Diseases** Chair: Matt Watt	8:30-10:45 AM: Concurrent Symposia VII: **Impact of Exercise on Adipose Tissue Metabolism-Beyond Browning** Chair: Matthijs Hesselink	
	10:45-11:10 AM: **Break**	10:45-11:10 AM: **Break**	
	11:10-12:00 Noon: Plenary Lecture: **Cross-species Genetics and 'Omics to Map New Players in Mitochondria and Aging** Speaker: Johan Auwerx	11:10-12:00 Noon: Plenary Lecture: **Adaptive Responses of Neuronal Mitochondria to Exercise** Speaker: Mark Mattson	
	12:00 Noon-2:00 PM: Lunch	12:00 Noon-1:00 PM: Lunch	
	2:00-3:00 PM: **Career Development Session**	1:00-3:00 PM **Poster Session II**	
	3:00-5:15 PM: Concurrent Symposia IV: **The Physiology of Sedentary Behavior, How is it Distinguished from Physical Inactivity** Chair: Roger Fielding	3:00-5:15 PM: Concurrent Symposia VIII: **Brains, Blood Vessels, and Hearts: Can Exercise Treat the Molecular Mechanisms Underlying Cardiovascular Disease?** Chair: Craig Emter	
	3:00-5:15 PM: Concurrent Symposia V: **Mitochondrial Signaling and Inter-Organelle Crosstalk** Chair: Deborah Muoio	3:00-5:15 PM: Concurrent Symposia IX: **Exercise and Aging: Responsiveness of Skeletal Muscle to Exercise Training as a Function of Age** Chair: Sue Bodine	
	5:15-7:15 PM: **Poster Session I**	6:30-7:30 PM **Happy Hour Reception** 7:30-9:30 PM: **Closing Banquet and Awards Ceremony** Plenary Lecture: **Sensorimotor Training of Spinal Networks to Restore Function in Spinal Cord Injured Patient**s Speaker: Reggie Edgerton	

Location:

The 2016 APS Intersociety Meeting: The Integrative Biology of Exercise VII will be held November 2—4, 2016 at the Hyatt Regency Phoenix located at: 122 North Second St., Phoenix, AZ 85004, telephone (602) 252-1234.

Onsite Registration Hours:

Wednesday, November 2……2:00—8:00 PM
Thursday, November 3……7:00 AM—5:30 PM
Friday, November 4……..7:30 AM—4:00 PM

On-Site Registration Fees:

APS Member	$850
APS Retired Member	$500
ACSM Member	$850
Nonmember	$1,050
APS Postdoctoral Member	$600
Postdoctoral Nonmember	$700
APS Student Member	$500
Student Nonmember	$550

Payment Information:

Registrants may pay by institutional or personal check, traveler's check, MasterCard, VISA or American Express or in United States Dollars. Checks must be payable to "*The American Physiological Society"* and drawn on a United States bank payable in US dollars.

Student Registration:

Any student member or regularly matriculated student working toward a degree in one of the biomedical sciences is eligible to register at the student fee. Nonmember postdoctoral fellows, hospital residents and interns, and laboratory technicians do not qualify as students. Nonmember students who register onsite must provide a valid university student ID card. APS student members should present their current APS membership card indicating their student category status.

Postdoctoral Registration:

Any person who has received a Ph.D. degree in physiology or related field, **within four years** of this meeting, as attested to by the department head is eligible to register at the postdoctoral fee. **A statement signed by the department head must accompany the registration form and remittance when registering.**

Included in your Registration:

Your registration to this meeting includes entry into all scientific sessions, program book, opening reception, poster sessions, networking socials, and the closing banquet meal. **There are no substitutions or refunds.** You must pay the registration fee regardless of whether you are not able to stay for the entire meeting or partake in any of the meals during the meeting program. Guests of attendees are not permitted in the scientific sessions.

Press Registration:

Press badges will be issued at the APS registration desk, only to members of the working press and freelance writers bearing a letter of assignment from an editor. Representatives of allied fields (public relations, public affairs, etc.) must register as nonmembers.

Photograph/Video Recording:

The photographing and/or the video recording of any the meeting sessions for personal or private use is strictly prohibited.

Code of Conduct:

APS is committed to providing a friendly, safe, and welcoming environment for all, regardless of gender, sexual orientation, disability, race, ethnicity, religion, national origin, or other protected characteristics. We expect all attendees, media, speakers, volunteers, organizers, venue staff, guests, and exhibitors to help us ensure a safe and positive workshop experience for everyone. Alert the APS Registration Desk if you notice a dangerous situation, someone in distress, or violations of this Code of Conduct.

Program Objective:

The goal of IBE VII is to further support the momentum created by the Common Fund effort by helping to facilitate the expansion of research in this field. PA challenges homeostasis in nearly every organ system in the body, and activates both acute and long-term adaptive mechanisms to preserve and/or re-establish homeostasis. To unlock these mechanisms will require the expertise and integration of researchers in different fields, many of whom have not previously been engaged in PA research. This was precisely the motivation behind the NIH workshop - to bring together experts from different fields to identify the major gaps in knowledge regarding the mechanisms underlying the health benefits of PA, potential obstacles to obtaining that knowledge, and possible solutions to facilitate major progress. It is envisioned that the IBE series will be an important mechanism for catalyzing and sustaining this important NIH effort.

Target Audience:

The intended audience for this meeting includes all professionals involved in teaching, research, and clinical fields related to exercise biology.

Did you register early?

The drawing for the iPad Pro will be held on Friday, November 4 during the Closing Banquet and Awards Ceremony

Winner must be in attendance to receive prize

WEDNESDAY, NOVEMBER 2, 2016

Symposia I

1.0 TOWARD DECIPHERING THE EXERCISE RESPONSE

Wednes., 4:00—6:15 PM, Regency AB.

Chair: **P. Darrell Neufer,** *East Carolina Univ.*

4:00 PM **1.1** Connecting the Exersome Response to Health Benefits. **Marc Tarnopolsky.** *McMaster Univ., Canada.*

4:30 PM **1.2** Influence of Exercise and Circadian Biomarkers on Multi-Omie Integrated Networks in Children. **Eric Hoffman.** *Children's Natl. Med. Ctr.*

5:00 PM **1.3** Gut Microbiota to Brain Signaling in Exercise-Induced Stress Robustness. **Monika Fleshner.** *Univ. of Colorado, Boulder.*

5:30 PM **1.4** Exercise-Regulated Phosphoproteome Reveals New AMPK Substrates and Signaling Pathways. **David James.** *Univ. of Sydney, Australia.*

THURSDAY, NOVEMBER 3, 2016

Concurrent Symposia II

2.0 EXERCISE TRIGGERS ADAPTIVE BRAIN CELL STRESS RESPONSES

Thurs., 8:30—10:45 AM, Regency AB.

Chairs: **Mark Mattson,** *NIH, NIA.*
Monika Fleshner, *Univ. of Colorado, Boulder.*

8:30 AM **2.1** Exercise Protects the Brain Against Alzheimer's Dementia and Sleep Deprivation. **Karim Alkadhi.** *Univ. of Houston.*

9:00 AM **2.2** Exercise and Brain Plasticity. **Henriette van Praag.** *NIH, NIA.*

9:30 AM **2.3** Exercise and Endocannabinoid Signaling in Humans. **Dave Raichlen.** *Univ. of Arizona, Tucson.*

10:00 AM **2.4** Visceral Fat Hijacks the Immune System to Interfere with Memory and Cognition. **Alexis Stranahan.** *Augusta Univ.*

Join your colleagues for the Opening Reception
Wednesday, November 2, 2016
6:15—8:00 PM
Regency CD

Concurrent Symposia III

3.0 SUBSTRATE CONTROL DURING EXERCISE: NOVEL INSIGHTS FOR HALTING THE PATHOGENESIS OF METABOLIC DISEASES

Thurs., 8:30—10:45 AM, Regency CD.

Chair: **Matt Watt,** *Monash Univ., Australia.*

8:30 AM **3.1** Cellular Energy Sensing and the Regulation of Metabolism. **Gregory Steinberg.** *McMaster Univ., Canada.*

9:00 AM **3.2** Exercise Training, Lipid Droplets and the Oxidative Phenotype. **Matthjs Hesselink.** *Maastricht Univ., The Netherlands.*

9:30 AM **3.3** Phosphatidylethanolamine Synthesis in Regulating Skeletal Muscle Lipid Content and Mitochondrial Function: Implications for Insulin Action. **Clinton Bruce.** *Deakin Univ., Burwood, Australia.*

10:00 AM **3.4** Exercise and Adipose Tissue Remodeling: Pathways for Halting Diabetes Pathogenesis. **Laurie Goodyear.** *Joslin Diabetes Ctr.*

Plenary Lecture

4.0 PLENARY LECTURE

Thurs., 11:10 AM—12:00 Noon, Regency AB.

11:10 AM **4.1** Cross-Species Genetics and 'omics to Map New Players in Mitochondria and Aging. **Johan Auwerx.** *Ecole Poly. Fed. de Lausanne, Switzerland.*

Career Workshop

5.0 CAREER WORKSHOP

Thurs., 1:30—2:30 PM, Regency AB.

1:30 PM **5.1** Careers in Industry. **Magdalena Alonso-Galicia.** *Bayer HealthCare, LLC.*

Concurrent Symposia IV

6.0 THE PHYSIOLOGY OF SEDENTARY BEHAVIOR: HOW IS IT DISTINGUISHED FROM PHYSICAL INACTIVITY

Thurs., 3:00—5:15 PM, Regency AB.

Chair: **Roger Fielding,** *Tufts Univ.*

3:00 PM **6.1** Epidemiology of Sedentary Behavior. **Peter Katzmarzyk.** *Pennington Biomed. Res. Ctr., Baton Rouge, LA.*

3:30 PM **6.2** Physiology of Sedentary Behavior and its Relationship to Health Outcomes.

David Dunstan. *Baker IDI Heart & Diabetes Inst., Australia.*

4:00 PM **6.3** Genetics of Exercise Avoidance. **Rod Dishman.** *Univ. of Georgia.*

4:30 PM **6.4** Novel Strategies and Approaches for Sedentary Behavior Physiology Research. **William Kraus.** *Duke Univ. Sch. of Med.*

Concurrent Symposia V

7.0 MITOCHONDRIAL SIGNALING AND INTER-ORGANELLE CROSSTALK

Thurs., 3:00—5:15 PM, Regency CD.

Chair: **Deborah Muoio,** *Duke Univ. Sch. of Med.*

3:00 PM **7.1** Mitochondrial-Derived Peptides Regulate Energy Homeostasis. **Pinchas Cohen.** *Univ. of Southern California, Davis.*

3:30 PM **7.2** Role of the Acetylome in Mitochondrial Energy Sensing and Signaling. **Michael Sack.** *NIH, NHLBI.*

4:00 PM **7.3** Mitochondrial Remodeling Relevant to Exercise and Disease. **Dan Kelly.** *Sanford Burnham Prebys. Med. Discovery Inst.*

4:30 PM **7.4** The Role of Diet and Exercise in the Transgenerational Epigenetic Landscape of Type 2 Diabetes. **Juleen Zierath.** *Karolinska Inst., Sweden.*

Poster Session I

8.0 ACUTE AND INTEGRATIVE RESPONSES

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

1 **8.1** Local Heating Promotes the Expression of Angiogenic Regulators in Human Skeletal Muscle. **K. Kim, Y. Nie, A.N. Blaize, S. Kuang, T. P. Gavin, and B. T. Roseguini** *Purdue Univ.*

2 **8.2** Evaluation of Dual Stress-Response Systems in an Elite Ultra-Marathon Runner. **A. Jones and W. DeNeen** *Northeastern State Univ.*

3 **8.3** Increases in Metabolite Concentrations in Glycolysis and Pentose Phosphate Pathway and Signal Phosphorylations in C2C12 Myotubes After High Frequency Electrical Stimulation. **D. Hoshino, K. Kunida, T. Wada, A. Hatano, K. Yugi, T. Soga, and S. Kuroda.** *Univ. of Tokyo, and Keio Univ., Japan.*

Poster Board

4 **8.4** Effects of Acute and Long-Term Peppermint Oil Inhalation on Cardiovascular Responses and Heart Rate Variability. **T-Y.Mao, and C-F. Huang.** *St. Mary's Junior Coll. of Med., Nursing, and Management, and Natl. Yang-Ming Univ. Hosp., Taiwan.*

5 **8.5** Concomitant Assessment of Oxidative DNA Damage and Bone Resorption Over a Rapid Weight Reduction Period in Female Judo Players. **N. Yasuda, and T. Yano.** *Intl. Pacific Univ., Okayama, Japan.*

6 **8.6** Heat Shock Protein 72 Activation in the Liver with Exercise. **A. E. Archer, R. S. Rogers, D. R. Wilson, J. L. Wheatley, J. A. Fletcher, G. M. Meers, E. M. Morris, J. P. Thyfault, R. Sc. Rector, and P. C. Geiger.** *Univ. of Kansas Med. Ctr., Univ. of Texas Southwestern Med. Ctr., and Univ. of Missouri, Columbia.*

7 **8.7** The Effect of Acute Exercise and Serum Carnosinase on Circulating and Muscle Histidine-Containing Dipeptides in Mice. **J. Stautemas, I. Everaert, S. Baba, S. Hauske, B. Yard, and W. Derave.** *Ghent Univ., Belguim, Univ. of Louisville, and Univ. of Heidelberg, Germany.*

8 **8.8** Weight Loss-Induced Changes in Integrated Muscle Protein Synthesis and Markers of Proteolysis in Young Men: Effects of Dietary Protein Intake and Resistance Exercise. **A. Hector, C. McGlory, F.Damas, and S. Phillips** *McMaster Univ., Canada, and Univ. of Sao Paulo, Brazil.*

9 **8.9** New Methods to Interrogate the Metabolome of Muscle Interstitial Fluid During Exercise. **J. Zhang, S. Bhattacharyya, A. Light, C. Lambert, B. Gale, O. Fiehn, C. Hoppel, and S. Adams.** *Univ. of Utah, Univ. of Arkansas for Med. Sci., Univ. of California, Davis, and Case Western Res. Univ.*

10 **8.10** Muscle IL-6 and Fasting Induced Regulation of PDH in Mouse Skeletal Muscle. **S. Ringholm, A. Gudiksen, L. Bertholdt, and H. Pilegaard** *Univ. of Copenhagen, Denmark.*

11 **8.11** Heart Rate Recovery After Maximal Exercise Is Blunted in Adults Born Preterm in Normoxia and Hypoxia. **K. Haraldsdottir, A. Beshish, L. Tetri, G. Barton, D. Pegelow, M. Palta, K. Goss, A. Watson,**

Poster Board

and M. Eldridge. *Univ. of Wisconsin, Madison.*

12 **8.12** Response of Skeletal Muscle Exosome Markers to Acute Resistance Exercise in Lean and Obese. **R. Garner, Y. Nie, J. Weiss, and Tim Gavin** *Purdue Univ.*

13 **8.13** Withdrawn.

14 **8.14** Characterization of Differential Metabolic Responses to Various Treadmill Exercise Protocols in Mice. **S. Fuller, S. Collier, H. Batdorf, J. Simon, M. Scott, J. Collier, and R. Noland.** *Univ. of Louisiana at Lafayette, and Pennington Biomed. Res. Ctr., Baton Rouge, and Louisiana State Univ., Baton Rouge.*

15 **8.15** Is It Safe to Exercise During Hemodialysis? **C. King-VanVlack, T. Parsons, and D. Hopkins-Rosseel.** *Queen's Univ., Kingston, Canada.*

16 **8.16** The Effect of an Acute Bout of Exercise on Markers of Autophagy in the Livers of Diet-Induced Obese Mice. **C. Summers, K. Fuller, and R. Valentine.** *Iowa State Univ.*

Poster Session I

9.0 EXERCISE AND DRUG INTERACTIONS

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

17 **9.1** Circulating Levels of Endocannabinoids Respond Acutely to Voluntary Exercise, Are Altered in Mice Selectively Bred for High Voluntary Wheel Running, and Differ Between the Sexes. **Z. Thompson, D. Argueta, J. Kaur, T. Garland, Jr., and N. V. DiPatrizio** *Univ. of California, Riverside.*

18 **9.2** Time of Day and Training Status Both Mediate the Benefit of Caffeine for Cycling Performance. **J. Boyett, G. Giersch, C. Womack, M. Saunders, and N. Luden.** *James Madison Univ.*

19 **9.3** Exercise Tolerance of Statin Users with Myopathy: An Important Role for Mitochondrial Function. **E. Allard, R. Verheggen, M. Hopman, and S. Timmers.** *Radboud Univ. Med. Ctr., Nijmegen, The Netherlands.*

20 **9.4** Rapid and Reversible Effects of Esmolol on O_2 Extraction in Exercising Muscles. **D. Proctor, C. Luck, S. Maman, U. Leuenberger, and M. Muller** *Penn. State Univ.*

Poster Board

21 **9.5** High Intensity Exercise Preserves Myocellular Size Throughout Doxorubicin Treatment. **A. D'Lugos, C. Cosgrave, W. Dedmon, B. Astill, S. Patel, M. Katsma, R. Gonzales, T. Hale, C. Carroll, S. Angadi, and J. Dickinson** *Arizona State Univ., Midwestern Univ., and Univ. of Arizona.*

22 **9.6** Does Daily Exercise Prevent Metabolic Dysregulation During Unloading? **M. M. Downs, L. Ploutz-Snyder, E. Goetchius, R. Buxton, K. Randolph, C. Danesi, M. Sheffield-Moore, R. Urban, and L. Dillon.** *Univ. of Houston, Univ. Space Res. Assn., Houston, TX, and Univ. of Texas Med. Branch, Galveston.*

23 **9.7** High Intensity Exercise Preserves Skeletal Muscle MTOR Signaling During Doxorubicin Treatment in Ovariectomized Female Rats. **J. Dickinson, A. D'Lugos, T. Mahmood, L. Salvo, C. Cosgrove, L. Dedmon, B. Astill, S. Patel, M. Katsma, R. Gonzales, T. Hale, S. Angadi, and C. Carroll.** *Arizona State Univ., Midwestern Univ., and Univ. of Arizona.*

Poster Session I

10.0 CARBOHYDRATE METABOLISM

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

24 **10.1** The Effect of Endurance Exercise Duration, Intensity and Fitness Status on Skeletal Muscle Glycogen Utilization: A Meta-Analysis. **J. Areta, and W. Hopkins.** *Norwegian Sch. of Sport Sci., Oslo, Norway, and Victoria Univ., Melbourne, Australia.*

25 **10.2** A Novel Method Reveals a Fiber Type Selective Effect of Acute Exercise on Glucose Uptake by Single Skeletal Muscle Fibers. **M. Pataky, E. Arias, C. Yu, Y. Nie, K. Dent, and G. Cartee.** *Univ. of Michigan.*

26 **10.3** Pre-Exercise High-Fat/low-Carbohydrate Diet for 3 Days Affects Post-Exercise Skeletal Muscle Glycogen Repletion. **Y. Takahashi, Y. Matsunaga, Y. Tamura, S. Terada, and H. Hatta.** *Univ. of Tokyo, Japan.*

Poster Board

27 **10.4** Using a Triple Glucose Tracer Technique to Quantify Postprandial Glucose Flux After Acute Exercise and Exercise Training. **D. Morrison, C. Bruce, G. Kowalski, and G. Wadley** *Deakin Univ., Burwood, Australia.*

28 **10.5** Effects of a 4-Day Low-Carbohydrate Diet with or Without Post-Meal Walking on Glucose Control in Type 2 Diabetes. **E. Myette-Cote, C. Durrer, H. Neurdoff, and J. P. Little.** *Univ. of British Columbia, Kelowna, Canada.*

29 **10.6** Ten Weeks of High Intensity Interval Training in Men and Women with Prediabetes is Associated with Improved Glucose Metabolism and Altered Adipokine Production. **L. Willis, C. Slentz, K. Huffman, J. Lord, W. Kraus, and D. Bartlett.** *Duke Univ., and Univ. of Birmingham Sch. of Med., UK.*

30 **10.7** Fasting Affects Blood Lactate Concentrations During High Intensity Exercise. **K. Takahashi, Y. Sato, M. Banjo, Y. Takahashi, and H. Hatta.** *Univ. of Tokyo, Japan.*

31 **10.8** Chronic High Dietary Sucrose Consumption Increases Energy Expenditure Independent of Physical Activity or Body Weight in Mice. **E. Stephenson, K. Cyrus, J. Han, and D. Bridges.** *Univ. of Tennessee Hlth. Sci. Ctr., Memphis, and Univ. of Michigan.*

Poster Session I

11.0 ADIPOSE AND LIPID METABOLISM

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

32 **11.1** Enhanced Fatty Acid Oxidation and the Response to Exercise in Mice. **S. Kolwicz Jr., C. Halterman, S. Nguyen, and S. Curtis.** *Univ. of Washington.*

33 **11.2** Overexpression of Skeletal Muscle Phosphatidylethanolamine Methyltransferase Does Not Affect Whole Body Metabolism in Mice. **P. Ferrara, E. Wentzler, A. Verkerke, T. Narowski, A. Balotti, and K. Funai.** *East Carolina Univ.*

34 **11.3** Exercise Training Alters Expression of Developmental Genes and Adipogenic Potential in Adipocytes and Adipose-Derived Stem Cells Isolated from Subcutaneous and Visceral Fat Depots. **H. Kato, H. Takakura, M. Hieda, Y. Ohira, and T. Izawa** *Doshisha Univ., Kyotanabe City, Japan.*

Poster Board

35 **11.4** Impact of Skeletal Muscle IL-6 on Metabolic Regulation in Adipose Tissue During Prolonged Exercise. **L. Bertholdt, A. Gudiksen, C. L. Schwartz, J. G. Knudsen, and H. Pilegaard.** *Univ. of Copenhagen, Denmark.*

36 **11.5** Phosphatidylethanolamine Methyltransferase is Required for Mitochondrial Uncoupling and Cardiolipin Content in Brown Adipose Tissue. **J. Johnson, A. Verkerke, T. Heden, T. Narowski, A. Balotti, S. Strong, C-T. Lin, and K. Funai.** *East Carolina Univ.*

37 **11.6** The Combination of Prolonged Fasting and Prior Exercise Increases Peak fat Oxidation and Fatmax in Highly Trained Athletes. **J. Frandsen, S. Vest, S. Larsen, F. Dela, and J. W. Helge.** *Univ. of Copenhagen, Denmark.*

38 **11.7** A Single Session of Aerobic Exercise Reduces Markers of Inflammation in Subcutaneous Adipose Tissue. **D. W. Van Pelt, L. M. Guth, K. C. Karabetsos, and J. F. Horowitz.** *Univ. of Michigan.*

39 **11.8** Human Serum Collected Immediately After Exercise Does Not Alter mRNA Expression Related to Fatty Acid Metabolism or Inflammation in Cultured 3T3-L1 Adipocytes. **F. Yuan, L. M. Guth, D. W. Van Pelt, H. S. Jawanda, and J. F. Horowitz.** *Univ. of Michigan.*

40 **11.9** Systemic Fatty Acid Mobilization Rates Are Elevated in Endurance-Trained Obese/overweight Adults, But Are Blunted the Day After Acute Exercise. **L. M. Guth, D. W. Van Pelt, Z. Yi, and J. F. Horowitz** *Univ. of Michigan, and Wayne State Univ.*

41 **11.10** Effects of Exercise on Adipose Tissue Responses to Short-Term Overeating in Healthy Adults. **A. C. Ludzki, J. B. Gillen, L. M. Guth, K. C. Karabetsos, and J. F. Horowitz.** *Univ. of Michigan.*

42 **11.11** Adiponectin Incubation Decreases Skeletal Muscle Glycogen Content After Reverting to a Chow Diet Following Diet Induced Obesity. **C. Meza, C. Montenegro, C. De La Peña, L. O'Keefe, S. Nau-**

Poster Board

ghton, A. Simcocks, D. Hryciw, M. Mathai, A. McAinch, and S. Bajpeyi. *Univ. of Texas at El Paso, Victoria Univ., Melbourne, Australia, and Univ. of Melbourne, Australia.*

43 **11.12** Protein vs Carbohydrate Intake Post-Exercise and the Effect on Whole-Body Fat Oxidation. **U. Andersson Hall, F. Edin, S. Pettersson, and K. Madsen.** *Aarhus Univ., Denmark, and Gothenburg Univ., Sweden.*

44 **11.13** Human Preadipocyte Fatty Acid Sensitivity Correlates with Improvements in Insulin Sensitivity Following 12-Week Exercise Training. **J. Shine, J. White, T. Heden, B. Davis, R. Hickner, and J. Robidoux.** *East Carolina Univ.*

45 **11.14** Skeletal Muscle Glycogen Content is Unaffected by Dietary Fatty Acid Composition. **C. De La Pena, C. Meza, C. Montenegro, A. Simcocks, S. Naughton, L. O'Keefe, D. Hryciw, M. Mathai, A. McAinch, and S. Bajpeyi.** *Univ. of Texas at El Paso, Victoria Univ., Melbourne, Australia, and Univ. of Melbourne, Australia.*

46 **11.15** Impact of Endurance Exercise Training on Adipocyte miRNA Expression in Overweight Men. **T. Tsiloulis, J. Pike, D. Powell, F. J. Rossello, B. J. Canny, R. C. R. Meex, and M. J. Watt.** *Monash Univ., Clayton, Australia.*

47 **11.16** Adiponectin is More Effective in Sparing Glycogen Content with High Fat Diet in Dietary Monounsaturated Fat Compared to Diets High in Saturated and Polyunsaturated Fat. **C. Montenegro, C. De La Pena, C. Meza, S. Naughton, A. Simcocks, L. O'Keefe, D. Hryciw, M. Mathai, A. McAinch, and S. Bajpeyi.** *Univ. of Texas at El Paso, Victoria Univ., Melbourne, Australia, and Univ. of Melbourne, Australia.*

48 **11.17** Mitochondrial Oxidative Phosphorylation Capacity in Human Adipose Tissue and Adaptations with Exercise Training. **J. White, T. Heden, R. Alleman, J. Shine, J. Robidoux, and R. Hickner.** *East Carolina Univ.*

Poster Session I

12.0 GENOMICS , METABOLOMICS, AND PROTEOMICS

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

49 **12.1** Short-term Heat Stress Stimulates Glycogen and Protein Metabolism in Rat Skeletal Muscle. **A. Goto, T. Egawa, K. Sekine, I. Sakon, R. Oshima, S. Tsuda, and T. Hayashi.** *Kyoto Univ., Japan, and Juntendo Univ., Tokyo, Japan.*

50 **12.2** Skeletal Muscle Microbiopsy Technique and Deuterated Water Used to Detect Skeletal Muscle Protein Fractional Synthesis Rate During Testosterone Therapy in Older Men. **L. Piner, K. Huffman, L. Elliott-Penry, M. Shankaran, W. Evans, M. Hellerstein, S. Andrews, A. Walker, R. Miller, R. Clark, and W. Kraus.** *Duke Univ., KineMed, Inc., Emeryville, CA, Univ. of California, Berkeley, and GlaxoSmithKline.*

51 **12.3** Acute Exercise Exacerbates Muscle Ceramide Levels in Diabetic and Obese Humans. **J. Brozinick, H. H. Bui, P. Sanders, M-S. Kuo, B. Bergman, L. Perreault, and D. Hunerdosse.** *Eli Lilly and Co., and Univ. of Colorado, Aurora.*

52 **12.4** Withdrawn.

53 **12.5** Genetic Variation of Both the Beta-2 Adrenergic Receptor and Phenylethanolamine-N-Methyltransferase have a Combined Effect on Airway Function During Exercise in Healthy Humans. **E. Peitzman, E. Snyder, M. Johnson, and B. Johnson.** *Univ. of Minnesota, Minneapolis, and Mayo Clinic.*

Poster Session I

13.0 EPIGENETICS

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

54 **13.1** Maternal Exposure to Western Diet Affects Body Composition But Not Adult Activity Levels in Mice Bred for High Voluntary Exercise. **L. Hiramatsu, W. Agnew Svoboda, M. Blick, G. Claghorn, J. Kay, R. Lacerda de Albuquerque, J. Singleton, Z. Thompson, J. Colbath, B. Ho, B. Ho, G. Sanchez, D. Thai, and T. Garland, Jr.** *Univ. of California, Riverside.*

55 **13.2** Marine Corps Martial Arts Program Does Not Cause Global DNA Methylation Changes in Female Marines. **J. Deckert, J. Ward, J. Siedlik, E. Barnes, E. Landes, J. Vardiman, and P. Gallagher.** *Univ. of Kansas, Creighton Univ., and Kansas State Univ.*

Poster Board

56 **13.3** A New RRBS Application to Assess DNA Methylation in Human Slow-And Fast-Twitch Skeletal Muscle Fibers with Low-DNA Input. **G. Begue, U. Raue, B. Jemiolo, and S. Trappe.** *Ball State Univ., Muncie, IN.*

57 **13.4** DNA Methylation and Gene Expression in Human Slow-And Fast-Twitch Skeletal Muscle Fibers: An Exploratory Analysis. **G. Begue, U. Raue, B. Jemiolo, and S. Trappe.** *Ball State Univ., Muncie, IN.*

58 **13.5** Maternal Exercise Alters Offspring Adipogenesis. **L. Reynolds, J. Preston, L. Carter, and K. Pearson.** *Univ. of Kentucky.*

59 **13.6** Eight Week Exercise Training Alters the Global DNA Methylation Patterns in Human Skeletal Muscle. **S. Day, R. Coletta, L. Garcia, T. Benjamin, L. Roust, E. De Filippis, L. Mandarino, and D. Coletta.** *Arizona State Univ., Mayo Clinic, and Univ. of Arizona.*

Poster Session I

14.0 GENDER DIFFERENCES

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

60 **14.1** Relationship Between Body Composition and Menstrual/Premenstrual Symptoms in Japanese Young Women. **K. Ohno, H. Naito, and S. Machida.** *Juntendo Univ., Inzai, Japan.*

61 **14.2** Hypovolemic Men and Women Regulate Cerebral Blood Flow Differently Following Exposure to Artificial Gravity. **M. Favre, M. Falvo, J. Evans, and J. Serrador.** *Rutgers Univ., Vet. Affairs NJ Hlth. Care Sys, East Orange, and Univ. of Kentucky.*

62 **14.3** Differences in Exercise Capacity in Adults Born Preterm Appear to be Driven by Males and Not Females. **L. Tetri, K. Haraldsdottir, E. Farrell, M. Palta, D. Pegelow, and M, Eldridge.** *Univ. of Wisconsin, Madison.*

Photography and video <u>are not</u> permitted in the session rooms or at the posters

Poster Session I

15.0 MOLECULAR TRANSDUCERS

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

63 **15.1** Defining Nutrient-Sensitive Pathways of mTOR Activation in Human Skeletal Muscle. **N. Hodson, J. Dent, D. Craig, M. McLeod, J. Murray, D. L. Hamilton, L. Breen, and A. Philp.** *Univ. of Birmingham, UK, Trinity Coll. Dublin, Ireland, and Univ. of Stirling, UK.*

64 **15.2** Theoretical and Molecular Resolution of the Link Between Low Exercise Capacity and Disease. **L. G. Koch, S. L. Britton, S-J. Park, and J. H. Chung.** *Univ. of Michigan, and NIH, NHLBI.*

65 **15.3** Exercise-Training Increases Basal Autophagy-Related Gene Expression in Murine Arterial Endothelial Cells. **J. S Kim, L. P Bharath, J. Allsop, T. Bean, T. Bonn, G. Hestwood, D. Nelson, M. Drummond, P. V. A. Babu, T. E. Graham, and J. D. Symons.** *Univ. of Utah.*

66 **15.4** Exercise Serum Increases GLUT4 Content in Human Primary Adipocytes. **M. Flores-Opazo, A. Raajendiran, M. Watt, and M. Hargreaves.** *Univ. of Melbourne, and Monash Univ., Clayton, Australia.*

Poster Session I

16.0 MITOCHONDRIAL FUNCTION

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

67 **16.1** A Single Bout of Aerobic Exercise Increases Citrate Synthase Specific Activity and ATP Production Rate in Isolated Mitochondria from Human Skeletal Muscle. **K. Kras, W. Willis, E. De Filippis, L. Roust, N. Hoffman, and C. Katsanos.** *Arizona State Univ. and Mayo Clinic in Arizona.*

68 **16.2** Physical Activity Reduces the Risk of Type 2 Diabetes Associated with m.1382A>C Polymorphism Encoding 12S rRNA and Mitochondria Derived MOTS-c. **N. Fuku, H. Zempo, Y. Nishida, Y. Higaki, H. Naito, M. Hara, and K. Tanaka.** *Juntendo Univ., Inzai, Saga Univ., and Fukuoka Univ., Japan.*

69 **16.3** PGC-1α and β Not Required for Exercise-Induced Oxidative Capacity in Adult Skeletal Muscle. **Y. Tang, C. Ballmann, Z.**

Poster Board

Bush, and G. C. Rowe. *Univ. of Alabama at Birmingham.*

70 **16.4** The Role of IL15/IL15Ra Signaling in Muscle Oxidative Metabolism. **E. Loro, E. L. Seifert, D. W. Frederick, M. K. Mishra, J. A. Baur, and T. S. Khurana.** *Univ. of Pennsylvania, and Thomas Jefferson Univ.*

71 **16.5** Absence of Mitochondrial Phosphatidylethanolamine Synthesis Impairs Skeletal Muscle Respiration and Promotes Rapid Death. **T. Heden, E. Wentzler, T. Narowski, R. Renegar, J. Brault, and K. Funai.** *East Carolina Univ.*

72 **16.6** Overexpression of Skeletal Muscle Phosphatidylserine Decarboxylase Increases Respiratory Capacity and Attenuates H_2O_2 Production in Tafazzin Deficiency. **J. Johnson, T. Heden, A. Balotti, E. Wentzler, T. Narowski, and K. Funai.** *East Carolina Univ.*

73 **16.7** Skeletal Muscle-Specific Deletion of p53 does not Impair Mitochondrial Content or Enzyme Activity. **B. Stocks, S. Bullard, C. Adams, and A. Philp.** *Univ. of Birmingham, UK, and Univ. of Iowa.*

74 **16.8** Mechanistic Flexibility of Mitochondrial Complex I and its Associated H_2O_2 Emitting Potential. **M. J. Torres, P. D. Neufer, and T. N. Zeczycki.** *East Carolina Univ.*

75 **16.9** Effects of Acute Aerobic Exercise on Mitochondrial Morphology in Endurance-Trained Rats. **D. Nakano, K. Takagi, and S. Machida.** *Juntendo Univ., Inzai, Japan.*

76 **16.10** Palmitoyl-CoA Induces Mitochondrial Uncoupling in Rat Myofibres Exposed to Heat Stress. **A. Malgoyre, P. E. Tardo Dino, J. Touron, and N. Koulmann.** *Inst. de Res. Biomed. des Armees, Bretigny Sur Orge, Univ. Claude Bernard Lyon, Villeurbanne, Univ. d'Evry, and Ecole du Val de Grâce, Paris, France.*

77 **16.11** Adenine Nucleotide Translocase (ANT) Control of Oxidative Flux in Human Skeletal Muscle Mitochondria: Influence of Lysine Acetylation. **W. Willis, E. Willis, J. Hudgens, J. Finlayson, P. Langlais, and L. Mandarino.** *Arizona State Univ., Univ. of Arizona, and Mayo Clinic Arizona.*

Poster Board

78 **16.12** A Single Bout of Heat Stress Treatment Increases Mitochondrial-Associated Gene Expression in Mouse Skeletal Muscle. **Y. Tamura, Y. Kitaoka, A. Tsutaki, K. Nakazato, and H. Hatta.** *Nippon Sport Sci. Univ., Tokyo, and Univ. of Tokyo, Japan.*

79 **16.13** Interleukin-15 Improves Skeletal Muscles Glucose Uptake and Mitochondrial Function in Association with AMPK Activation. **L. Nadeau, M. Foretz, P. Haddad, B. G. Anderson, L. Quinn, and C. Aguer.** *Inst. de Res. de l'Hôpital Montfort, Ottawa, Univ. of Ottawa, Canada, INSERM U1016, Paris, Univ. Paris Descartes, France, Education & Clinical Ctr., Seattle, and Univ. of Washington.*

80 **16.14** The Mitochondrial Reticulum of the Heart. **B. Glancy, L. M. Hartnell, C. A. Combs, A. Fenmou, J. Sun, E. Murphy, S. Subramaniam, and R. S. Balaban.** *NIH, NHLBI, NIH, NIAMS, and NIH, NCI.*

81 **16.15** Evidence of Membrane Potential-Dependent and Independent Redox Circuits Linking Fatty-Acid Oxidation Enzymes and the Antioxidant Protein Network in Skeletal Muscle Mitochondria. **C. Smith, C-T. Lin, K. H. Fisher-Wellman, D. M. Muoio, and P. D. Neufer** *East Carolina Univ. and Duke Univ.*

82 **16.16** Cardiac Ischemia Results in Decreased Intermediate Mitochondrial Respiration Rates and Impairs Every Step of the Oxidation Phosphorylation Pathway. **S. Kuzmiak-Glancy, B. Glancy, and M. Kay.** *George Washington Univ., and NIH, NHLBI.*

83 **16.17** Effects of Fasting and Wheel Running on *in Vivo* Hepatic Autophagy Through the Use of the Autophagy Inhibitor Leupeptin. **C. McCoin, E. M. Morris, J. Allen, and J. Thyfault** *Kansas Univ. Med. Ctr., and Kansas City VA Med. Ctr.*

84 **16.18** Differential Enrichment of Sub-Sarcolemmal Mitochondria with Individual Proteins Between Lean and Obese, Insulin-Resistant Subjects. **C. Katsanos, K. Kras, P. Langlais, W. Willis, L. Mandarino, E. De Filippis, and L. Roust.** *Arizona State Univ., and. Mayo Clinic in Arizona.*

Poster Session I

17.0 REDOX BIOLOGY

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

85 **17.1** Nrf2 Deficiency Aggravates Denervation-Induced Oxidative Stress but not Atrophy in Skeletal Muscle. **Y. Kitaoka, K. Takeda, Y. Tamura, S. Fujimaki, T. Takemasa, and H. Hatta.** *Univ. of Tokyo, and Univ. of Tsukuba, Japan.*

86 **17.2** Trans-Plasma Membrane Electron Transport and Ascorbate Efflux in Skeletal Muscle Cells. **A. M. Kaverman, R. M. Prasad, and J. S. Fisher** *St. Louis Univ.*

87 **17.3** Peroxidase Activity of Myoglobin. **M. Mannino, R. Patel , B. Janowiak, and J. S. Fisher** *St. Louis Univ.*

88 **17.4** Changes in Energy State Acutely Alter Redox State and Insulin Sensitivity in Healthy Humans. **C-T. Lin, L. A. Gilliam, T. E. Ryan, M. J. Torres, C. D. Smith, P. M. Brophy, A. H. Clark, R. C. Hickner, and P. D. Neufer.** *East Carolina Univ.*

Poster Session I

18.0 MUSCLE FUNCTION AND ADAPTATION

Thurs., 5:15—7:15 PM, Atrium Lobby.

Poster Board

89 **18.1** A Long-Term High Fat Diet Causes Muscle Dysfunction in Mouse Fast-Twitch Skeletal Muscle. **H. Eshima, Y. Tamura, S. Kakehi, R. Kawamori, and H. Wataba.** *Juntendo Univ., Tokyo, Japan.*

90 **18.2** The Effect of Chronic Resistance Training on Myonuclear Abundance in OLETF Rat Skeletal Muscle. **S. Ato, K. Kido, K. Sato, and S. Fujita.** *Ritsumeikan Univ., Kasatsu, and Kobe Univ., Japan.*

91 **18.3** Relationship Between Training Frequency and Muscle Protein Synthesis in Resistance Exercise Elicited by Electrical Stimulation. **J. Takegaki, R. Ogasawara, A. Tsutaki, R. Takagi, K. Nakazato, and N. Ishii.** *Univ. of Tokyo, Nagoya Inst. of Tech., Showa-ku, and Nippon Sport Sci. Univ., Setagaya-ku, Japan.*

92 **18.4** Nuclear and Cytoplasmic Muscleblind-like 1 in Mouse Skeletal Muscle in Response to Aging and Unloading with or Without Reloading. **A. Nakamura, R. Ito, N. Ikegaya, M. Higa, S. Yokoyama, Y. Ohno, T. Sugiura, Y. Ohira, T. Yoshioka,**

Poster Board

L. M. Baehr, S. C. Bodine, and K. Goto. *Toyohashi Sozo Univ., Nishio Municcipal Hosp., Yamaguchi Univ., Doshisha Univ., Kyotanabe, Japan, and Univ. of California, Davis.*

93 **18.5** Training Status and PDH Regulation in Human Skeletal Muscle During Exercise. **A. Gudiksen, L. Bertholt, T. Stankiewicz, J. Tybirk, P. Plomgaard, J. Bangsbo, and H. Pilegaard.** *Univ. of Copenhagen, Denmark.*

94 **18.6** A Novel Method to Quantify Resting and Contraction-Stimulated O_2 Consumption in Isolated Mouse Skeletal Musce. **P. Ferrara, A. Verkerke, A. Balotti, T. Narowski, E. Spangenburg, and K. Funai.** *East Carolina Univ.*

95 **18.7** Reduced Non-Bicarbonate Skeletal Muscle Buffering Capacity in Mice with the Mini-Muscle Phenotype. **J. Kay, Z. Thompson, E. Contreras, J. Ramirez, and T. Garland, Jr.** *Univ. of California, Riverside.*

96 **18.8** Can Aged Skeletal Muscle Inflammation Susceptibility Be Modulated with Daily Consumption of an Anti-Inflammatory Food? **V. Georgescu, C. Demczar, C. Behrens, S. McAnulty, L. McAnulty, and E. Merritt.** *Appalachian State Univ.*

97 **18.9** Overexpression of the α7β1 Integrin Accelerates Skeletal Muscle Hypertrophy Following Chronic Overload. **Z. Mahmassani, K. Garg, M. Munroe, S. Dvoretskiy, T. A. Hornberger, and M. D. Boppart.** *Univ. of Illinois at Urbana-Champaign, and Univ. of Wisconsin at Madison.*

98 **18.10** Absence of Phosphatidylethanolamine Methylation Increases Skeletal Muscle Energy Expenditure and Prevents Obesity. **A. Verkerke, P. Ferrara, C-T. Lin, T. Heden, T. Ryan, E. Wentzler, A. Balotti, P. D. Neufer, and K. Funai.** *East Carolina Univ.*

99 **18.11** Dissociation Between Short-Term Unloading and Resistance Training Effects on Skeletal Muscle Na^+,K^+-ATPase, Muscle Function and Fatigue in Humans. **B. Perry, V. Wyckelsma, R. Murphy, C. Steward, M. Anderson, I. Levinger, A. Petersen, and M. McKenna.** *Victoria Univ., Melbourne, Australia, Emory Univ., La Trobe*

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Univ., Melbourne, and Baker IDI Heart and Diabetes Inst., Melbourne, Australia.

100 **18.12** Internal or External Control? A Methodology Report for Designing Denervation Studies. **H. Liu, and LaDora Thompson.** *Univ. of Minnesota.*

101 **18.13** Conditional Knockout of the Lysine Acetyltransferase GCN5 Does Not Result in Metabolic or Fibre-Type Remodelling in Mouse Skeletal Muscle. **J. R. Dent, S. A. LaBarge, E. H. Buckner, S. Schenk, and A. Philp.** *Univ. of Birmingham, UK, and Univ. of California, San Diego.*

102 **18.14** High-Fat Diet Induces LKB1-Dependent Attenuation of Skeletal Muscle P70S6k Phosphorylation by Insulin. **M. Matsumura, T. Chen, and D. Thomson.** *Brigham Young Univ.*

103 **18.15** Effects of Statin Treatment on Muscle Hypertrophy and Function Induced by Functional Overload in Mice. **K. Huey, and A. Herold.** *Drake Univ., Des Moines, IA.*

104 **18.16** Overexpressing SIRT1 in skeletal Muscle of Adult Mice does not Affect Markers of Mitochondrial Biogenesis. **K. Svensson, S. A. LaBarge, and S. Schenk.** *Univ. of California, San Diego.*

105 **18.17** AMPK-Dependent Attenuation of Skeletal Muscle Protein Synthesis by Cooling. **E. Cheung, B. T. Colton, and D. M. Thomson.** *Brigham Young Univ.*

106 **18.19** Effects of Chronic Inactivity on Physiological and Biochemical Characteristics of Rat Skeletal Muscle. **H. Xu, G. Lamb, and R. Murphy.** *La Trobe Univ., Melbourne, Australia.*

107 **18.20** Individual Response to High-Intensity Interval Training (HIIT): Preliminary Data from the Gene SMART Study. **X. Yan, N. Eynon, I. Papadimitriou, J. Kuang, F. Munson, O. Tirosh, L. O'Kee-fe, A. Garnham, and D. Bishop.** *Victoria Univ., and The Royal Children's Hosp., Melbourne, Australia.*

108 **18.21** Life-Long Reduction in myomiR Expression does not Adversely Affect Skeletal Muscle Morphology. **I. Vechetti Junior., Y. Wen, K. Murach, L. Peterson, G. Ming, M. Dal-Pai, and J. McCarthy.**

Poster Board

Univ. of Kentucky, and Sao Paulo State Univ., Brazil.

109 **18.22** Influence of 70 Days of Bedrest and the Next Generation Exercise Countermeasures Program (SPRINT) on Thigh and Calf Muscle Metabolic Enzymes and Capillary Content. **K. Lavin, B. Jemiolo, R. Perkins, S. Ratchford, H. Finch, E. L. Dillon, M. Sheffield-Moore, R. Urban, J. Ryder and L. Ploutz-Snyder, S. Trappe, and T. Trappe.** *Ball State Univ., Univ. of Texas Med. Branch, and NASA Johnson Space Ctr.*

110 **18.23** β-Catenin Regulation of Skeletal Muscle Hypertrophy. **Y. Wen, T. Kirby, A. Alimov, I. Vechetti, and J. McCarthy.** *Univ. of Kentucky, and Cornell Univ.*

111 **18.24** Role of Monocarboxylate Transporter 4 (MCT4) in Muscle Metabolism and Physiology. **S. Bisetto, E. Loro, T. Khurana, and N. Philp.** *Thomas Jefferson Univ. and Univ. of Pennsylvania.*

112 **18.25** Skeletal Muscle Phenotype and Exercise in Age and Disease: Neuromuscular Junction Instability and Type I Myofiber Grouping. **K. Hammond, N. Kelly, and M. Bamman.** *Univ. of Alabama at Birmingham.*

113 **18.26** Influence of 70 Days of Bedrest and the Next Generation Exercise Countermeasures Program (SPRINT) on soleus Single Muscle Fiber Size and Function. **T. Trappe, K. Minchev, G. Grosicki, R. Perkins, H. Finch, E. L. Dillon, M. Sheffield-Moore, R. Urban, J. Ryder, L. Ploutz-Snyder, and S. Trappe.** *Ball State Univ, Univ, of Texas Med. Branch, and NASA Johnson Space Ctr.*

114 **18.27** Influence of 70 Days of Bedrest and the Next Generation Exercise Countermeasures Program (SPRINT) on vastus Lateralis Single Muscle Fiber Size and Function. **S. Trappe, K. Minchev, G. Grosicki, R. Perkins, H. Finch, E. L. Dillon, M. Sheffield-Moore, R. Urban, J. Ryder, L. Ploutz-Snyder, and T. Trappe.** *Ball State Univ. Univ. of Texas Med. Branch, and NASA Johnson Space Ctr.*

115 **18.28** Expression of Muscle Specific Ribosomal Protein L3-Like Is Up-Regulated During Post-Natal Development. **L. Peter-**

son, A. Alimov, and J. McCarthy.** *Univ. of Kentucky.*

FRIDAY, NOVEMBER 4, 2016

Concurrent Symposia VI

19.0 ACTIVITY AND EXERCISE DURING PREGNANCY AND EARLY DEVELOPMENT: IMPLICATIONS FOR LONG-TERM HEALTH

Fri., 8:30—10:45 AM, Regency AB.

Chair: **John Thyfault,** *Kansas Univ. Med. Ctr.*

8:30 AM **19.1** Paternal Exercise Reduces Energy Expenditure in Offspring and Alters DNA Methylation and Sperm MicroRNA Content. **Alexander Murashov.** *East Carolina Univ.*

9:00 AM **19.2** Exercise During Pregnancy and Long-Term Impact on Offspring Health. **Kevin Pearson.** *Univ. of Kentucky.*

9:30 AM **19.3** Impact of Early-Life Exercise on Adult Physical Activity and Related Phenotypes. **Theodore Garland, Jr.** *Univ. of California, Riverside.*

10:00 AM **19.4** Placental and Offspring Adaptations to Maternal Exercise and Obesogenic Diets. **Kartik Shankar.** *Univ. of Arkansas Med. Ctr.*

Concurrent Symposia VII

20.0 IMPACT OF EXERCISE ON ADIPOSE TISSUE METABOLISM-BEYOND BROWNING

Fri., 8:30—10:45 AM, Regency CD.

Chair: **Matthijs Hesselink,** *Maastrict Univ., The Netherlands.*

8:30 AM **20.1** Weight Loss and Adipose Tissue Inflammation. **Carey Lumeng.** *Univ. of Michigan.*

9:00 AM **20.2** Exercise Effects on Adipocyte Cell Size and Expandability. **Jeffrey Horowitz.** *Univ. of Michigan.*

9:30 AM **20.3** Exercise and Regulation of Adipose Tissue Blood Flow and Metabolism. **Fredrik Karpe.** *Oxford Univ., UK.*

10:00 AM **20.4** Exercise Training, Adipocyte Precursors and the Regulation of Lipid Metabolism. **Matt Watt.** *Monash Univ., Clayton, Australia.*

Plenary Lecture

21.0 PLENARY LECTURE

Fri., 11:00 AM—12:00 Noon, Regency AB.

11:00 AM **21.1** Adaptive Responses of Neuronal Mitochondria to Exercise. **Mark Mattson.** *NIH, NIA.*

Poster Session II

22.0 SIGNALING

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

1 **22.1** Fiber-Type Dependent Differences in Anabolic Response of Rat Skeletal Muscle to Resistance Exercise. **R. Takagi, R. Ogasawara, J. Takegaki, A. Tsutaki, K. Nakazato, and N. Ishii.** *Univ. of Tokyo, Nagoya Inst. of Tech., and Nippon Sport Sci. Univ., Tokyo, Japan.*

2 **22.2** Skeletal Muscle-Specific Deletion of TAK1 Activates AMPK and Autophagy in Mice. **S. Sato, S. Hindi, G. Xiong, and A. Kumar.** *Univ. of Louisiana at Lafayette, and Univ. of Louisville Sch. of Med.*

3 **22.3** Resistance Training Improves Insulin-Stimulated Akt Activation Concomitant with Increased APPL1 Expression in Skeletal Muscle of Type 2 Diabetic Rats. **K. Kido, S. Ato, Y. Nishimura, T. Miyake, K. Sato, and S. Fujita.** *Ritsumeikan Univ., Kusatsu, and Kobe Univ., Japan.*

4 **22.4** Inhibition of LPCAT3 Enhances Insulin Signaling and Decreases PPARγ Transcriptional Activity in Skeletal Muscle. **P. Ferrara, and K. Funai.** *East Carolina Univ.*

5 **22.5** Prolonged Fasting Suppresses mTORC1 Signaling in Response to Resistance Exercise in Rat Skeletal Muscle. **K. Sase, S. Ato, K. Kido, T. Miyakee, and S. Fujita.** *Ritsumeikan Univ., Kasutsu, Japan.*

6 **22.6** The Role of Integrins in the Regulation of Mechanical Stress-Induced Myotube Hypertrophy *in vitro*. **M. Iwata, W. Tsuchida, Y. Ohno, S. Matsuo, M. Fujiwara, Y. Asai, and S. Suzuki.** *Nihon Fukushi Univ. Handa, Nagoya Univ. Grad. Sch. of Med., and Kamiiida Rehab. Hosp., Nagoya, Japan.*

Poster Board

7 **22.7** Resistance Exercise and Protein Carbohydrate Ingestion Alters mTORC1 Cellular Localization and Protein Complex Interaction in Human Skeletal Muscle. **C. McGlory, N. Hodson, E. Nunes, S. Oikawa, E. Tsakiridis, and S. Phillips.** *McMaster Univ., Hamilton, Canada, and Univ. of Birmingham, UK.*

8 **22.8** Possible Role of Mitochondrially-Derived Peptides in Mediating Retrograde Signaling in Mammalian Muscle. **A. Oliveira, and D. Hood.** *York Univ., Toronto, Canada.*

9 **22.9** High Intensity Interval Cycling Performed Prior to Resistance Exercise Stimulates Autophagy Signaling to a Larger Extent Than Resistance Exercise Alone. **W. Apró, M. Moberg, B. Ekblom, H-C. Holmberg, and E. Blomstrand.** *The Swedish Sch.of Sport and Hlth. Sci., Stockholm, Mid Sweden Univ., Östersund, and Karolinkska Univ., Stockholm, Sweden.*

10 **22.10** Intracellular Sodium is not Sufficient to Activate Endogenous Calpain-3 in Skeletal Muscle, but Ionic Conditions that do not Resemble the Physiological Environment Result in Aberrant Calpain-3 Behavior. **R. Murphy, S. Wette, and G. Lamb.** *La Trobe Univ., Melbourne, Australia.*

Poster Session II

23.0 BRAIN AND NEURAL RESPONSES

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

11 **23.1** Running for REST: Exercise Attenuates Impaired Cognition, Sickness Behavior and Neuroinflammation in the Hippocampus of Aged Animals. **A. Aguiar Jr., K. Dallagnol, A. Remor, R. Silva, R. Prediger, and A. Latini.** *Univ. Fed. de Santa Catarina, Brazil.*

12 **23.2** Motivation for Wheel Running is Enhanced by Peripheral PPAR-Alpha Stimulation in Mice. **T. Shiuchi, and Y. Kito.** *Tokushima Univ. Grad. Sch., and Japan Sci. and Tech. Agency, Tokyo, Japan.*

13 **23.3** The Effects of Calcitonin Gene-Related Peptide on the Expression of Nerve Growth Factor and Glial Cell Line-Derived Neurotrophic Factor in Cardiac Cells. **G. Almeida Alves, J-M.Vianney, and J. M. Spitsbergen.** *Western Michigan Univ.*

Poster Board

14 **23.4** A Ketogenic Diet is Beneficial to Pain Sensitivity as Compared to a High Fat Diet in Mice. **M. Cooper, J. Ryals, and D. Wright.** *Univ. of Kansas Med. Ctr.*

15 **23.5** Effort, the Central Pressor Response and Muscle Fatigue During Human Standing. **R. Fitzpatrick, and B. Luu.** *Univ. of New South Wales, Sydney, Australia.*

16 **23.6** Exercise Preconditioning Reduces TRPA1-Mediated Joint Pain in Mice: Peripheral Versus Central Factors. **T. Griffin, E. Barboza, J. Hudson, P. Parrack, K. Gaffney, C. Fernandez, T. Kovats, and M. Kinter.** *Oklahoma Med. Res. Fdn., Oklahoma City.*

17 **23.7** Cannabinoid Receptors in the VMH Impair Exercised-Induced Improvements in Glucose Tolerance. **C. Castorena, T. Fujikawa, N. Ahmed, C. Lord, C. Lee, C. Vianna, S. Lee, and J. Elmquist.** *Univ. of Texas Southwestern Med. Ctr.*

Poster Session II

24.0 BEHAVIOR

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

18 **24.1** Loss of Nucleus Accumbens Cdk5 Function Decreases Voluntary Wheel Running and May Mediate Age-Related Declines in Physical Activity. **G. Ruegsegger, R. Toedebusch, T. Childs, and F. Booth.** *Univ. of Missouri, Columbia.*

19 **24.2** Mu-Opioid Receptor Inhibition Decreases Running in High Voluntary Running Rats in a Dopamine-Dependent Manner. **G. Ruegsegger, and F. Booth.** *Univ. of Missouri, Columbia.*

20 **24.3** Long-Term Performance, Energetic, and Morphological Consequences of Fatherhood in the Biparental California Mouse (*Peromyscus californicus*). **J. Andrew, T. Garland Jr., W. Saltzman, and M. Chappell.** *Univ. of California, Riverside.*

21 **24.4** Habitual Aerobic Exercise Increases Serum Testosterone Levels in Overweight and Obese Men. **H. Kumagai, T. Yoshikawa, K. Myoenzono, T. Kaneko, A. Zempo-Miyaki, T. Tsujimoto, K. Tanaka, and**

Poster Board

S. Maeda. *Univ. of Tsukuba, and Ryutsu Keizai Univ., Ryugasaki, Japan.*

22 **24.5** Effects of Early-Life Exposure to Western Diet and Voluntary Exercise on Adult Activity Levels, Exercise Physiology, and Associated Traits in Mice. **M. Cadney, J. Kay, L. Hiramatsu, Z. Thompson, J. Singleton, R. Albuquerque, M. Schmill, and T. Garland, Jr.** *Univ. of California, Riverside.*

23 **24.6** Effects of Regularly Scheduled Exercise on Exercise Performance of Mice During the Inactive Period. **N. Takei, H. Minagawa, Y. Matsunaga, Y. Tamura, and H. Hatta.** *Univ. of Tokyo, Japan.*

24 **24.7** Changes in Satisfaction with Physical Function and Appearance After STRRIDE AT/RT and STRRIDE PD. **L. Elliot-Penry, C. Slentz, L. Willis, L. Bateman, E. Granville, L. Piner, C. Bales, and W. Kraus.** *Duke Univ. Med. Ctr.*

Poster Session II

25.0 ADAPTIVE RESPONSES

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

25 **25.1** Acute Exercise Stress Elicits Differential Gene Expression Profiles in Sedentary vs. Detrained Soleus Muscles. **J. P. Hyatt, E. Brown, E. Bienenstock, and G. McCall.** *Arizona State Univ. and Univ. of Puget Sound, Tacoma, WA.*

26 **25.2** Role of β-Adrenergic Signalling in PGC-α Mediated Mitochondrial Adaptations in Skeletal Muscle. **N. Brandt, L. Nielsen, J. Bangsbo, and H. Pilegaard.** *Univ. of Copenhagen, Denmark.*

27 **25.3** Mild-Intensity Exercise Training Alters Skeletal Muscle Phospholipid Composition in Obese Adults. **J. B. Gillen, R. K. Nelson, D. W. Van Pelt, L. M. Guth, and J. F. Horowitz** *Univ. of Michigan.*

28 **25.4** Baseline Irisin Concentrations Not Altered by High-Intensity Resistance Training. **M. Short, E. Chung, J. McComb, S. Kloiber, E. Larumbe-Zabala, L. Ramalingam, and M. Fernandez del Valle.** *Texas Tech. Univ., Lubbock.*

29 **25.5** Impact of PGC-1α in Lifelong Exercise Training-Induced Regulation of UPR in Mouse Liver. **C. Kristensen, S. Ringholm,**

Poster Board

J. Olesen, and H. Pilegaard. *Univ. of Copenhagen, Denmark.*

30 **25.6** The Impact of Hydration Status During Heat Acclimation on Physiological Strain and Exercise Performance. **M. Schleh, B. Ruby, and C. Dumke.** *Univ. of Montana.*

31 **25.7** Effects of Marathon Training on Heart Rate Variability During Submaximal Exercise: A Comparison of Analysis Domains. **C. Lundstrom, G. Biltz, S. Pulice, K. Uithoven, M. Betker, and E. Snyder.** *Univ. of Minnesota, Minneapolis.*

32 **25.8** Individual Responses of Older Women in Traditional Health Risk Factors to Moderate-Intensity Exercise. **X. Wang, K. Bowyer, C. Breneman, R. Porter, and S. Custer.** *Univ. of South Carolina, Columbia.*

33 **25.9** Effects of Resistance Exercise Training With/Without Protein Supplementation in Barth Syndrome. **W. Cade, A. Bittel, K. Bohnert, L. Peterson, M. Corti, B. Byrne, and D. Reeds.** *Washington Univ. Sch. of Med., and Univ. of Florida, Gainesville.*

34 **25.10** Response and Adaptation of Skeletal Muscle to Endurance Training Based on Circadian Rhythms of Clock Gene Expression. **H. Takakura, H. Kato, S. Masuda, D. Ueno, M. Hieda, and T. Izawa.** *Doshisha Univ., Kyontanabe City, Natl. Hosp. Org. Kyoto Med. Ctr., and Nara Inst. of Sci. and Tech., Ikoma City, Japan.*

35 **25.11** CD36 Is Essential for Exercise Training-Induced Improvement in Running Endurance. **M. C. Manio, S. Matsumura, D. Masuda, and K. Inoue.** *Kyoto Univ., and Osaka Univ., Japan.*

36 **25.12** Six Weeks of Sprint Training Improves Sprint Time and Aerobic Fitness Independent of Training Performed on a Track or Treadmill. **M. Amador, C. Meza, J. Perales, S. Dorgo, and S. Bajpeyi.** *Univ. of Texas at El Paso.*

37 **25.13** Exercise Training Reduces Liver Fat Content and Improves Peripheral but not Hepatic Insulin Sensitivity in Overweight and Obese Men with Non-Alcholic Fatty Liver. **B. Brouwers, V. B. Schrauwen-Hinderling, T. Jelenik, A. Gemmink, B. Havekes, Y. Bruls, D. Dahlmans, M. Ro-**

Poster Board

den, P. Schrauwen, and M. Hesselink. *Maastricht Univ. Med. Ctr., The Netherlands, and Heinrich-Heine Univ., Düsseldorf, Germany.*

38 **25.14** Physical Training Prevents the Impaired Thermal Balance in Hypertensive Animals During Exercise. **C. C. Coimbra, H. O. Campos, L. R. Drummond, G. K. Gonçalves, P. M. A. Lima, N. A. C. Horta, and T. N. Prímola-Gomes.** *Univ. Fed. de Minas Gerais, Belo Horizonte, and Univ. Fed. de Viçosa, Brazil.*

39 **25.15** Regular Exercise Induces Changes in Basal Daily Turnover of Dopamine and Serotonin in the Pre-optic Area. **C. C. Coimbra, F. Machado, Q. Rodrigues, N. A. C. Horta, T.Araújo, N. Aquino, R. Szawka, and M. Poletini.** *Univ. Fed. de Minas Gerais, Belo Horizonte, Brazil.*

Poster Session II

26.0 CARDIOVASCULAR

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

40 **26.1** Postnatal Undernutrition Alters Female Mouse Cardiomyocyte Structure and Function Leading to Impairment in Exercise Capacity. **D. Ferguson, T. Monroe, R. Fleischmann, G. Rodney, G. Taffet, and M. Fiorotto.** *Michigan State Univ., and Baylor Coll. of Med.*

41 **26.2** Leg Resistance High-Intensity Interval Exercise Improves Endothelial Function in Older Adults with and Without Type 2 Diabetes. **M. Francois, C. Durrer, and J. Little.** *Univ. of British Columbia, Kelowna, Canada.*

42 **26.3** Lifestyle and Occupational Influences on Cardiovascular Health in Police Officers. **M. Betker, I. West, G. Brewer, Z. Peters, and E. Snyder.** *Univ. of Minnesota, Minneapolis.*

43 **26.4** Determining the Threshold for Protective Effects of Aerobic Exercise on Aortic Structure in a Mouse Model of Marfan Syndrome Associated Aortic Aneurysm. **C. P. Gibson, M. Farney, D. Gaufin, R. Rahimian, T. Broderick, J. Vallejo-Elias, and M. Esfandiarei.** *Midwestern Univ., and Univ. of the Pacific.*

44 **26.5** Chronic Low-Intensity Exercise Training Prevents BK_{Ca} Channel-Dependent Coronary Vascular Dysfunction in Aortic-Banded Mini-Swine. **T. D. Olver, B. Ferguson, J. Hiemstra, P. Thorne, J. Ivey, M. Cobb, M. Hill, M. H. Laughlin, C. Emter.** *Univ. of Missouri, Columbia.*

Poster Board

45 **26.6** Effect of Glucagon-Like Peptide-1 and Aerobic Exercise on Cardiovascular Function in Goto-Kakizaki Rats. **R. Scalzo, L. Knaub, A. Keller, L. Walker, and J. Reusch.** *Univ. of Colorado, Denver.*

46 **26.7** Reduction of Arterial Stiffness by Aerobic Exercise Training is Associated with Endothelial Nitric Oxide Synthase Activation Via Increasing Arterial Adropin Levels in Type 2 Diabetic Rats. **S. Fujie, N. Hasegawa, N. Horii, K. Sato, and M. Iemitsu.** *Ritsumeikan Univ., Shiga, Japan Soc. for the Promotion of Sci., Tokyo, and Kobe Univ., Japan.*

47 **26.8** Evidence of Legacy Effects of Three 8-Month Exercise Programs on Cardiometabolic Health: Group-Specific Benefits Observed 10 Years Later. **J. Johnson, C. Slentz, and W. Kraus.** *Duke Univ. Med. Ctr.*

48 **26.9** Recruiting for Large Exercise Studies: Efficiency of Different Recruiting Strategies. **L. Kelly, C. Slentz, L. Bateman, J. Johnson, L. Willis, and W. Kraus.** *Duke Univ. Med. Ctr.*

49 **26.10** Left Ventricle Transcriptomic Analysis Reveals Connective Tissue Accumulation Associates with the Initial Age-Dependent Decline in VO_{2peak} from Its Lifetime Apex. **F. Booth, G. Ruegsegger, and R. Toedebusch.** *Univ. of Missouri, Columbia.*

50 **26.11** Associations Between Antioxidant Enzymes in Cardiomyocytes and Skeletal Muscle During Doxorubicin Treatment. **C. L. Jarrett, A. C. D'Lugos, T. Mahmood, R. J. Gonzales, T. M. Hale, C. C. Carroll, J. M. Dickinson, and S. S. Angadi.** *Arizona State Univ., Univ. of Arizona, and Midwestern Univ.*

51 **26.12** Effects of Exercise Amount and Intensity Versus a Combined Exercise and Lifestyle Intervention on Metabolic Syndrome in Adults with Prediabetes: From STRRIDE PD a Randomized Trial. **C. Slentz, L. Willis, L. Bateman, E. Granville, L. Piner, C. Bales, and W. Kraus.** *Duke Univ. Med. Ctr.*

Poster Session II

27.0 BLOOD FLOW REGULATION

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

52 **27.1** Withdrawn.

Poster Session II

28.0 MICROCIRCULATION

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

53 **28.1** Circulating Factors from Patients with T2DM Impair Capillary-Like Network Formation. **R. Landers-Ramos, J. Blumenthal, and S. Prior.** *Univ. of Maryland Sch. of Med. and the Baltimore Vet. Affairs.*

54 **28.2** Mechanisms of Coronary Microcirculation Dysfunction in Heart Failure: What Can We Learn from the Heart's Response to Acute Exercise? **D. Merkus, O. Sorop, S. Bender, I. Heinonen, M. H. Laughlin, and D. Duncker.** *Erasmus MC, Rotterdam, The Netherlands, Univ. of Missouri, Columbia, and Univ. of Turku, Finland.*

55 **28.3** Skeletal Muscle Derived Exosomes Regulate Endothelial Cell Functions by Transferring MiR-130a. **Y. Nie, and T. Gavin** *Purdue Univ.*

Poster Session II

29.0 FATIGUE

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

56 **29.1** Mechanisms for the Age-Related Increase in Power Loss During Fatiguing Dynamic Contractions in Men and Women. **C. W. Sundberg, H. Hassanlouei, A. Kuplic, and S. K. Hunter.** *Marquette Univ.*

57 **29.2** Effects of Acute Digoxin Intake on Skeletal Muscle Na^+,K^+-ATPase Content, Plasma K^+ Regulation and Fatigue During Intense Excise in Healthy Young Adults. **M. McKenna, T. Atanasovska, R. Smith, C. Wong, A. Garnham, A. Petersen, T. Farr, M. Anderson, and H. Krum.** *Victoria Univ., Melbourne, Western Health, Melbourne, Univ. of Melbourne, Baker IDI, Melbourne, and Monash Univ., Melbourne, Australia.*

Don't forget to visit the exhibits during the poster sessions

Poster Session II

30.0 MUSCLE INJURY

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

58 **30.1** Leucine-Enriched Essential Amino Acids Attenuate Inflammation and Enhance Muscle Repair After Eccentric Contraction in Rat. **H. Kato, K. Miura, T. Takeda, Y. Inoue, S. Nakano, K. Suzuki, and M. Bannai.** *Ajinomoto Co., Inc., Kawasaki, Japan.*

59 **30.2** Pathological Lipid Accumulation After Skeletal Muscle Injury. **J. Gumucio, B. McDonagh, and C. Mendias.** *Univ. of Michigan, and Univ. of Liverpool, UK.*

60 **30.3** Massage-Induced Changes in Membrane Permeability are Associated with Elevated Satellite Cells and MURF-1 Protein. **E. Hunt, A. Hayek, A. Confides, S. Abshire, T. Butterfield, and E. Dupont-Versteegden.** *Univ. of Kentucky, Lexington.*

61 **30.4** Circulating mMiRNAs as Early Biomarkers of Skeletal Muscle Denervation in Rats. **N. Koulmann, J. Siracusa, C. Chapus, S. Bourdon, M-E. Goriot, and S. Banzet.** *Inst. de Res. Biomed. des Armees, Bretigny Sur Orge, and Clamart, Ecole, du Valde Grâce, Paris, and U1197 INSERM, Clamart, France.*

62 **30.5** Early Inflammatory Chemokines and Markers in Muscle Injury. **G. Le, H. G. Johnson, M. Jergenson, M. Lenz, G. Warren, and D. Lowe.** *Univ. of Minnesota, and Georgia State Univ.*

Poster Session II

31.0 EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

63 **31.1** Sex-Based Differences in Tendon Structure and Function. **D. Sarver, K. Sugg, Y. A. Kharaz, J. Gumucio, E. Comerford, and C. Mendias.** *Univ. of Michigan, and Univ. of Liverpool, UK.*

64 **31.2** Effect of Acetaminophen Consumption and Resistance Exercise on Extracellular Matrix Gene Expression in Human Skeletal Muscle. **S. H. Patel, A. C. D'Lugos, E. R. Eldon, J. M. Dickinson, and C. C. Carroll.** *Purdue Univ., Arizona State Univ., and Midwestern Univ.*

Poster Session II

32.0 IMMUNOLOGY AND INFLAMMATION

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

65 **32.1** T Cell Activation and Proliferation Following Acute Exercise in Human Subjects Is Altered by Storage Conditions and Mitogen Selection. **J. Siedlik, J. Deckert, S. Benedict, A. Bhatta, A. Dunbar, J. Vardiman, and P. Gallagher.** *Creighton Univ., Univ. of Kansas, and Kansas State Univ.*

66 **32.2** Acute Interval Exercise Decreases Monocyte and Neutrophil Interleukin-6 Receptor Alpha in Healthy Older Adults and in Individuals with Type 2 Diabetes. **C. Durrer, M. Francois, H. Neudorf, and J. Little.** *Univ. of British Columbia, Kelowana, Canada.*

67 **32.3** Endurance Exercise Training Decreases mRNA Expression of Inflammatory Genes in Peripheral Blood Mononuclear Cells in Overweight and Obese Adults. **H. S. Jawanda, D. W. Van Pelt, L. M. Guth, and J. F. Horowitz.** *Univ. of Michigan.*

68 **32.4** Short-Term High-Intensity Interval Training and Moderate-Intensity Continuous Training Alter Chemokine Receptor Expression in Overweight/obese Adults. **J. Barry, C. Durrer, S. Simtchouk, M. Jung, and J. Little.** *Univ. of British Columbia, Kelowana, Canada.*

69 **32.5** The Influence of Physical Activity and Monocyte Phenotype on Circulating Platelet-Monocyte Complexes in Overweight/Obese Persons. **M. Levitt, C. Glass, C. Haston, A. Anzalone, S. Turner, M. Flynn, and M. Phillips.** *Texas Christian Univ., Fort Worth, and Coll. of Charleston, SC.*

70 **32.6** Neutrophil Functional Changes are Associated with Metabolic Alterations Following Ten Weeks of High Intensity Interval Exercise Training in Men and Women with Prediabetes. **D. Bartlett, C. Slentz, L. Willis, K. Huffman, W. Kraus, and J. Lord.** *Duke Univ., and Univ. of Birmingham, UK.*

71 **32.7** Association of the Composite Inflammatory Biomarker, Glyca, with Exercise-Induced Changes in Body Habitus in Men and Women with Prediabetes. **D. Bartlett, C.**

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Slentz, M. Connelly, L. Piner, L. Willis, L. Bateman, E. Granville, C. Bales, K. Huffman, and W. Kraus. *Duke Univ., Lab. Corp. of America Holdings, Raleigh, NC, and Univ. of North Carolina.*

72 **32.8** Aspirin as a COX Inhibitor and Anti-Inflammatory Drug in Human Skeletal Muscle. **T. Trappe, S. Ratchford, K. Lavin, R. Perkins, B. Jemiolo, and S. Trappe.** *Ball State Univ.*

73 **32.9** Exercise Training Reverses the Accumulation of Marrow Adipose Tissue and Pro-Inflammatory Cytokines Following Diet-Induced Obesity. **R. Emmons, A. Kriska, H. Chen, and M. De Lisio.** *Univ. of Illinois at Urbana-Champaign.*

74 **32.10** A Comparison of Cold Water Immersion and Active Recovery on Inflammation and Cell Stress Responses in Human Skeletal Muscle After Resistance Exercise. **J. Markworth, J. Peake, L. Roberts, V. Figueiredo, I. Egner, S. Krog, S. Aas, K. Suzuki, J. Coombes, D. Cameron-Smith, and T. Raastad.** *Univ. of Auckland, New Zealand, Queensland Univ. of Tech., Queensland Acd. of Sport, Univ. of Queensland, Brisbane, Australia, Univ. of Oslo, Norwegian Sch. of Sport Sci., Oslo, Norway, and Waseda Univ., Saitama, Japan.*

75 **32.11** Menopausal Status Impairs Transient Inflammatory Recovery After Acute Hypertrophic Resistance Exercise. **C. Axelrod, E. Kullman, K. Sparks, and K. Little.** *Cleveland State Univ.*

76 **32.12** Doxorubicin Attenuates Proinflammatory Mediator Expression in Brain and Pial Arteries from Ovariectomized Female Rats Following High Intensity Exercise. **N. Vijayavel, P. Raman, M. So, J. Dickinson, C. Carroll, S. Angadi, and R. Gonzales.** *Univ. of Arizona, Midwestern Univ., and Arizona State Univ.*

Poster Session II

33.0 STEMS CELLS AND REGENERATION

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

77 **33.1** Bed Rest for 5-Days Is Accompanied by Robust Satellite Cell Depletion in Skeletal Muscle of Older Adults. **A. McKenzie, P. Reidy, D. Nelson, K. Barrows, P. Brun-**

Poster Board

ker, P. LaStayo, and M. Drummond. *Univ. of Utah.*

78 **33.2** Cycle Training Alters Satellite Cell and Transcriptional Responses to a Bout of Resistance Exercise. **K. Murach, G. Walton, C. Fry, S. Michaelis, J. Groshong, B. Finlin, P. Kern, and C. Peterson.** *Univ. of Kentucky, and Univ. of Texas Med. Branch.*

79 **33.3** Skeletal Muscle Pericytes Transition to a Mesenchymal Stromal Cell Phenotype Following an Acute Bout of Electrical Stimulation. **S. Dvoretskiy, K. Garg, M. Munroe, Y. Pincu, Z. Mahmassani, and M. Boppart.** *Univ. of Illinois at Urbana-Champaign.*

Poster Session II

34.0 PHYSICAL INACTIVITY AND CHRONIC DISEASE

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

80 **34.1** Breaking Up Prolonged Sitting Alters the Postprandial Plasma Lipidomic Profile in Adults with Type 2 Diabetes. **M. Grace, P. Dempsey, J. Weir, N. Mellett, P. Sethi, P. Mundra, N. Owen, D. Dunstan, P. Meikle, and B. Kingwell.** *Baker IDI Heart & Diabetes Inst., Melbourne, Australia.*

81 **34.2** Induced Urinary Bladder Distension and Physical Activity Patterns in Mice. **R. Bowen, B. Cates, B. Dillard, B. Foster, S. Patterson, and T. Spivey.** *Truett McConnell Univ., Cleveland, GA.*

82 **34.3** Physical Inactivity May Decreases Insulin Sensitivity Through the Accumulation of Intramyocellular Diacylglycerol, and it is Further Facilitated by High Fat Diet. **S. Kakehi, Y. Tamura, R. Kawamori, and H. Watada.** *Juntendo Univ., Tokyo, Japan.*

83 **34.4** Examination of Physical Activity and Family History of Type 2 Diabetes on Serum FGF21. **G. Davis, J. Guillory, T. Deville, D. Bellar, and A. Nelson.** *Univ. of Louisiana at Lafayette, Louisiana Tech Univ., Ruston, and Louisiana State Univ., Baton Rouge.*

84 **34.5** Withdrawn.

85 **34.6** Breaking Sitting with Light Activities Versus Structured Exercise: Benefits for Glycemic Control and Insulin Sensitivity in Type 2 Diabetes. **B. M. F. M. Duvivier, N.**

Poster Board

C. Schaper, M. K. C. Hesselink, L. van Kan, N. Stienen, B. Winkens, A. Koster, and H. H. C. M. Savelberg. *Maastricht Univ. Med. Ctr., The Netherlands.*

86 **34.7** Intrinsic High Aerobic Capacity is Associated with Protection of Mitochondrial Respiratory Capacity and Decreased Inflammation Following Chronic High-Fat/High-Cholesterol Diet Challenge. **E. M. Morris, C. McCoin, L. Koch, S. Britton, and J. Thyfault.** *Univ. of Kansas Med. Ctr., Univ. of Michigan, and Kansas City VA Med. Ctr.*

87 **34.8** Effect of a Novel Workstation Device on Increasing Metabolic Rate. **C. Horswill, H. Scott, and D. Voorhees.** *Univ. of Illinois at Chicago.*

88 **34.9** Brain Serotoninergic System has an Essential Role in Regulating Physical Inactivity in Rats. **S. Yanagita, N. Kubota, M. Umezawa, and K. Takeda.** *Tokyo Univ. of Sci., Japan.*

89 **34.10** Skeletal Muscle Autophagy and Mitophagy in Endurance-Trained Runners, and in Response to a High-Fat Meal. **M. D. Tarpey, R. P. McMillan, S. Bowser, T. M. Halliday, N. E. Boutagy, K. P. Davy, M. I. Frisard, and M. W. Hulver.** *Virginia Tech.*

Poster Session II

35.0 AGING

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

90 **35.1** Withdrawn.

91 **35.2** Effects of Endurance and Resistance Exercise on Bone Turnover in Premenopausal Women Undergoing Ovarian Hormone Suppression. **S. Wherry, P. Wolfe, E. Gibbons, R. Boxer, and W. Kohrt.** *Univ. of Colorado, Aurora,*

92 **35.3** Endurance Exercise Promotes Telomere Transcription. **L. Deldicque, A. Diman, J. Boros, F. Poulain, J. Rodriguez, M. Purnelle, H. Episkopou, L. Bertrand, M. Francaux, and A. Decottignies.** *Univ. Catholique de Louvain, Belguim.*

93 **35.4** The Relationship Between Cognitive Function, Heart Rate Variability, Insulin and Ghrelin in Older Adults: A Pilot Study. **D. Bellar, E. Glickman, and J. Gunstad.** *Univ. of Louisiana at Lafayette, and Kent State Univ.*

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94	**35.5**	Effect of Lifelong Exercise-Training on Mitochondrial Quality Control Mechanisms in Aged Human Muscle. **J. F. Halling, H. Møller, P. Plomgaard, B. Regenberg, and H. Pilegaard.** *Univ. of Copenhagen, and Rigshospitalet, Copenhagen, Denmark.*
95	**35.6**	Sestrin, a Novel Target in the mTOR Pathway That Extends Healthspan and Mobility. **A. Sujkowski, M. Kim, B. Kim, J-H. Lee, and R. Wessells.** *Wayne State Univ., and Univ. of Michigan.*
96	**35.7**	Metabolic Changes Underpinning Aging Flight Muscles in the Hawk Moth, *Manduca sexta*. **B. Wone, E. R. Kaup, J. M. Kinchen, and B. W. M. Wone.** *Univ. of South Dakota, and Metabolon Inc., Durham, NC.*
97	**35.8**	Protein Translational Responses to Healthspan-Extending Treatments in Skeletal Muscle. **C. Wolff, C. Wilusz, A. Schenkel, F. Peelor, B. Miller, and K. Hamilton.** *Colorado State Univ., Fort Collins.*
98	**35.9**	Age-Related Responses to Hindlimb Unloading and Re-Ambulation Result in Divergent Skeletal Muscle Macrophage Polarization Patterns as Determined by Flow Cytometry. **P. Reidy, D. Nelson, A. Mckenzie, C. Lindsay, J. Gardner, A. Keefe, G. Kardon, T. Huffaker, R. O'Connell, and M. Drummond.** *Univ. of Utah.*
99	**35.10**	PGC-1α and P53 Interaction: The Impact of Age and Lifelong Exercise Training. **M. Munk Nielsen, S. Ringholm, and H. Pilegaard** *Univ. of Copenhagen, Denmark.*
100	**35.11**	The Aging Athlete: DNA Content in Slow- and Fast-Twitch Skeletal Muscle Fibers. **G. Begue, U. Raue, B. Jemiolo, K. Minchev, H. Finch, T.Trappe, and S. Trappe.** *Ball State Univ.*
101	**35.12**	The Aging Athlete: General Health and Exercise Profile. **A. Voss, K. Gries, U. Raue, B. Graham, L. Kaminsky, H. Finch, T. Trappe, and S. Trappe.** *Ball State Univ.*
102	**35.13**	Effect of Age on Muscle Sympathetic Nerve Traffic During Dynamic and Static Exercise. **C. Notarius, P. Millar, C. Doherty, A. Incognito, N. Haruki, E. O'Donnell, and J. Floras.** *UHN and Mount Sinai Hosp., Toronto, Univ. of Toronto, and Univ. of Guelph, Canada.*
103	**35.14**	The Aging Athlete: Circulating Inflammatory Regulators of Skeletal Muscle Health. **R. Perkins, K. Lavin, T. Burnett, U. Raue, T. Trappe, and S. Trappe.** *Ball State Univ.*
104	**35.15**	The Aging Athlete: Single Muscle Fiber Size and Contractile Function. **G. Grosicki, K. Minchev, U. Raue, H. Finch, T. Trappe, and S.Trappe.** *Ball State Univ.*
105	**35.16**	The Aging Athlete: Cardiovascular Fitness with Exercise Intensity. **K. Gries, A. Voss, B. Overstreet, B. Graham, L. Kaminsky, H. Finch, T. Trappe, U. Raue, and S. Trappe.** *Ball State Univ.*
106	**35.17**	The Aging Athlete: Whole Muscle Size and Function. **T. Burnett, U. Raue, G. Lee, H. Finch, T. Trappe, and S. Trappe.** *Ball State Univ.*
107	**35.18**	Mitochondrial Proteins in Human Skeletal Muscle: The Effect of Aging and 12 Weeks High-Intensity Interval Training in Aged Individuals. **V. Wyckelsma, L. Formosa, M. Ryan, I. Levinger, M. McKenna, and R. Murphy.** *Victoria Univ., Melbourne, La Trobe Univ., Bundoora, and Monash Univ., Melbourne, Australia.*
108	**35.19**	Resistance Training Prevents Aging-Induced Muscle Fibrosis in Mice. **N. Horii, S. Fujie, N. Hasegawa, M. Uchida, T. Hashimoto, E. Oyanagi, H. Yano, and M. Iemitsu.** *Ritsumeikan Univ., Kusatsu, Japan Soc. for the Promotion of Sci., Tokyo, Natl. Inst. of Hlth. and Nutrition, Tokyo, and Kawasaki Univ. of Med. Welfare, Okayama, Japan.*
109	**35.20**	Effect of Resistance Exercise Training on Amino Acid Sensing and Anabolic Resistance in Older Adults. **T. Moro, R. R. Deer, T. G. Graber, E. Volpi, B. B. Rasmussen.** *Univ. of Texas Med. Branch, Galveston.*
110	**35.21**	Dysregulation of Circulating microRNA Expression After Resistance Exercise in Older Men Associated with Anabolic Resistance. **D. Rivas, L. Margolis, S. Lessard, Y. Ezzyat, and R. Fielding.** *Tufts Univ. and Joslin Diabetes Ctr.*

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111 **35.22** Mitophagy Flux with Aging and Chronic Exercise in Skeletal Muscle. **H. Carter, D. Zarrin-Khat, Y. Kim, A. Erlich, and D. Hood.** *York Univ., Toronto, Canada.*

Poster Session II

39.0 LATE-BREAKING ABSTRACTS

Fri., 1:00—3:00 PM, Atrium Lobby.

Poster Board

112 **39.1** Exercise Increases Resting-state Brain Activity in Parkinson's Disease. **K. H. Wood, N. A. Kelly, J. B. Allendorf, M. P. Ford, C. S. Bickel, J. Marstrander, A. W. Amara, T. Anthony, M. M. Bamman, and F. M. Skidmore.** *Univ. of Alabama at Birmingham, and Samford Univ.*

113 **39.2** Acute Mental Stress and its Impact on Systemic Vascular Endothelial Function in Obese Adults. **J. V. Brugniaux, D. Hodson, C. J. Marley, and D. M. Bailey.** *Univ. of South Wales, UK, and Western Sydney Univ., Australia.*

114 **39.3** Metabolic Benefits of Endurance Exercise Training in Pregnancy for Females Born Small on High Fat Diet. **G. D. Wadley, D. Mahizier, K. Anevska, A. J. Jefferies, K. M. Moritz, M. E. Wlodek.** *Deakin Univ., Burwood, Australia, Univ. of Melbourne, Parkville, Australia, and Univ. of Queensland, St. Lucia, Australia.*

115 **39.4** Long-term Cardiac Programming by Short-term Juvenile Exercise Training. **G. D. Wadley, M. E. Wlodek, M. J. Black, A. P. Russell, P. Soeding, and Y. Asif.** *Deakin Univ., Burwood, Australia, Univ. of Melbourne, Parkville, Australia, and Monash Univ., Clayton, Australia.*

116 **39.5** Physiological Responses to Treadmill Running in Trained College Aged and Master Level Female Runners. **L. J. D'Acquisto, R. Perkins, V. Nethery, R. Pritchett, D. D'Acquisto, A. Brown, C. Carriker, S. Liu, and A. Layton.** *Central Washington Univ., Ball State Univ., Good Samaritan Hosp., Sioux Falls, SD, High Point Univ., Univ. of Washington, and Central Oregon Comm. Coll., Bend.*

117 **39.6** Decreased HETE-12 and -15 are Associated with Glucose Regulation Following High Intensity Exercise in People with Prediabetes. **S. K. Malin, C. A. Rynders, J. Y. Weltman, E. J. Barrett, J. Nadler, and A. Weltman.** *Univ. of Virginia, Charlottesville, Univ. of Colorado, Denver, and Eastern Virginia Med. Sch., Norfolk.*

Poster Board

118 **39.7** HIT does not Alleviate Intensified Training-induced Reductions in Muscle Cytokine Response to Acute Exercise. **M. A. Cardenas, M. Levitt, M. D. Phillips, B. Burgess, and C. Haston.** *Texas Christian Univ. Fort Worth.*

119 **39.8** Energy Substrate Oxidation During Cycling and Running in the Cold and Heat. **D. D. Gagnon, L. Perrier, M. Laurence, S. Dorman, C. Lariviere, and O. Serresse.** *Laurentian Univ., Sudbury, Canada.*

120 **39.9** Randomized, Four-Arm, Dose-Response Clinical Trial to Optimize Resistance Exercise Training for Older Adults with Age-Related Muscle Atrophy. **B. M. Roberts, M. J. Stec, A. Thalacker-Mercer, D. L. Mayhew, N. A. Kelly, S. C. Tuggle, E. K. Merritt, C. J. Brown, S. T. Windham, L. J. Dell'Italia, C. S. Bickel, K. M. Vaughn, I. Isakova-Donahue, G. Many, and M. M. Bamman.** *Univ. of Alabama at Birmingham, and Vet. Affairs Med. Ctr., Birmingham, AL.*

121 **39.10** Adverse Ultrastructural Remodeling and Mitochondrial Dysfunction of Skeletal Muscle in Heart Failure. **M. Rogowski, P. Powell, L. Fu, J. Collawn, M. M. Bamman, and L. J. Dell'Italia.** *Univ. of Alabama at Birmingham.*

122 **39.11** Mitochondrial Protein Content is Enhanced by Lifelong Physical Activity. **S. Joanisse, R. Pollock, K. O'Brien, N. R. Lazarus, K. Smith, D. J. Wilkinson, B. E. Phillips, S. D. R. Harridge, P. J. Atherton, and A. Philp.** *Univ. of Birmingham, UK, Kings Coll., London, UK, Univ. of Nottingham, UK.*

123 **39.12** Effects of Heightened Inflammation on Arginine Transporters and Metabolic Enzyme Expression in Differentiated Primary Human Progenitor Cells. **A. Thalacker-Mercer, J. Blum, H. Roman, E. Riddle, and D. Gupta.** *Cornell Univ.*

124 **39.13** Skeletal Muscle Phenotypes in Mkx-Null Mice. **T. Akimoto, Y. Kano, K. Na-**

kamura, S. Miyaki, H. Asahara, and T. Ushida. *Waseda Univ., Japan, Univ. of Tokyo, Japan, Univ. of Electro-Communications, Japan, Hiroshima Univ. Hosp., Japan, and Tokyo Med. and Dental Univ., Japan.*

Symposia VIII

36.0 BRAINS, BLOOD VESSELS, AND HEARTS: CAN EXERCISE TREAT THE MOLECULAR MECHANISMS UNDERLYING CARDIOVASCULAR DISEASE?

Fri., 3:00—5:15 PM, Regency AB.

Chair: **Craig Emter,** *Univ. of Missouri, Columbia.*

3:00 PM **36.1** Utilizing Exercise to Treat the Cardiomyocyte. **Tim Domeier.** *Univ. of Missouri, Columbia.*

3:30 PM **36.2** Mechanisms of Coronary Microcirculation Dysfunction in Heart Failure: What can we Learn from the Heart's Response to Acute Exercise? **Daphne Merkus.** *Erasmus MC, Rotterdan, The Netherlands.*

4:00 PM **36.3** Exercise and Stem Cells in the Heart. **Joseph Libonati.** *Univ. of Pennsylvania.*

4:30 PM **36.4** Connecting the Brain to the Heart: Cardiogenic Dementia and Exercise Therapy. **T. Dylan Olver.** *Univ. of Missouri, Columbia.*

Symposia IX

37.0 EXERCISE AND AGING: RESPONSIVENESS OF SKELETAL MUSCLE TO EXERCISE TRAINING AS A FUNCTION OF AGE

Fri., 3:00—5:15 PM, Regency CD.

Chair: **Sue Bodine,** *Univ. of California, Davis.*

3:00 PM **37.1** Impact of Voluntary Exercise on Frailty in Old Mice. **LaDora Thompson.** *Univ. of Minnesota, Minneapolis.*

3:30 PM **37.2** Novel Roles for Satellite Cells in Muscle Hypertrophy and Aging. **Charlotte Peterson.** *Univ. of Kentucky, Lexington.*

4:00 PM **37.3** Metabolic and Molecular Networks of Human Adaptation to Exercise and Age. **Philip Atherton.** *Univ. of Nottingham, UK.*

4:30 PM **37.4** Exerciser is Regenerative Medicine: Optimizing the Dose to Combat Aging Muscle Atrophy. **Marcus Bamman.** *Univ. of Alabama at Birmingham.*

Plenary Lecture

38.0 PLENARY LECTURE

Fri., 8:00—9:00 PM. Regency CD.

8:00 PM **38.1** Sensorimotor Training of Spinal Networks to Restore Function in Spinal Cord Injured Patients. **Reggie Edgerton.** *Univ. of California, Los Angeles.*

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2016 APS Intersociety Meeting
The Integrative Biology of Exercise VII

Abstracts of Invited and Contributed Presentations

1.0 TOWARD DECIPHERING THE EXERCISE RESPONSE

1.2
INFLUENCE OF EXERCISE AND CIRCADIAN BIO-MARKERS ON MULTI-OMIC INTEGRATED NET-WORKS IN CHILDREN

Eric P. Hoffman[1], Heather Gordish-Dressman[2], Rebecca Place[3], and Paul Visich[3].
[1]Sch. of Pharmacy, Binghamton Univ., SUNY, [2]Ctr. for Genetic Med., Children's Natl. Med. Ctr., [3]Dept. of Exercise and Sport Performance, Univ. of New England.

The transition to a Western lifestyle is associated with increased incidence of chronic inflammatory states and associated health concerns, including asthma, allergic disease, metabolic syndrome and type 2 diabetes in both children and adults. There are strong associations with diet, obesity and physical activity with this increased chronic inflammatory disease burden. Preventive interventions targeting diet, obesity and physical activity in children show a significant effect, but effect sizes at reversing disease burden can be viewed as unsatisfying compared to success of other interventions to common childhood morbidities (e.g. immunizations or injury prevention). Here, we present a hormonal/biological model for the increased pro-inflammatory states in children – namely the blunting of diurnal cortisol rhythms due to reduction in environmental and physiological cues. This model follows from a series of *in vitro* studies where we show that the pro-inflammatory state in airway epithelial cells is dependent on diurnal cortisol levels. The model discussed, with data supporting this model, is that current lifestyles systematically remove night/day cues that would otherwise serve to bolster the strength of diurnal cortisol rhythms – decreasing exposure to sunlight, decreasing physical activity, and diet provide inadequate feedback to keep strong diurnal cortisol rhythms. As a result, cortisol peaks become blunted, and, as we have shown in published data, cells become increasingly pro-inflammatory due to poor synchronization of mitotic and regenerative cycles. In preliminary data, we describe results from a population-based study of children that validates this model (n=689 Southern Maine 4th and 5th graders; 8,298 salivary samples and cortisol measures). We show that increased BMI is associated with decreased morning cortisol (test cohort n=474 children $p<0.001$; validation cohort n=448 children $p<0.001$). Further, pilot studies of the pediatric salivary proteome using somaSCAN profiling has identified pro-inflammatory pharmacodynamic biomarkers of prednisone that are also diurnal pro-inflammatory biomarkers in Maine school children. These population-based findings, couple with our published *in vitro* studies of asthmatic and non-asthmatic airway epithelial cells, provide compelling data supportive of a 'diurnal health' model to explain the increased disease burden associated with the modern lifestyle.

1.3
GUT MICROBIOTA TO BRAIN SIGNALING IN EXERCISE-INDUCED STRESS ROBUSTNESS

Monika Fleshner, PhD
Dept. of Integrative Physiology and the Ctr. for Neuroscience, Univ. of Colorado at Boulder.

Regular physical activity positively impacts mental and physical health. The benefits of physical activity are often revealed in the face of challenge, including mental/physical stressors. Evidence suggests that physical activity status is an important determinant of stress robustness. Organisms that are stress robust can endure more intense and prolonged stressors before suffering negative health consequences; and they recover more quickly from those challenges. To better understand the mechanisms of stress robustness using a preclinical model, we varied physical activity status by housing juvenile or adult rats (inbred and outbred strains) with access to either a mobile or locked running wheel in their home cages. After 3-6 weeks, rats housed with mobile running wheels display physical changes indicative of improved fitness, including increased endurance when tested on the treadmill, reduced abdominal adiposity when fed a high fat diet, increased lean body mass, changes in muscle citrate synthase etc. Most importantly for our work, however, is that physically active compared to sedentary rats have reduced adipose inflammation, no antibody suppression, no anxiety-like or depressive-like behaviors, and faster diurnal rhythm and sleep disturbance recovery, after exposure to an acute intense stressor (100, 1.5mA, 5-s tailshocks). Using this paradigm, we exploited the differences in stress robustness to reveal unique adaptations in stress responsive neurocircuitry that were necessary and sufficient for specific outcomes, including adaptations in serotonergic dorsal raphe neuronal responses responsible for anxiety-like and depressive like behaviors, and central sympathetic drive associated with immunomodulation. Our current work extends our assessment of adaptations produced by exercise to include commensal intestinal microbes (gut microbiota). The gut microbiota contributes to many aspects of host physiology. Changes in the gut microbiota early in development, for example, can impact host metabolism, immune function, and behavior that persist across the lifespan. In addition, the developing microbial ecosystem is more sensitive to change. We will present new evidence that physical activity 1) changes the gut microbial structure favoring a lean-promoting composition; 2) increases the abundance of beneficial microbial species; 3) increases butyrate-producing bacteria and butyrate, a short chain fatty acid implicated in metabolism and epigenetic processes. These effects are greater when running is initiated in adolescence compared to adulthood. Thus early life presents a window of opportunity for producing adaptive changes in microbial composition that may contribute to some of the enduring positive impacts of exercise on mental and physical health. References: Mika, A and Fleshner, M. Early life exercise may promote lasting brain and metabolic health through gut bacterial metabolites. *Immunology and Cell Biology, (*2016) doi:10.1038/icb.2015.113. Mika, A; Van Treuren, W; González, A; Herrera, AJ; Knight, R; Fleshner, M. Exercise is more effective at altering gut microbial composition and producing stable changes in lean mass in juvenile versus adult male F344 rats. *PlosONE,* 10 (2015) 10.1371/journal.pone.0125889.

1.4
EXERCISE-REGULATED PHOSPHOPROTEOME REVEALS NEW AMPK SUB-STRATES AND SIGNALING PATHWAYS

David James[1]
[1]Charles Perkins Ctr., Univ. of Sydney, D17, Sydney, 2006, Australia.

Exercise is essential in regulating energy metabolism and whole body insulin sensitivity. To explore the exercise signaling network we undertook a global analysis of exercise-induced changes in protein phosphorylation in human skeletal muscle biopsies revealing 1,004 unique exercise-regulated phosphosites on 562 proteins. These included substrates of known exercise-regulated kinases (AMPK, PKA, CaMK, MAPK, mTOR), yet the majority of phosphorylation sites have not previously been implicated in exercise signal transduction. Given the importance of AMPK in exercise metabolism we performed a targeted *in vitro* AMPK screen and employed a machine learning approach to predict exercise-regulated AMPK substrates. We identified eight highly predicted AMPK substrates including AKAP1, STIM1 and VAPA. Functional characterization revealed a previously undescribed role for AMPK-dependent phosphorylation of AKAP1 in mitochondrial respiration. These data expose the unexplored complexity of exercise signaling and provide new insights into the role of AMPK in mitochondrial biochemistry.

2.0 EXERCISE TRIGGERS ADAPTIVE BRAIN CELL STRESS RESPONSES

2.1
EXERCISE PROTECTS THE BRAIN AGAINST ALZHEIMER'S DEMENTIA AND SLEEP DEPRIVATION

Karim Alkadhi[1]
[1]PPS-Pharmacology, Univ. of Houston, 3455 Cullen Blvd., 521 Science Res. 2 Bldg., Coll. of Pharmacy, Houston, TX, 77204.

Healthy diet and physical activity have emerged as promising low-cost measures for protection against a variety of brain disorders including Alzheimer's disease. We have examined the effect of moderate regular treadmill exercise on rat models of Alzheimer's disease (AD), REM sleep deprivation (SD) and posttraumatic stress disorder (PTSD). The AD model (icv infusion of β-amyloid), SD model (modified multiple platform) and PTSD (single prolonged stress) showed profound negative effects on learning and memory when tested in the radial arm water maze. At the cellular level, electrophysiological recording from area CA1 and dentate gyrus of the hippocampus revealed marked impairment of early long-term potentiation (E-LTP) as well as late long-term potentiation (L-LTP), which are considered to be cellular correlates of learning and memory. At the subcellular level, AD and SD caused marked decrease in the levels of signaling molecules essential for memory including CaMKII, CaMKIV, BDNF and CREB. In all of the models, prior regular treadmill exercise prevented the negative effects of these disorders. References: Dao AT, Zagaar MA, Alkadhi KA. Moderate Treadmill Exercise Protects Synaptic Plasticity of the Dentate Gyrus and Related Signaling Cascade in a Rat Model of Alzheimer's disease. Mol Neurobiol. 52:1067-1076, 2015. Zagaar Munder, An Dao, Amber Levine, Ibrahim Alhaider, Samina Salim, Karim Alkadhi. Regular treadmill exercise prevents sleep deprivation-induced disruption of synaptic plasticity and associated signaling cascade in the dentate gyrus. Mol. Cell. Neuroscience. 56:375-383, 2013. Patki G, Li L, Allam F, Solanki N, Dao AT, Alkadhi K, Salim S. Moderate treadmill exercise rescues anxiety and depression-like behavior as well as memory impairment in a rat model of posttraumatic stress disorder. Physiol Behav. 130:47-53, 2014.

2.2
EXERCISE AND BRAIN PLASTICITY

Henriette van Praag[1]
[1]Lab. of Neurosciences, NIA/NIH, Biomedical Research Ctr., 251 Bayview Blvd., Ste. 100, Baltimore, MD, 21224.

Human and animal research indicates that exercise benefits brain function and may delay the onset of neurodegenerative disease. In rodents, running improves synaptic plasticity as well as spatial and contextual memory. Research into mechanisms underlying effects of running on cognition has mainly focused on changes in neurotransmitters, neurotrophins, spine density, and adult neurogenesis in the hippocampus, a brain area important for learning and memory. However, the peripheral triggers of the central cellular and molecular cascades that lead to improved memory function have remained unclear. Indeed, the possibility that skeletal muscle activation underlies cognitive effects of aerobic activity has been sparsely explored. This has become particularly relevant with the identification of muscle fiber contractile and metabolic genes. These can be activated by exercise, pharmacological agents, and overexpression of selected transcription factors, resulting in enhanced running endurance. We have begun to investigate how factors produced by muscle during running, affect brain function. Our work evaluating the relationship between myokines and adult hippocampal neurogenesis, neurotrophin levels aims to further our understanding of effects of exercise on brain function. Support: National Institute on Aging, Intramural Research Program. Reference: Moon HY, Becke A, Berron D, Becker B, Sah N, Benoni G, Janke E, Lubejko ST, Greig NH, Mattison JA, Duzel E and van Praag H. Running-Induced Systemic Cathepsin B Secretion Is Associated with Memory Function. Cell Metabolism 24, 1-9, 2016.

2.3
EXERCISE AND ENDOCANNABINOID SIGNALING IN HUMANS

David Raichlen[1]
[1]Sch. of Anthropology, Univ. of Arizona, 1009 E. S. Campus Dr., Tucson, AZ, 85721.

Recent work suggests that physical activity has several beneficial effects on the human brain. Specifically, aerobic activity elevates mood and improves cognition across the lifespan. We suggest that these effects may be adaptations to an evolutionary history that included a shift to a highly aerobic hunting and gathering lifestyle nearly 2 million years ago. Endocannabinoids (eCBs) are endogenous neurotransmitters that appear to play a role in generating these neurobiological effects, and here, we explore the question of whether exercise-induced eCB signaling is a product of our evolutionary history as aerobic athletes. To begin testing this evolutionary hypothesis, we review data showing that exercise-induced eCB signaling is shared by taxa that are adapted to high levels of aerobic physical activity. For example, in humans and dogs, another mammal that evolved to run long distances, moderate intensity aerobic activity significantly increases circulating eCBs. However, in ferrets, a mammal with-

out a highly aerobically active evolutionary history, aerobic exercise has no effect on plasma eCBs. This example of a possible evolutionary convergence suggests that exercise-induced eCB signaling may be an adaptation for endurance athletic performance. We examine two adaptive hypotheses for this evolutionary linkage. First, it is possible that selection linked eCBs with exercise to reward, motivate, and improve performance over long periods of exercise. Enhancing mood through eCB signaling may provide a motivation to engage in a behavior that is otherwise energetically taxing and physically fatiguing. Second, exercise-induced eCB activity may have evolved to improve foraging success through cognitive enhancements during long distance bouts (e.g., enhanced spatial memory). While more work is needed, we believe that adding an evolutionary context to our understanding of the effects of exercise on the brain can improve health interventions as well as inform basic research into exercise physiology. For example, species-level differences in evolutionary history should be taken into account when using animal models to study exercise physiology. Support: NSF BCS-0820270. Reference: Raichlen, D.A., Foster, A.D., Gerdeman, G.L., Seillier, A., Giuffrida, A. (2012) Wired to run: Exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the runner's high. *Journal of Experimental Biology*. 215:1331-1336.

2.4
VISCERAL FAT HIJACKS THE IMMUNE SYSTEM TO INTERFERE WITH MEMORY AND COGNITION

Alexis Stranahan[1]
[1]Neuroscience, Med. Coll. of Georgia, 1120 15th St., CA 3009, Augusta, GA, 30912.

Visceral obesity is accompanied by peripheral inflammation and promotes vulnerability to age-related cognitive impairment in human studies. Resident microglia represent the first line of defense against inflammation in the central nervous system (CNS). While CNS exposure to peripheral inflammation is normally limited by the blood-brain barrier (BBB), obesity breaks down the BBB, exposing microglia to circulating inflammatory cytokines. Microglia regulate neuronal function by releasing signals that support or suppress synaptic transmission, and by physically interposing their processes at the synapse. Previous work from my lab indicates that microglial internalization of synaptic terminals contributes to cognitive dysfunction in obesity, and in followup studies, we have tracked pro-inflammatory cytokines from visceral fat into the brain. Findings from these experiments indicate that microglial detection of peripheral cytokines promotes synaptic internalization or 'stripping' in obesity. Suppression of visceral adipose inflammation rescues cognition in obese mice, and transplantation of visceral fat from an obese donor impairs cognition in lean recipients. Synaptic loss and cognitive deficits were eliminated by blocking microglial responses to inflammatory cytokines, suggesting that visceral fat uses the immune system to interfere with memory and cognition. (NIH K01DK100616) REFERENCES: Hao S, Dey A, Yu X, Stranahan AM (2016) Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. Brain, Behavior, and Immunity, 51, 230-239.

3.0 SUBSTRATE CONTROL DURING EXERCISE: NOVEL INSIGHTS FOR HALTING THE PATHOGENESIS OF METABOLIC DISEASES

3.1
CELLULAR ENERGY SENSING AND THE REGULATION OF METABOLISM

Gregory R. Steinberg[1]
Div. of Endocrinology and Metabolism, Dept. of Med., McMaster Univ., 1280 Main St. W., Hamilton, ON, L8N 3Z5, Canada.

The AMP-activated protein kinase (AMPK) is a cellular sensor of energy homeostasis, responding to various physiological, hormonal and nutritional stimuli to balance energy production and substrate availability with consumption. AMPK is activated in numerous tissues including skeletal muscle, liver and adipose tissue by endurance exercise, fasting and cold suggesting it may be a critical integrative switch coordinating metabolic responses. Commonly used medications that lower blood glucose in individuals with type 2 diabetes including, metformin, salsalate and the SGLT2 inhibitor Canagliflozin also activate AMPK. AMPK elicits its effects through phosphorylation of key metabolic substrates that are involved in multiple branches of metabolism. In regards to fatty acid metabolism, AMPK-mediated inhibition of acetyl-CoA carboxylase (ACC) reduces malonyl CoA resulting in increases in fatty acid oxidation and reductions in fatty acid synthesis. AMPK also plays a critical role in regulating mitochondrial quality in skeletal muscle and brown adipose tissue by increasing mitophagy. This presentation will discuss upstream regulators and downstream effectors of the AMPK signaling pathway that are important for maintaining metabolic homeostasis. References: Steinberg and Kemp Physiol Rev 2009; O'Neill et al. PNAS 2011, Hawley et al. Science 2012, Fullerton et al. Nat Med 2013, Bujak et al. Cell Metabolism 2015, Hawley et al. Diabetes 2016, Mottillo et al. Cell Metabolism 2016.

3.2
EXERCISE TRAINING, LIPID DROPLETS AND THE OXIDATIVE PHENOTYPE

Matthijs Hesselink[1]
[1]Human Biology and Human Movement Sci., Maastricht Univ. Med. Ctr., PO Box 616, Maastricht, 6200 MD, Netherlands.

Endurance training promotes the capacity for myocellular storage and oxidation of substrates like glycogen and triacylglycerol. The vast majority of triacylglycerol stored in the muscle is packed in lipid droplets (LD). While conventionally considered as inert storage sites of lipids spilled over from adipose tissue lipolysis, LDs are nowadays viewed as dynamic organelles with a major impact on (muscle) cell physiology. Excess storage of myocellular lipids in the untrained state associates with impeded insulin signaling, this apparently is not the case in the (endurance) trained athlete. In fact, excess myocellular fat storage seems to have a dual face, it can be benign if combined with a high fat oxidative capacity and a balanced presence of the machinery involved in LD synthesis and degradation, but may become deleterious in the absence of dynamic regulation of lipid droplet synthesis and degradation. Using a variety of models,

and an array of microscopy tools, we modulated myocellular LD content and explored characteristics of LDs (number, size, subcellular distribution, interorganelle interaction and lipid droplet composition) under benign and pathogenic conditions. We were particularly interested in the putative role of the LD coat protein PLIN5 in modulation of the LD 'phenotype'. While coating of the droplet with PLIN5 seems to prevent lipotoxicity and lipid-mediated insulin resistance in a physiological model of insulin resistance (prolonged fasting), this protective effect of PLIN5 is not obvious in muscles of patients with type 2 diabetes who also display poor oxidative capacity. This has led us to hypothesize that the protective effect of PLIN5 may require some kind of lipid droplet-mitochondrial interaction. Moreover, we observed that subcellular distribution and size of lipid droplets was markedly different between trained athletes and patients with type 2 diabetes: While trained athletes store their excess muscle fat predominantly in many, small sized lipid droplets, localized in the intermyofibrillar space, in type I muscle fibers, patients with type 2 diabetes predominantly store their fat in fewer but larger lipid droplets, dispersed in the subsarcolemmal region of type II muscle fibers. Characterization of fatty acid chain length and unsaturation in individual lipid droplets did not reveal major differences in lipid composition between athletes and patients with type 2 diabetes.

3.3
PHOSPHATIDYLETHANOLAMINE SYNTHESIS IN REGULATING SKELETAL MUSCLE LIPID CONTENT AND MITOCHONDRIAL FUNCTION: IMPLICATIONS FOR INSULIN ACTION

Clinton Bruce[1], Greg Kowalski[1], and Ahrathy Selathurai[1]
[1]Sch. of Exercise and Nutrition Sciences, Inst. for Physical Activity and Nutrition, 221 Burwood Hwy., Burwood, 3125, Australia.

Accumulation of lipid in skeletal muscle, particularly diacylglycerol (DAG), is believed to cause insulin resistance. DAG is a precursor for phospholipids, thus phospholipid synthesis could play an important role in regulating muscle DAG content. Surprisingly, relatively little is known about the interaction between phospholipid synthesis, DAG content and insulin action in skeletal muscle. To explore this relationship, we determined whether disrupting muscle phospholipid synthesis, specifically phosphatidylethanolamine (PE), would influence muscle DAG content and thereby impact on insulin action. Cre-lox technology was used to disrupt muscle PE synthesis by deleting CTP: phosphorphoethanolamine cytidylyltransferase (ECT), the rate-limiting enzyme in the CDP-ethanolamine pathway which is the major route for PE production in mammals. As expected, eliminating the CDP-ethanolamine pathway in muscle caused marked DAG accumulation and significant alterations in PE content and composition, but these changes did not alter whole-body or skeletal muscle insulin sensitivity, as determined by euglycemic hyperinsulinemic clamp. However, disrupting muscle PE synthesis resulted in a number of surprising and unanticipated effects. The muscle-specific ECT KO mice exhibited smaller muscles that had increased mitochondrial content due to enhanced mitochondrial biogenesis. This was associated with enhanced skeletal muscle oxidative capacity and improved endurance performance. However, when placed on a high fat, high sucrose diet, the increase in muscle oxidative capacity failed to protect the ECT KO mice from developing insulin resistance and glucose intolerance. These findings highlight important, yet unexpected, roles of PE synthetic pathways in regulating muscle function and substrate metabolism. This work was supported by the National Health and Research Council of Australia.

4.0 PLENARY LECTURE

4.1
CROSS-SPECIES GENETICS AND 'OMICS TO MAP NEW PLAYERS IN MITOCHONDRIA AND AGING

Johan Auwerx[1]
[1]Swiss Fed. Inst. of Technology in Lausanne, Ecole Polytechnique Fed. de Lausanne, Lab. of Integrative and Systems Physiology, Lausanne, Switzerland.

Our understanding of genetic mechanisms that define complex traits has been hindered by the difficulty of obtaining comprehensive omics datasets across a broad range of biological "layers". Complete data on the genome of individuals can be readily obtained, but the full complexity of the transcriptome, proteome, metabolome, and phenome have remained largely out of reach. This is, however, beginning to change, with the development of robust multi-layered omics strategies that are pioneered in model organisms. We here profiled the healthspan and lifespan in >80 cohorts of the BXD mouse genetic reference population. Large variability was observed across all omics layers; to understand how these differences stem from genetic variance, we exploited a multilayered set of molecular phenotypes—genomics, transcriptomics, proteomics, and metabolomics. With this multi-omics strategy, large networks of proteins could be analyzed and causal variants identified in proteins involved in determination of lifespan (e.g. *Mrps5, Jmjd3*), hypertension (*Ubp1*) and in mitochondrial metabolism (e.g. *Dhtkd1, Cox7a2l*). These new candidates were then validated using cross-species genetic strategies in *C. elegans*, mouse, and human. Our large-scope multi-omics measurements in mouse populations combined with cross-species validation hence provided us with robust conserved and mechanistically defined pathways that underpin complex traits involved in metabolism and aging. Funding of the EPFL, SNF (310030B-160318), and NIH (R01AG043930) is acknowledged. R. H. Houtkooper, L. Mouchiroud, D. Ryu, N. Moullan, E. Katsyuba, G. Knott, R.W. Williams, J. Auwerx. Mitonuclear protein inbalance as a conserved longevity mechanism. Nature, 2013, 497, 451-457. Y. Wu, E.G. Williams, S. Dubuis, A. Mottis, V. Jovaisaite, S.M. Houten, C.A. Argmann, P. Faridi, W. Wolski, Z. Kutalik, N. Zamboni, J. Auwerx*, R. Aebersold* (*co-corresponding authors). Multilayered genetic and omics dissection of mitochondrial activity in a mouse genetic reference population. Cell, 2014, 158, 1415-1430. E. G. Williams and J. Auwerx. The convergence of systems and reductionist approaches in complex trait analysis. Cell, 2015, 162, 23-32. C. Merkwirth, V. Jovaisaite, J. Durieux, O. Matilainen, S.D. Jordan, P.M. Quiros, K.K. Steffen, E.G. Williams, L. Mouchiroud, S.N. Uhlein, V. Murillo, S.C. Wolff, R.J. Shaw, J. Auwerx*, A. Dillin* (*co-corresponding authors). A Conserved Class of Histone Demethylases Regulate Longevity in Response

to Mitochondrial Stress. Cell, 2016, 165, 1209-23. E.G. Williams, Y. Wu, S. Dubuis, P. Blattmann, C.A. Argmann, S.M. Houten, T. Amariuta, W. Wolski, N. Zamboni, R. Aebersold*, J. Auwerx* (*co-corresponding authors). Systems proteomics and trans-omic integration illuminate new mechanisms in mitochondrial function. Science, 2016, 352: doi: 10.1126/ science.aad0189.

6.0 THE PHYSIOLOGY OF SEDENTARY BEHAVIOR: HOW IS IT DISTINGUISHED FROM PHYSICAL IN-ACTIVITY

6.1
EPIDEMIOLOGY OF SEDENTARY BEHAVIOR

Peter Katzmarzyk[1]
[1]Population and Public Hlth. Sciences, Pennington Biomedical Res. Ctr., 6400 Perkins Rd., Baton Rouge, LA, 70808.

Sedentary behavior is generally defined as any waking behavior characterized by low energy expenditure (<1.5 METs) while in a sitting or reclining posture. Time spent in sedentary behavior is typically estimated by questionnaires that assess overall time spent sitting or time spent in specific sedentary behaviors such as television viewing or computer use. Sedentary time can also be measured objectively by accelerometry, using low intensity thresholds such as <100 counts/minute to operationally define sedentary behavior. Data from the U.S. National Health and Nutrition Examination Survey indicate a trend for more daily sitting time with advancing age in women, and with increasing levels of education in both men and women. Further, obese women (but not men) reported sitting more than normal weight and overweight women. Several cohort studies have shown consistent results demonstrating positive associations between time spent sitting or viewing television and several health outcomes, such as incident type 2 diabetes mellitus, cardiovascular disease, and premature all-cause mortality. The degree to which the association between sedentary behavior and health outcomes is truly independent of the effects of physical inactivity is still not well understood. Studies are beginning to appear which use isotemporal substitution analysis to estimate the theoretical reduction in mortality risk associated with replacing sedentary time with light activity or moderate-to-vigorous activity (MVPA). The results generally show that replacing sedentary time with MVPA produce greater reductions in mortality risk compared to replacement with light activity. More research is required to better understand the interactions between sedentary behavior and physical activity *per se* and the identification of potential dose-response associations. References: Harrington D.M., Staiano A.E., Barreira T.V & Katzmarzyk P.T. The descriptive epidemiology of sitting among US adults: NHANES 2009/2010. *J Sci Med Sports* 2014;17:371-5. Gibbs B.B., Hergenroeder A., Katzmarzyk P.T., Lee I.-M. & Jakicic J.M. Definition, measurement and health risks associated with sedentary behavior. *Med Sci Sports Exerc* 2015; 47:6:1295-1300.

6.2
PHYSIOLOGY OF SEDENTARY BEHAVIOR AND ITS RELATIONSHIP TO HEALTH OUTCOMES

David Dunstan[1,2]
[1]Physical Activity, Baker IDI Heart and Diabetes Inst., 99 Commercial Rd., Melbourne, 3004, Australia, [2]Mary MacKillop Inst. for Hlth. Res., Australian Catholic Univ., Level 5, 215 Spring St., Melbourne, 3000, Australia.

Epidemiological and meta-analytic evidence indicates that excessive time spent in sedentary behaviors (too much sitting) is associated with the increased risk of premature mortality, cardiovascular disease, diabetes and some cancers, even when controlling for the influence of leisure-time moderate-vigorous physical activity. The epidemiological evidence has been fundamental to the generation of specific hypotheses relating to excessive sedentary behavior, including the importance of not only reducing overall sitting time but also the avoidance of prolonged periods of unbroken sitting. In recognition that sitting is a highly prevalent risk behavior, human experimental studies have begun to address the impact of prolonged sitting time on cardio-metabolic health parameters. These studies have been informed by the extensive mechanistic insights generated from decades of inactivity physiology research (bed rest, space flight, and animal studies). Specifically, attention has been directed at the establishment of experimental models that are solutions-focused, that is, understanding the impact of various counter-measures to prolonged sitting to offset the deleterious health impacts. Recent studies have consistently showed clinically meaningful acute improvements in postprandial glucose metabolism following the initiation of frequent (every 20–30 min) short (2–3 min) interruptions during prolonged sitting involving either light-intensity or moderate-intensity ambulation, standing, or simple resistance activities. Some have also demonstrated improved responses in blood pressure, lipids and haemostatic markers. The next logical step is to identify the longer-term effects of daily exposure to reducing and breaking up prolonged sitting time on various health risk markers. Nonetheless, the emerging evidence from these experimental studies is supportive of recent calls for practitioners and public health experts to expand their thinking beyond just 'purposeful health-enhancing exercise' and give serious consideration to also advocating reductions in sitting time. Already, some leading health agencies have taken a proactive stance on this issue through the release of new recommenddations/advice within physical activity recommendations on the likely importance of reducing sedentary behavior. Dunstan is supported by an NHMRC Senior Research Fellowship (APP1078360).

6.3
GENETICS OF EXERCISE AVOIDANCE

Rodney Dishman[1]
[1]Kinesiology, Univ. of Georgia, 330 River Rd., Athens, GA, 30602-6554.

Healthful and adverse outcomes of physical activity depend in large part on exposure, which is hard to measure repeatedly in population studies. Also, exposure is often imperfectly controlled in clinical trials of exercise because of poor adherence to sessions or varying compliance with the prescribed amount of exercise. Furthermore, whether exercise adherence and compliance are influenced by genetic traits, either directly or indirectly through mediating or moderating behavioral factors, has not been well elaborated. Understanding how personal motivation and genes operate to influence physical activity exposure and

outcomes will require, in part, multivariate modeling of known behavioral mediators (e.g., enjoyment and self-regulatory traits and processes) and moderators (e.g., personality) of physical activity together with neural-signaling genes (e.g., DRDR2, DRDR4, HTR2A HTR2C, OXR2, PRO-ENK) involved with motivational systems of behavior. Also required will be improved assessments of exposure, including repeated surveillance of cohorts in observational studies and measures of both adherence and compliance in clinical trials. Some examples from studies of humans and from rats selectively bred for running performance will be presented. Support: NIH-NIDDK R01 DK062148. Reference: Dishman RK. 2008. Gene-physical activity interactions in the etiology of obesity: behavioral considerations. Obesity 16 Suppl 3:S60-5.

6.4

NOVEL STRATEGIES AND APPROACHES FOR SEDENTARY BEHAVIOR PHYSIOLOGY RESEARCH

William Kraus[1]
[1]Duke Molecular Physiology Inst., Duke Univ. Sch. of Med., 300 N. Duke St., Durham, NC, 27701.

For over fifty years, physical activity epidemiology has relied upon assessments of physical activity and exercise as exposure, with health and disease, including mortality, as outcomes. Originally, validated and reliable self-report survey tools were used as exposure assessments. Unfortunately, such tools are very poor in assessing low levels of physical activity; they require complex and time-intensive interviews to accurately and reproducibly assess exposures. Over the last twenty or so years, objective measurement tools, most commonly triaxial accelerometers, have provided more accurate and reliable measures of physical activity and exercise exposure. Accelerometers are better than survey tools; but they are expensive, and provide challenges in assessments of low and very low levels of physical activity, and with sedentary behavior. As physical activity and exercise can have strong effects on outcomes in clinical trials, there is interest in incorporating physical activity measures in pharmacologic studies; this would allow critical assessments of interactions between exercise and pharmacologic therapies on health and disease outcomes. Indeed, we have used simple tools, pedometers, to understand these relations in the NAVIGATOR trial of nateglinide and valsartan on incident diabetes and cardiovascular disease in a metabolic syndrome population. We found that baseline and change in physical activity were strongly associated with these major clinical outcomes. Similarly, human physiology studies call for assessments of off-exercise physical activity as control variables, and as measures of the effects of structured exercise regimens on overall physical activity behavior. Indeed, in STRRIDE, we used accelerometers to investigate whether exercise programs of different intensities and doses have effects on off-exercise physical activity. Recently, there has blossomed an increased interest in studies of low levels of physical activity, inactivity, and sedentary behavior, independent of structure exercise, on health and disease. An entire industry has developed around wearable motion monitors and health bands used to record and assess physical activity and sedentary behavior. This development promotes epidemiologic studies of physical activity and sedentary behavior in large diverse populations; and in physiology studies where exercise, physical activity and sedentary behavior are major outcomes or control variables. These issues will be discussed.

7.0 MITOCHONDRIAL SIGNALING AND INTER-ORGANELLE CROSSTALK

7.1

MITOCHONDRIAL-DERIVED PEPTIDES REGULATE ENERGY HOMEOSTASIS

Pinchas Cohen[1], Su-Jeong Kom[1], Junxiang Wan[1], Joyce Xiao[1], and Kelvin Yen[1]
[1]Sch. of Gerontology, USC, 3715 McClintock Ave., Ste. 103, Los Angeles, CA, 90089.

Mitochondrial-Derived Peptides are a class of novel peptides encoded within the mtDNA, which serves as signals related to cell and organismal protection and energy expenditure. The first peptide identified, humanin, is encoded from the 16S rRNA region and has broad protective effects in vivo and in vitro. We recently identified six additional peptides encoded from the 16S Region named small humanin-like peptides or SHLPs, that also have potent activities on physiological functions. Another peptide we discovered is called MOTS-c and is encoded from the 12S rRNA region of the mtDNA, and has insulin sensitizing activity and potent weight-loss inducing abilities. In vitro, MDPs, are capable of protecting cells from a host of insults such as amyloid-ß in neurons and oxidized-LDL in endothelial cells. MDPs have direct and potent effects on mitochondrial function and cellular respiration and are able to increase mitochondrial copy number and regulate oxygen consumption rates. MDPs have been administered to a variety of animal models of disease and have been shown to delay the onset of atherosclerosis in APOE-KO mice, delay the progression of Alzheimer's and ALS, prevent chemotherapy-induced side effects, and importantly, improve insulin sensitivity in the liver through direct central effects on the hypothalamus (in the case if humanin) and in muscle (in the case of MOTS-c). MOTS-c has the remarkable ability to dramatically prevent weight gain in mice fed a high-fat diet by increasing energy expenditure while maintaining muscle mass. Humanin, SHLP2, and MOTS-c are all reduced in older rodents and humans, and humanin levels correlate with endothelial function and the GH-IGF status. In summary, MDPs are a new class of mitochondrial hormones that have diagnostic and therapeutic potential in human disease especially in obesity and related disorders. NIH R01GM090311, R01ES020812, P01AG034906, Lee et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obe-sity and insulin resistance. *Cell Metabolism*. 2015; 21, 443–454.

7.2

ROLE OF THE ACETYLOME IN MITOCHONDRIAL ENERGY SENSING AND SIGNALING

Michael N. Sack[1] Javier Traba[1], and Iain Scott[1].
[1]Cardiovascular Branch, NHLBI, NIH, Bld. 10, Rm. 5-3150, 10 Center Dr., MSC 1454, Bethesda, MD, 20892-1454.

It is now well established that nutrient-sensing regulatory programs controlling mitochondrial adaptation are orchestrated, in part, by non-histone protein lysine-residue acetylation. Deacety-

lation is controlled by NAD^+-dependent activation of the sirtuin family of proteins with SIRT3 being localized to mitochondria where it functions as the major mitochondrial deacetylase. The deacetylation of mitochondrial proteins modulates mitochondrial metabolic pathways and organelle integrity. At the same time, mitochondrial protein acetylation may be a non-enzymatic mass-action effect reflecting the mitochondrial concentration of acetyl-coA. Despite this, we have identified GCN5L1 as a protein that plays a pivotal role in mitochondrial protein acetylation and its depletion resulted in restricted mitochondrial protein deacetylation. In this presentation I will explore these two proteins to show the effect of fasting SIRT3 activation to regulate: (1) mitochondrial-integrity linked pathophysiology (The NLRP3 inflammasome) and (2) explore the role of restricted mitochondrial deacetylation (GCN5L1 KO as a putative signature of energy depletion) on mitochondrial retrograde signaling. In brief - (1) We explored the role of fasting and refeeding on the regulation of the NLRP3 inflammasome. Refeeding increased susceptibility to inflammasome activation, in part, via activation of NF□B signaling. Moreover, a 24-hour fast in human subjects activated SIRT3 biology that, in turn, conferred resistance to NLRP3 inflammasome activation via blunting of mitochondrial ROS levels. This inflammasome provoking effect of refeeding after a 24-hour fast was inhibited by SIRT3 activation using nicotinamide riboside. These data have identified a potentially modifiable SIRT3-dependent program to enhance mitochondrial integrity which functions to blunt the NLRP3 inflammasome. (2) We found that the genetic modulation of the mitochondrial acetylome by the depletion of GCN5L1 was sufficient to initiate both mitophagy and modulate mitochondrial stress 'susceptibility'. Furthermore, we found that in a dose- and temporal-dependent fashion the depletion of GCN5L1 initiated retrograde signaling to coordinately regulate mitochondrial and lysosomal biogenesis programs to control cellular mitochondrial content. (NHLBI Division of Intramural Research - HL006047-06, HL005102-11) References: Traba J*, et al.* (2015) Fasting and refeeding differentially regulate NLRP3 inflammasome activation in human subjects. *The J. Clin. Investigation* 2015. Scott I*, et al.* (2014) GCN5-like protein 1 (GCN5L1) controls mitochondrial content through coordinated regulation of mitochondrial biogenesis and mitophagy. *The J. Biol. Chemistry* 289(5):2864-2872.

7.3

MITOCHONDRIAL REMODELING RELEVANT TO EXERCISE AND DISEASE

Daniel Kelly[1]
[1]Ctr. for Metabolic Origins of Dis., Sanford Burnham Prebys Med. Discovery Inst., 6400 Sanger Rd., Orlando, FL, 32827.

We are interested in delineating the transcriptional regulatory circuitry involved in the coordinate control of striated muscle energy metabolism, structure, and function. We have defined transcriptional factors that control mitochondrial function and fuel selection downstream of the exercise-inducible coregulators, PGC-1α and β, including the nuclear receptors PPARs and ERRs. We recently demonstrated that a PPARδ/ERRγ-driven transcriptional regulatory pathway coordinately controls genes involved in mitochondrial energy metabolism and skeletal muscle fiber type relevant to the re-programming that occurs with endurance exercise. Studies conducted in cells and with muscle biopsy tissue from well-characterized human subjects provide evidence that ERRγ cooperates with the myogenic factor MEF2A to regulate endurance fitness genes. Conversely, the PGC-1/ERR regulatory axis is downregulated with disuse atrophy in elderly human subjects and in mice subjected to hindlimb unloading. An intervention designed to reduce disuse muscle atrophy in elderly humans (HMB supplementation) reactivates the ERR circuit, unveiling regulatory "cross-talk" between the control of muscle mitochondrial function and mass. In a separate project, we probed the mysterious connection between muscle lipid accumulation and insulin resistance using an unbiased chemical biology screening approach. This work identified the muscle-enriched transcription factor, MondoA, as a key regulator of both myocyte lipid stores and insulin signaling. The mechanisms involved in this metabolic homeostatic control will be described. Taken together, our work has identified transcriptional regulatory mechanisms that orchestrate mitochondrial energy and fuel metabolism, muscle mass, and insulin signaling. This regulatory circuitry responds to exercise and disuse. The effectors of these regulatory mechanisms will be tested as candidate therapeutic targets aimed at primary muscle diseases, as well as common acquired diseases such as obesity, diabetes, and sarcopenia. Support: NIH R01DK045416 & R01HL058493. References: Gan Z, Burkart-Hartman EM, Han D-H, Finck B, Leone TC, Smith EY, Ayala JE, Holloszy J, Kelly DP: Nuclear receptor PPARβ/δ programs muscle glucose metabolism in cooperation with AMPK and MEF2. ***Genes Dev.*** 2011; 25:2619-2630. Gan Z, Rumsey J, Hazen BC, Lai L, Leone TC, Vega RB, Xie H, Conley KE, Auwerx J, Smith SR, Olson EN, Kralli A, Kelly DP: Nuclear receptor/microRNA circuitry links muscle fiber type to energy metabolism. ***J Clin Invest.*** 2013; Jun 3;123(6):2564-2575. Ahn B, Soundarapandian MM, Sessions H, Peddibholta S, Roth G, Li J-L, Sugarman E, Koo A, Malany S, Wang M, Yea K, Brooks J, Leone TC, Han X, Vega RB, Kelly DP: MondoA links skeletal myocyte lipid homeostatsis to insulin signaling. ***JCI,*** In press.

7.4

THE ROLE OF DIET AND EXERCISE IN THE TRANSGENERATIONAL EPIGENETIC LANDSCAPE OF TYPE 2 DIABETES

Juleen Zierath[1,2]
[1]Molecular Med. and Surgery, Karolinska Inst., Section for Integrative Physiology, von Eulers väg 4a IV, Stockholm, 17177, Sweden, [2]The Novo Nordisk Ctr. for Basic Metabolic Res., Univ. of Copenhagen, Fac. of Hlth. and Med. Sciences, Blegdamsvej 3B, Copenhagen, 2200, Denmark.

Type 2 diabetes mellitus (T2DM) is a life threatening metabolic disease that is reaching epidemic proportions. Defects in multiple organ systems that control glucose homeostasis, including the brain, pancreas and peripheral tissues (liver, adipose tissue and skeletal muscle), lead to impaired insulin action and secretion and ultimately the clinical manifestation of T2DM. Although the molecular basis for this pathology is incompletely understood, genetic and environmental factors, probably in a synergistic. manner, contribute to the risk of developing T2DM.

Environmentally driven epigenetic modifications of the genome provide a potential molecular basis for the missing heritability in T2DM. Epigenetic changes are caused by biochemical regulators of gene expression that can be transferred across generations or through cell division. Epigenetic modifications can arise from a variety of environmental exposures including undernutrition, obesity, physical activity, stress and toxins. Transient epigenetic changes across the entire genome can influence metabolic outcomes and might or might not be heritable. These modifications direct and maintain the cell-type specific gene expression state. Transient epigenetic changes can be driven by DNA methylation and histone modification in response to environmental stressors. A detailed understanding of the epigenetic signatures of insulin resistance and the adaptive response to exercise might identify new therapeutic targets that can be further developed to improve insulin sensitivity and prevent obesity. This Lecture will focus on the current understanding of mechanisms by which lifestyle factors affect the epigenetic landscape in T2DM and obesity. Evidence from the past few years about the potential mechanisms by which diet and exercise affect the epigenome over several generations will be discussed.

8.0 ACUTE/INTEGRATIVE RESPONSES

8.1
LOCAL HEATING PROMOTES THE EXPRESSION OF ANGIOGENIC REGULATORS IN HUMAN SKELETAL MUSCLE

Kyoungrae Kim[1], Yaohui Nie[1,2], A.Nicole Blaize[1], Shihuan Kuang[2], Timothy P. Gavin[1], and Bruno T. Roseguini[1]
[1]Dept. of Hlth. & Kinesiology, Purdue Univ., 800 W Stadium Ave., West Lafayette, IN, 47907, [2]Dept. of Animal Sci., Purdue Univ., 901 W. State St., West Lafayette, IN, 47909.

Introduction: Emerging evidence derived from animal studies indicates that heat therapy (HT) induces capillary growth in skeletal muscle. Whether HT promotes angiogenic signaling in human skeletal muscle remains unknown. We hypothesized that a single 90 min session of local HT application increases the mRNA expression of angiogenic mediators in human skeletal muscle. **Methods**: Fourteen healthy young adults (21±0.8 yrs, BMI 23.9±0.8) completed two experimental sessions. A custom-made water-circulating garment was used to heat one randomly selected thigh, while the opposite thigh served as a control. Water at ~52ºC was circulated through the garment in the heated thigh to increase skin temperature to ~40ºC. In the control thigh, water at ~32ºC was perfused through the garment to maintain skin temperature at baseline levels. On session 1, biopsy samples were obtained from the vastus lateralis muscle prior to and 30 min after the interventions. On session 2, blood flow in the femoral artery, core body temperature, blood pressure, and heart rate were measured before, during, and after the interventions. **Results**: By study design, exposure to HT led to a local increase in skin temperature from 32.8±0.2ºC to 40.3±0.1ºC, whereas in the control thigh, skin temperature remained at ~33ºC. Femoral artery blood flow increased markedly during HT application, reaching peak levels at 60 min (Control: 283.2±39.0 ml/min vs. HT: 434.9±58.2 ml/min, p=0.001). There were no significant changes in core temperature, blood pressure, and heart rate during and after the interventions. Compared to the control intervention, HT application induced a significant increase in the mRNA expression of key angiogenic regulators, including vascular endothelial growth factor (fold change from baseline, Control: 1.0±0.1 vs. HT: 1.3±0.1, p=0.02), angiopoietin 1 (Control: 1.0±0.1 vs. HT: 1.3±0.1, p=0.01), angiopoietin 2 (Control: 0.8±0.1 vs. HT: 1.1±0.1, p=0.01), and C-C motif chemokine ligand 2 (Control: 0.5±0.1 vs. HT: 0.7±0.1, p=0.04). **Conclusion**: Taken together, these findings suggest that HT may be a simple and practical therapeutic tool to promote angiogenic signaling in human skeletal muscle. Future studies are needed to determine the impact of repeated HT on skeletal muscle capillarization in humans.

8.2
EVALUATION OF DUAL STRESS-RESPONSE SYSTEMS IN AN ELITE ULTRA-MARATHON RUNNER

Alexis Jones[1], and Whitney DeNeen[2]
[1]Hlth. Professions, Northeastern State Univ., 3100 E. New Orleans, Broken Arrow, OK, 74014, [2]Nat. Sci., Northeastern State Univ., 3100 E. New Orleans, Broken Arrow, OK, 74014.

Exercise studies typically involve subjects reporting to the laboratory to complete a bout of exercise under strictly monitored conditions. While this provides important information about the effects of exercise on humans, it is necessary to also study human subjects engaging in athletic events in order to truly evaluate the myriad of physiological and psychological changes occurring during exercise. Stress hormones, such as cortisol, often increase during exercise and this can positively affect athletic performance. However, continual activation of this stress response system can be detrimental to the body. Activation of the sympathetic nervous system is also increased during exercise but there is limited information delineating the effect of continual activation of this stress response system, such as during sustained extreme exercise. This report provides a comparison of the body's chief stress-response systems, the hypothalamic-pituitary-adrenocortical (HPA) axis and the autonomic nervous system release of catecholamines, in an elite athlete during an ultra-marathon race. Saliva was collected from the winner of a 100 kilometer trail race in northeastern Oklahoma in October 2015 and analyzed for cortisol concentration and alpha-amylase activity. In contrast to what many studies of exhaustive exercise have shown, cortisol levels and alpha-amylase activity decreased after 100 kilometers in this runner compared to pre-race levels. This suggests that continued HPA axis and sympathetic nervous system activation in an elite athlete may be suppressed in order to continue exercise at high intensity for an extended period of time.

8.3
INCREASES IN METABOLITE CONCENTRATIONS IN GLYCOLYSIS AND PENTOSE PHOSPHATE PATHWAY AND SIGNAL PHOSPHORYLATIONS IN C2C12 MYOTUBES AFTER HIGH FREQUENCY ELECTRICAL STIMULATION

Daisuke Hoshino[1], Katsuyuki Kunida[1], Takumi Wada[1], Atsushi Hatano[1], Katsuyuki Yugi[1], Tomoyoshi Soga[2], and Shinya Kuroda[1]

[1]Dept. of Biological Sci., Univ. of Tokyo, 7-3-1,Hongo, Bunkyo-ku, Tokyo, 1310033, Japan, [2]Inst. for Advanced Biosciences, Keio Univ., Tsuruoka, Yamagata, 997-0052, Japan.
Muscle contraction changes metabolite concentrations and signal phosphorylations in skeletal muscle. Several signals and metabolism may also be affected after muscle contraction. However, during and after muscle contraction, differences between low and high frequency muscle contractions in signals and metabolism have not yet been examined. The purpose of this study is to clarify the differences between low and high frequency muscle contractions in metabolite concentrations and signal phosphorylations during and after stimulation. C2C12 mouse muscle cells were differentiated to myotubes and performed 0, 2 and 20 Hz electrical induced muscle contractions of 3 ms duration at 50 V for 1hr. Samples were harvested at 0, 2, 5, 15, 30 and 60 min during muscle contractions and at 1h, 3h and 6h after muscle contractions. Metabolite concentrations were globally measured using capillary electrophoresis-mass spectrometry (CE-MS). Phosphorylation levels of several protein kinases were detected using western blotting. Metabolite concentrations in glycolysis and pentose phosphate pathway and phosphorylation levels of Akt, mitogen-activated protein kinase p38 (p38) and ERK increased during and after 20 Hz stimulation. Interestingly, these increases of metabolite concentrations and signal phosphorylations after the stimulation were stronger than those during the stimulation. Concentrations in fumarate and malate in TCA cycle and phosphorylation of AMP-kinase (AMPK) increased only during 2 and 20 Hz stimulation. Taken together, high frequency (20 Hz), not low frequency (2 Hz), stimulation activated glycolysis and pentose phosphate pathway and Akt, p38 and ERK signaling after muscle contractions. These results suggest that high frequency muscle contraction affected muscle metabolism and signaling after stimulation as well as during stimulation.

8.4

EFFECTS OF ACUTE AND LONG-TERM PEPPERMINT OIL INHALATION ON CARDIOVASCULAR RESPONSES AND HEART RATE VARIABILITY

Tso-Yen Mao[1], and Chun-Feng Huang[2]
[1]Dept. of Hlth. and Leisure Management, St. Mary's Junior Coll. of Med., Nursing and Management, No. 100, Lane 265, Sec. 2, Sanxing Rd., Sanxing Township., Yilan Country, 26644, Taiwan, [2]Dept. of Family Med., Natl. Yang-Ming Univ. Hosp., No.152, Xinmin Rd., Yilan City, Yilan County, 260, Taiwan.
Purpose: Mint is an herb, which is well known for anti-spasmodic, pain-killing, anti-inflammatory and antioxidant effects. However, the previous research showed that effects of peppermint oil on cardiovascular responses and HRV are still controversial. The purposes of this study were to investigate the effects of acute and long-term peppermint oil inhalation intervention on cardiovascular responses and HRV. **Methods:** Twelve healthy males (171.6±6.5cm; 74.0±14.0kg; 21.3±1.2yr) were recruited and randomly assigned into peppermint oil (P: inhaled peppermint oil in water) and control (C: inhaled water) groups for ten days. Cardiovascular responses and HRV were measured during peppermint oil tests before and after interventions. Mix designed two-way ANOVA was used to compare the differences between tests and interventions. The significant level was set at α =. 05. **Results:** VLF (140.8±2.4 vs. 170.0±3.3, $p < .05$), LF (190.0±4.7 vs. 218.6±4.2, $p < .05$), LF/HF (1.0±0.0 vs. 1.1±0.0, $p < .05$), HR (76.0±0.5 vs. 77.2±0.5 bpm, $p < .05$), SBP (109.7±0.4 vs. 112.8±0.4mmHg, $p < .05$) and DBP (77.4±0.1 vs. 79.4±0.1 mmHg, $p < .05$) all increased during expose to 50uL peppermint oil inhalation. Following 10 days interventions, the P group significantly decreased the VLF (147.1±5.1 vs. 127.0±6.8, $p < .05$), LF (217.9±1.1 vs. 210.8±1.8, $p < .05$), LF/HF (1.1±0.1 vs. 1.0±0.1, $p < .05$) and accompanied with increased HF (200.6±6.8 vs. 218.3±9.8, $p < .05$). HR (76.5±1.2 vs. 74.5±1.0 bpm, $p < .05$), SBP (112.0±0.9 vs. 110.3±1.0 mmHg, $p < .05$) and DBP (78.6±0.2 vs. 77.8±0.3 mmHg, $p < .05$) also declined after 10 days peppermint oil inhalation. But there were no changes after 10 days C treatment. **Conclusions:** We conclude that acute expose to peppermint oil increase sympathetic activity. The relaxed effects of 10 days peppermint oil inhalation maybe attributed by long-term sympathetic adaptation and further to down-regulated HRV and cardiovascular responses.

8.5

CONCOMITANT ASSESSMENT OF OXIDATIVE DNA DAMAGE AND BONE RESORPTION OVER A RAPID WEIGHT RE-DUCTION PERIOD IN FEMALE JUDO PLAYERS

Nobuo Yasuda[1], and Tomohiko Yano[1]
[1]Dept. of Physical Edu., International Pacific Univ., 721 Kannonji, Seto-cho, Higashi-ku, Okayama, 709-0863, Japan.
Purpose: The purpose of this study was to concomitantly determine oxidative DNA damage and bone resorption following a rapid weight reduction in association with caloric restriction and exercise training in female collegiate judo players. **Methods:** Eighteen nationally ranked university female judo players were recruited as participants in this study. All participants continuously managed to reduce their weight seven days prior to a competition. In order to detect cumulative effects, first-morning urine samples were collected on three different days (Day 1=the day after starting weight reduction; Day 4=mid-term of weight reduction; Day 7=the day before the competition) for the later analysis of 8-hydroxy-2'- deoxyguanosine (8-OHdG) as well as cross-linked N-terminal telopeptides of Type I collagen (NTx). Urinary 8-OHdG and NTx levels were determined with high performance liquid chromatography (HPLC) and enzyme-linked immunosorbent assay (ELISA), respectively. **Results:** One way analysis of variances (ANOVA) demonstrated no significant alterations in urinary 8-OHdG (Day 1: 4.1±1.6, Day 4: 3.6±1.6, Day 7: 3.5±1.4 ng/mg creatinine) or NTx (Day 1: 73.9±31.9, Day 4: 79.7±40.7, Day 7: 81.9±47.1 nmole/mmole creatinine) levels over a rapid weight reduction period. With regard to the relationship of urinary 17β-estradiol with urinary 8-OHdG and NTx levels, no significant correlations were observed. **Conclusions:** The findings of the present study indicate that female judo players appear to have relatively less oxidative DNA damage and bone resorption re-gardless of 17β-estradiol level following a rapid weight re-duction combined with caloric restriction and exercise training.

However, a magnitude of oxidative stress and bone turnover may depend on inter- and intra-individual variability related to energy balance, training status and hormonal fluctuations. Supported partly by funds from International Pacific University and Ryobi Teien Memorial Foundation.

8.6

HEAT SHOCK PROTEIN 72 ACTIVATION IN THE LIVER WITH EXERCISE

Ashley E. Archer[1], Robert S. Rogers[1], David R. Wilson[1], Joshua L. Wheatley[1], Justin A. Fletcher[2], Grace M. Meers[3], E. Matthew Morris[1], John P. Thyfault[1], R. Scott Rector[3], and Paige C. Geiger[1]

[1]Molecular and Integrative Physiology, Univ. of Kansas Med. Ctr., 3901 Rainbow Blvd., Kansas City, KS, 66160, [2]Pharmacology, Univ. of Texas Southwestern Med. Ctr., Seay Biomedical Bldg. (NC), Rm. NC8.308, 2201 Inwood Rd., Dallas, TX, 75390-9185, [3]Dept. of Nutrition and Exercise Physiology, Univ. of Missouri, 204 Gwynn Hall, Columbia, MO, 65211.

Heat shock proteins (HSPs) are molecular chaperones that aid in the recovery from stress and guard cells from future insults. Acute exercise and heat treatment both result in robust activation of HSPs. HSP72, in particular, plays an important role in maintaining insulin sensitivity and glucose homeostasis and is significantly decreased in skeletal muscle of insulin resistant and type 2 diabetic patients. Although HSP72 activation has been shown to improve metabolic function in skeletal muscle, there is a lack of knowledge about the role of HSPs in the liver – a tissue that plays a critical role in maintaining whole body glucose homeostasis. In previous studies, we have observed a dramatic increase in HSP72 activation in the liver following heat treatment, leading us to hypothesize that HSP72 could play an important role in liver metabolism. The liver also goes through adaptations to improve metabolic function following exercise, and we also hypothesize that HSPs are important in this process. The purpose of this study was to examine the ability of exercise to activate HSP72 in the liver and improve hepatic metabolism. Male Sprague Dawley rats were divided into sedentary (SED), voluntary wheel running (VWR), treadmill endurance (TM-END) or treadmill interval sprint training (TM-IST) groups for four weeks. We found that with endurance treadmill training, HSP72 protein content was robustly increased in the liver. Interval sprint training slightly increased HSP72 in the liver, while there was not a significant increase in HSP72 with voluntary wheel running. In response to an acute bout of exercise, increased HSP72 and changes in phosphorylation of the transcription factor HSF-1 were observed. Increased hepatic HSP72 in response to exercise correlated with changes in autophagy protein expression. Autophagy is the degradation of damaged cellular components and is important for maintaining proper cellular metabolic function. Our findings demonstrate that HSP72 expression in the liver is increased with both chronic and acute exercise in a time and intensity dependent manner. Among the many benefits of exercise, increased hepatic HSP72 expression could play an important role in treating and preventing hepatic insulin resistance, steatosis, obesity and type 2 diabetes. *Research funded by the Self Graduate Fellowship and the National Institute of General Medical Sciences of the National Institutes of Health P20 GM103418 and KUMC Research Institute, Inc.*

8.7

THE EFFECT OF ACUTE EXERCISE AND SERUM CARNOSINASE ON CIRCULATING AND MUSCLE HISTIDINE-CONTAINING DIPEPTIDES IN MICE

Jan Stautemas[1], Inge Everaert[1], Shahid Baba[2], Sibylle Hauske[3], Benito Yard[3], and Wim Derave[1]

[1]Dept. of Movement and Sports Sci., Ghent Univ., Watersportlaan 2, Ghent, Belgium, [2]Dept. of Med., Univ. of Louisville, S. Preston St., 580, Louisville, KY, 40202, [3]Dept. of Nephrology, Endocrinology and Rheumatology, Univ. of Heidelberg, Theodor-Kutzer-Ufer 1-3, Mannheim, Germany.

The histidine-containing dipeptides (HCD), carnosine and anserine, are mainly stored in skeletal muscle but they may fulfil several functions (e.g. carbonyl quencher, metal chelator, antioxidant) in other organs in our body[1]. Interestingly, Nagai et al. (2003) [2] reported enhanced circulating carnosine levels in mice that have access to a running wheel compared to resting mice. This myokine-like release from the muscles into the circulation could aid to partially explain the preventive and curative effect of exercise on metabolic diseases. However, caution is warranted as rodents lack the highly active HCD-degrading enzyme, serum carnosinase 1 (CN1), which is present in the human circulation. The objective of this study was to more profoundly investigate the HCD metabolism during acute exercise in healthy mice and in obese mice with or without overexpression of the human CN1 enzyme. After an acclimatization period, wild type (BTBR wt/wt) and obese (BTBR ob/ob) mice with or without CN1 transgenic overexpression were subjected to treadmill running for 1 hour at 15 and 10m/min, resp. Plasma and muscles were immediately collected following exercise and analysed by LC/MS^2 for HCD levels. First, plasma HCD levels tended to be significantly higher (+49%, $p < 0.05$) only in exercising compared to resting obese mice. This increase in HCD levels was predominantly evoked by carnosine (+75%, $p < 0.05$) and less by anserine (+35%, $p > 0.05$). Second, 1h running had no effect on soleus and gastrocnemius muscle HCD content. CN1, that is located in the serum, was able to markedly decrease soleus (-95%, $p < 0.05$) and gastrocnemius (-51%, $p < 0.05$) muscle HCD content in resting obese mice. On top of that, it eliminated most circulating HCD, thereby preventing a possible exercise-induced release in the CN1 transgenic obese mice. In order to preliminary test if these results are translatable to humans, urine collection was performed before and after a high-intensity cycling bout in 12 participants. Interestingly, the excretion of carnosine was increased following cycling (+154%, $p<0.05$). In summary, circulating carnosine levels were enhanced following an acute exercise bout in obese mice. The presence of CN1 resulted in a depletion of HCD levels, both in the circulation and in muscle, providing an interesting model to study the causative role of HCD in the preventive and curative effect of chronic exercise on different metabolic diseases. Funding: Research Foundation – Flanders. 1. Boldyrev AA, Aldini G, Derave W. Physiology and pathophysiology of carnosine. Physiol Rev 2013; 93:1803–1845. 2. Nagai K, Niijima

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8.8

WEIGHT LOSS-INDUCED CHANGES IN INTEGRATED MUSCLE PROTEIN SYNTHESIS AND MARKERS OF PROTEOLYSIS IN YOUNG MEN: EFFECTS OF DIE-TARY PROTEIN INTAKE AND RESISTANCE EXERCISE

Amy Hector[1], Chris McGlory[1], Felipe Damas[2], and Stuart Phillips[1]

[1]Dept. of Kinesiology, McMaster Univ., 1280 Main St. W., Hamilton, ON, L8S 4K1, Canada, [2]Sch. of Physical Edu. and Sport, Univ. of Sao Paulo, Av. Prof. Mello de Morais, 65, 05508-030, Sao Paulo, Brazil.

An unfavourable consequence of diet-induced weight loss is a loss of lean body mass (LBM), particularly muscle mass. Increased protein intake and resistance exercise during a hypoenergetic diet promote retention of LBM [1], which is dependent on the balance between rates of muscle protein synthesis (MPS) and muscle protein breakdown (MPB). Currently, the relative contribution of MPS and MPB to hypoenergetic diet-induced LBM loss, and the effect of protein intake and resistance exercise on these variables is not well characterized. In a single blind investigation, adult men (n=24, BMI=28.6±0.6kg/m^2, age=22±1y) underwent 10 days of a controlled hypoenergetic diet (40% reduction in energy requirements) while performing unilateral resistance exercise and consuming either lower protein (LP) (1.2g/kg/d protein, n=12) or higher protein (HP) (2.4g/kg/d protein, n=12). Pre- and post-intervention testing included DXA, deuterated water (D_2O) consumption to measure integrated MPS, and skeletal muscle biopsies to measure protein expression. Total weight loss (-1.7±0.1kg) and fat mass loss (-0.7±0.1kg) did not differ between groups; however, appendicular lean mass of the exercised leg was preserved compared to the rested leg in both groups (exercise= -0.1±0.1kg, rest= -0.4±0.1kg, $p<0.05$). Integrated MPS was significantly reduced in the rested leg in both groups following weight loss (HP = -14±3% and LP= -25±3%). Integrated MPS in the exercised leg was preserved in the HP group (5±4%, $p>0.05$) but only partially preserved in the LP group (-10±4%, $p<0.05$) following weight loss. Total protein ubiquitination, caspase-3 expression and the LC3II/LC3I ratio measured by western blot did not change with weight loss in either group. These results suggest that reductions in MPS are the likely reason for LBM loss during the early phase of a marked hypoenergetic diet-induced weight loss. Resistance exercise with higher protein intake can help to prevent the diet-induced decline in integrated MPS, which, in concordance with our earlier work [1], promotes LBM retention. Supported by NSERC and OGS 1. Longland, T.M., et al., Higher compared with lower dietary protein during an energy deficit combined with intense exercise promotes greater lean mass gain and fat mass loss: a randomized trial. Am J Clin Nutr, 2016. 103(3): p. 738-46.

8.9

NEW METHODS TO INTERROGATE THE METABOLOME OF MUSCLE INTERSTITIAL FLUID DURING EXERCISE

Jie Zhang[1], Sudeepa Bhattacharyya[2], Alan Light[1], Christopher Lambert[3], Bruce Gale[3], Oliver Fiehn[4], Charles Hoppel[5], and Sean Adams[2]

[1]Dept. of Anesthesiology, Univ. of Utah, 30 N. 1900 E. Rm. 3C444, Salt Lake City, UT, 84132, [2]Dept. of Pediatrics, Univ. of Arkansas for Med. Sci., Arkansas Children's Nutrition Ctr., 15 Children's Way, Little Rock, AR, 72202, [3]Dept. of Mechanical Eng., Univ. of Utah, 1495 E. 100 S. (1550 MEK), Salt Lake City, UT 84112, Salt Lake City, UT, 84112, [4]Genome Ctr., Univ. of California, Davis, 1 Shields Ave., Davis, CA, 95616, [5]Pharmacology Dept., Case Western Res. Univ., 10900 Euclid Ave., Cleveland, OH, 44106.

Understanding muscle metabolic physiology is relevant to the areas of insulin resistance and diabetes, fatigue and exertion biology, and fitness. Typically, blood- or biopsy-based approaches are applied to characterize a focused set of muscle metabolites of interest, i.e., lactate, lipid derivatives or amino acids to name a few. While quite valuable, these approaches have several limitations. Blood measures (unless derived from cross-muscle bed catheterization) involve metabolic interrogation of a large pool with inputs derived from multiple tissues, making it difficult to determine muscle-specificity of metabolite patterns. Biopsies do not readily enable assessment of secreted vs. intracellular metabolites, and are invasive, thus reducing one's ability to assess metabolism frequently during dynamic periods such as exercise. To overcome these limitations, a catheter was developed that enables insertion into the muscle bed in order to collect interstitial fluid (IF) for multi-platform metabolomics analyses. The PFA catheter (360 μm/150 μm O.D./I.D.) contains 150 μm through-holes placed orthogonally to the lumen axis and centered about the lumen, spaced 500 μm apart. In a proof-of-principle study, approximately 10 μL of gastrocnemius muscle interstitial fluid was collected from a resting rat anesthetized under i.p. ketamine/xylazine (80/10 mg/kg). Using a non-targeted, GC-MS-based small molecule metabolomics analysis of 5 μL IF, 71 metabolites were detected that had signals >2-fold that of the blank (water-washed catheter effluent). These included "novel" (non-annotated) metabolites and select sugars, fatty acids, amino acids and their derivatives. Using a targeted analysis on 5 μL IF, 26 acylcarnitine species were detected and 46 were non-detectable. We will also present results from analyses now underway that compare within-mouse muscle interstitial fluid metabolomics profiles at rest and following acute exercise (n=10), with an evaluation of the correspondence between plasma and muscle patterns. Altogether, the results highlight the feasibility of the novel catheterization approach to determine metabolite profiles in low sample volumes of muscle interstitial fluid, which may prove valuable in clinical experiments that aim to investigate metabolic phenotypes in exercise-challenged skeletal muscle. Supported in part by USDA-ARS Projects 5306-51530-016-00D, 5306-51530-019-00 and 6026-51000-010-05S, NIH-NIDDK R01DK078328, and NIH U24DK097154.

8.10

MUSCLE IL-6 AND FASTING INDUCED REGULATION OF PDH IN MOUSE SKELETAL MUSCLE

Stine Ringholm[1], Anders Gudiksen[1], Lærke Bertholdt[1], and Henriette Pilegaard[1]

[1]Biology, Univ. of Copenhagen, Universitetsparken 13, Copenhagen, Denmark.

Introduction: Skeletal muscle is known as a highly adaptable tissue that regulates substrate choice and utilization to metabolic needs and pyruvate dehydrogenase (PDH) is thought to be a key enzyme in this process. Fasting has previously been shown to be associated with increased plasma interleukin (IL)-6 and IL-6 injections to regulate PDH. **Aim:** The aim of the present study was to test the hypothesis that muscle IL-6 is required for fasting-induced regulation of PDH in skeletal muscle. **Methods:** Muscle-specific IL-6 knockout (MKO) mice and floxed littermate controls (Con) were either fasted for 6 hours (6h fast) or 18 hours (18h fast) or had free access to food and water and euthanized at the same time of the day as the fasted mice (6h fed and 18h fed). Quadriceps muscles were quickly removed and frozen in liquid nitrogen. **Results:** PDH Ser^{293} phosphorylation increased 1.7-2-fold with 18 hours of fasting in both Con and IL-6 MKO and tended to increase 1.3-fold with 6 hours of fasting only in IL-6 MKO. After 18 hours of fasting, PDH Ser^{293} phosphorylation was 20-25% lower in IL-6 MKO than Con. PDH Ser^{300} phosphorylation increased 2-3-fold with 18 hours of fasting in both Con and IL-6 MKO and increased 2-fold with 6 hours of fasting only in IL-6 MKO. PDH Ser^{300} phosphorylation was 2-fold higher in IL-6 MKO than in Con after 6 hours of fasting, while it was 40% lower in IL-6 MKO than Con after 18 hours of fasting. PDH Ser^{232} phosphorylation increased ~1.8-fold with 6 hours and 18 hours of fasting in both Con and IL-6 MKO. In addition, phosphorylation of PDH Ser^{232} was 40% lower in 18 hours fed than 6 hours fed IL-6 MKO mice. PDK4 protein content increased 1.3-2.5-fold with 6 and 18 hours of fasting in both Con and IL-6 MKO. In addition, PDK4 protein content was 20% lower in IL-6 MKO than in Con after 18 hours of fasting. PDP1 protein content increased 2-fold with 18 hours of fasting only in Con. Acetylation of PDH was 50% lower in 18h fed IL-6 MKO mice than 6h fed IL-6 MKO mice and there was a tendency for an overall effect at 18h fast that could not be localized further. **Conclusion:** Fasting regulated PDH phosphorylation and acetylation, as well as PDK4 protein content in part in a muscle IL-6 dependent manner, while fasting-induced regulation of PDP1 protein was independent of muscle IL-6. In addition, muscle IL-6 seems to affect circadian rhythm of PDH Ser^{232} phosphorylation and PDH acetylation. *Funded by The Danish Research Council for Natural Sciences.*

8.11

HEART RATE RECOVERY AFTER MAXIMAL EXERCISE IS BLUNTED IN ADULTS BORN PRETERM IN NORMOXIA AND HYPOXIA

Kristin Haraldsdottir[1,2], Arij Beshish[1], Laura Tetri[1], Greg Barton[1], David Pegelow[1], Mari Palta[3], Kara Goss[4], Andrew Watson[5], and Marlowe Eldridge[1]

[1]Pediatrics, Univ. of Wisconsin, Madison, 600 Highland Ave., H6/551 CSC, Madison, WI, 53792, [2]Kinesiology, Univ. of Wisconsin, Madison, 600 Highland Ave., H6/551 CSC, Madison, WI, 53792, [3]Biostatistics and Med. Informatics, Univ. of Wisconsin, Madison, 689 WARF, 610 Walnut St., Madison, WI, 53726, [4]Med., Univ. of Wisconsin, Madison, 600 Highland Ave., Madison, WI, 53792, [5]Orthopedics, Univ. of Wisconsin, Madison, 600 Highland Ave., Madison, WI, 53792.

Preterm birth affects millions of infants each year, and most survivors go on to lead active lives, participating in sports and other athletic events without incident. However, recent evidence shows that there are long term effects of preterm birth including right ventricular hypertrophy and diminished pulmonary gas exchange. Heart rate recovery (HRR) has been used as a predictor of cardiovascular disease, and is known to be associated with negative prognostic indications in pulmonary arterial hypertension. Adults born preterm (preterms) and age-matched term-born controls (controls) performed incremental exercise on a cycle ergometer to volitional exhaustion while breathing normoxic air (21% oxygen), followed by a second maximal exercise test in hypoxic air (12% oxygen) after a 45 minute rest. HR was recorded after 60 seconds of recovery after each maximal exercise test. HRR, HR as a percentage of HR reserve, maximal oxygen consumption (VO_{2max}) and maximal oxygen pulse (O_2 pulse; ml O_2 consumed per heart beat) were compared using two-way ANOVA for each group and condition. Preterms exhibited lower HRR in the first minute after maximal exercise in normoxia and hypoxia compared to controls (17.7±4.1 vs. 27.5±3.7 and 15.3±0.9 vs. 24.8±3.2 bpm, respectively, $p<0.05$). Additionally, preterms recovered a lower percentage of their HR reserve at 60 seconds of recovery after maximal exercise compared to controls in both normoxia and hypoxia (15.4±3.0 vs. 28.0±2.4% and 23.5±2.4 vs. 34.0±2.3%, respectively, $p<0.05$ all). VO_{2max} was lower in hypoxia compared to normoxia in both groups, and was lower in preterms compared to controls in both normoxia and hypoxia (controls: 34.3±7.1 and 44.7±7.9 ml/kg/min and preterms: 23.9±7.3 and 35.3±6.2 ml/kg/min, respectively, $p<0.05$ all). O_2 pulse was lower in preterms compared to controls in both normoxia and hypoxia (preterms: 13.4±2.1 and 9.1±1.8 ml/beat and controls: 19.9±4.6 and 15.5±3.2 ml/beat), and was lower in each group in hypoxia compared to normoxia ($p<0.05$ all). This data suggests that preterms have a diminished maximal aerobic capacity in normoxia and hypoxia, a lower O_2 pulse at maximal exercise in normoxia and hypoxia, and a blunted HRR response after maximal exercise, potentially due to an autonomic nervous system dysregulation during and following maximal exercise. Funding source: NIH NHLBI, R01 HL086897 (Eldridge); UW CVRC T32- HL 07936.

8.12

RESPONSE OF SKELETAL MUSCLE EXOSOME MARKERS TO ACUTE RESISTANCE EXERCISE IN LEAN AND OBESE

Ron Garner[1], Yaohui Nie[1], Jessica Weiss[1], and Tim Gavin[1]

[1]Hlth. and Kinesiology, Purdue Univ., 800 W. Stadium Ave., W. Lafayette, IN, 47906.

Introduction: Obesity is associated with poor skeletal muscle function, while exercise is well known to improve muscle func-

tion. Exosomes are a class of small microvesicles (30-100nm) shown to be important in cell-to-cell communication in viruses, bacteria, and cancerous tumors; exosomes are released from most cells. Exosomes contain mRNAs, proteins, and especially miRNAs. There are few studies investigating exosome regulation in skeletal muscle. We investigated if: 1) obesity impairs basal exosome regulation; 2) acute resistance exercise (RE) alters exosome regulation; 3) obesity alters the exosome response to RE; and 4) obesity alters miRNA expression. Methods: Sixteen subjects (8 lean (LN); 8 obese (OB)) completed three sets (8-12 reps) of knee extensor RE. Vastus lateralis muscle biopsies were obtained pre-RE and at 15 min and 3 hr post-RE. The mRNA for the exosome cell-surface markers alix, clathrin, TSG-101, and CD-63, as well as miRNA 206, was measured by rt-PCR. Results: At 15 min post-RE, alix mRNA was greater in OB than LN. There were no other effects of RE on exosome mRNA or miRNA. There were trends for elevated clathrin mRNA (~1.7-fold) and CD-63 mRNA (~1.5-fold) in OB compared to LN independent of sample time. There was a trend for elevated miR-206 (~1.7-fold) in OB compared to LN at rest, but not post-RE. Conclusion: Overall, resistance exercise does not alter the gene expression of the exosome markers alix, clathrin, TSG-101, and CD-63 at 15 min or 3 hr post-RE. There are elevated exosome markers in skeletal muscle from obese compared to lean individuals consistent with altered cell-to-cell communication in obesity.

8.13 Withdrawn

8.14

CHARACTERIZATION OF DIFFERENTIAL METABOLIC RESPONSES TO VARIOUS TREADMILL EXERCISE PROTOCOLS IN MICE

Scott Fuller[1,2], Susan Collier[3], Heidi Batdorf[2], Jacob Simon[2], Matthew Scott[4], Jason Collier[3], and Robert Noland[2]
[1]Kinesiology, Univ. of Louisiana at Lafayette, 225 Cajundome Blvd., #135-B, Lafayette, LA, 70503, [2]Skeletal Muscle Metabolism Lab., Pennington Biomedical Res, Ctr., 6400 Perkins Rd., Baton Rouge, LA, 70808, [3]Islet Cell Biology Lab., Pennington Biomedical Res. Ctr., 6400 Perkins Rd., Baton Rouge, LA, 70808, [4]Sch. of Kinesiology, LSU, Huey P. Long Fieldhouse, Baton Rouge, LA, 70803.

Introduction: Aerobic exercise imposes challenges to homeostasis that induce a broad range of physiological responses, including adaptive metabolic remodeling in various organ systems. This project characterized metabolic remodeling in liver and skeletal muscle in response to differing exercise modalities. **Methods:** In study 1, mice (n = 6-10/group) performed a single, mild-moderate intensity treadmill exercise bout (60 min) and metabolic parameters were assessed at the following time points: immediately post-exercise, as well as 3, 24, and 48 hours post-exercise. In study 2, 20 C57BL6 mice were randomly assigned to either 6 weeks of treadmill exercise training at mild-moderate intensity (5 days per week, 1 hour per day) or to a sedentary control group (n = 10/group). In study 3, mice (n = 11/group) performed an exhaustive treadmill exercise bout at high-intensity or moderate-intensity and results were compared to sedentary controls. We measured oxidation of several [^{14}C]-labeled substrates in tissue homogenates. Changes in gene expression, glycogen concentrations, and serum parameters were also tested. **Results**: An acute mild-moderate intensity exercise bout depleted liver glycogen stores immediately post-exercise. While metabolic changes in the liver occurred rapidly after exercise, adaptations in muscle were delayed until 3h after exercise. 6 weeks of chronic exercise training at a similar mild-moderate intensity limited weight gain and enhanced muscle glycogen stores; however, it was insufficient to induce alterations in gene expression and substrate oxidation capacity in either liver or skeletal muscle. Both moderate-intensity and high-intensity exhaustive exercise increased lactate. Lactate levels were greater in the high-intensity exercise group. While the high-intensity exercise group maintained normal circulating glucose levels, the endurance-to-exhaustion group exhibited decreases in circulating glucose which coincided with depletion of tissue glycogen. **Discussion**: Our experiments not only characterize a wide set of physiological changes induced by exercise, but also yield information on how best to modulate the intensity, frequency, and duration of mouse treadmill exercise protocols. Our results appear to suggest that training adaptations that limit weight gain and enhance tissue glycogen storage can be attained while exercising at mild-moderate intensity; however, remodeling of metabolic pathways may require training at higher intensity.

8.15

IS IT SAFE TO EXERCISE DURING HEMODIALYSIS?

Cheryl King-VanVlack[1], Trisha Parsons[1], and Diana Hopkins-Rosseel[1]
[1]Rehabilitation Therapy, Queens Univ., LDA Bldg., 31 George St., Kingston, ON, K7L 3N6, Canada.

In Ontario, the presence of exercise programs in hemodialysis (HD) clinics is low primarily due to lack of resources and concerns about patient safety attributing to lack of knowledge on patient handling and exercise protocols without the presence of exercise professionals (i.e. physiotherapists, kinesiologists). The current study represents a retrospective analysis of individual exercise sessions during HD to identify any adverse medical events. These sessions occurred from August 2012 to October 2013 in which individuals undergoing HD participated in a number of different research investigations. For each exercise session fluid loss goal (FLG, ml), systolic and diastolic blood pressure (SBP, DBP, mmHg), heart rate (HR, bpm), and Rating of Perceived Exertion (RPE, 10-point scale) were recorded prior to and at the end of each 30-minute exercise session. Reasons for declining or ceasing exercise prematurely during HD were documented. Participants (35 males, 33 females, 1 not indicated) exercised at their own self-selected intensity using a mini-stepper or Monarch Rehab Trainer ergometer stationed in front of the HD chair. Some individuals only exercised for one 30-min bout (n=400 sessions) while others exercised for 2 30-min bouts (n=1,284) separated by 30 minutes of rest. In total, 150 and 183 instances occurred in which individuals chose not to exercise or to stopped exercising with either one or two bouts of exercise; the most common reason being overall lower limb soreness overall fatigue/sickness, or abnormal changes in blood pressure. None of these instances could be labelled an 'adverse event' (negative physiological event which requires medical intervene-

tion). Another interesting finding was the relationship between the changes in FLG and SBP and RPE. FLG is an indicator of the amount of fluid load the individual has at the start of HD and must be removed during HD. A significant negative correlation was found between FLG with 2 exercise bouts in the same session (r=-0.14; r=-0.09) indicating that the lower the fluid load, the greater was the increase in SBP in response to exercise. Further, significant correlations were observed between FLG and RPE for both one- (r=-0.19) and two-bout (r=-0.11) exercise in a given HD session. These findings indicate that individuals who arrived with a greater fluid load exercised at a lower self-selected exercise intensity. In summary, no adverse events were observed in greater than 1,600 exercise sessions during HD. Further, when individuals had a high fluid load, they inherently exercised at a lower intensity which also acts to reduce risk. These findings indicate that there is a very low risk of an adverse medical event occurring with exercise during hemodialysis when individuals are able to work at a self-selected intensity.

8.16
THE EFFECT OF AN ACUTE BOUT OF EXERCISE ON MARKERS OF AUTOPHAGY IN THE LIVERS OF DIET-INDUCED OBESE MICE

Corey Summers[1], Kelly Fuller[1,2], and Rudy Valentine[1]
[1]Kinesiology, Iowa State Univ., Forker Bldg., Ames, IA, 50011, [2]Food Science and Human Nutrition, Iowa State Univ., Food Sciences Bldg., Ames, IA, 50011.

Background: Exercise has been shown to increase autophagic signaling, an important cellular metabolic process, in most peripheral tissues, especially skeletal muscle. While there have been mixed data on the effect of obesity on autophagic signaling, it nonetheless seems to alter this critical pathway for many tissues. **Purpose:** The purpose of this study was to examine the immediate effects of an acute bout of exercise on autophagic signaling in the liver of diet-induced obese mice. **Methods:** 16 Male C57BL/6 mice were assigned to either Low-fat (LF) or High-fat (HF) diet groups (n=8) for 12 weeks. At the end of the 12 week diet, an Insulin Tolerance Test was performed. LF and HF groups were further divided into sedentary (LF-SED, HF-SED) or exercised (LF-EX, HF-EX). Exercise groups ran on a treadmill for 30 min at a moderate intensity of 12 m/min (roughly 70% VO_2max). Immediately after exercise, mice were euthanized and livers were excised and snap-frozen. Liver samples were homogenized and analyzed via Western blot and densitometry. Data were analyzed either by two-way analysis of variance (ANOVA) or an unpaired t-test, with $\alpha = 0.05$. **Results:** The HF group gained more weight (33.8±1.1 vs 26.0±0.4, $p<0.01$) and were more insulin resistant than LF mice ($p<0.01$). Exercise tended to increase the phosphorylation of AMPK and mTOR (main effect of exercise $p<0.06$). HFD tended to increase basal markers of autophagy, including Atg3, LC3I and LC3II (all $p<0.1$), which were all elevated in the sedentary HF-SED vs LF-SED ($p<0.05$). Exercise tended to increase autophagic proteins Atg3, Atg12, and the ratio of bound (Atg12:Atg5) to free Atg12 (main effect of exercise $p<0.1$). In the LF group, exercise increased p-AMPK and Atg3, and tended to increase p-ACC, Atg12, LC3II/I ratio ($p<0.1$) whereas in the HF group no effect of exercise was observed (all $p>0.2$). **Conclusions:** Exercise appears to upregulate autophagic proteins involved in the initiation (p-AMPK), phagaphore formation (Atg12), and sequestration (LC3II/I) of autophagy, primarily in LF mice. HF diet led to increased basal expression of autophagic proteins, but hindered the acute exercise-induced increase in autophagy signaling, in the liver.

9.0 EXERCISE AND DRUG INTERACTIONS

9.1
CIRCULATING LEVELS OF ENDOCANNABINOIDS RESPOND ACUTELY TO VOLUNTARY EXERCISE, ARE ALTERED IN MICE SELECTIVELY BRED FOR HIGH VOLUNTARY WHEEL RUNNING, AND DIFFER BETWEEN THE SEXES

Zoe Thompson[1], Donovan Argueta[2], Jaspreet Kaur[2], Theodore Garland, Jr.[3], and Nicholas V. DiPatrizio[2]
[1]Neuroscience, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521, [2]Biomed. Sci., Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521, [3]Biology, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521.

The endocannabinoid system serves many physiological roles, including in the regulation of energy balance, food reward, and voluntary locomotion. Signaling at the cannabinoid type 1 (CB1) receptor has been specifically implicated in motivation for voluntary wheel running. We studied 4 replicate lines of high-runner (HR) mice that have been selectively bred for 75 generations based on total number of wheel revolutions on days 5 & 6 of a 6-day period of wheel access. Four replicate control (C) lines are bred without regard to wheel running. HR mice voluntarily run about 3 times as much as C, primarily by running faster. We hypothesized that circulating levels of endocannabinoids (specifically, anandamide [AEA] and 2-arachidonoylglycerol [2-AG]) might differ between HR and C mice, possibly in a sex-specific manner. 50 male and 50 female mice (half HR and half C) were allowed access to wheels for 6 days, while another 50 males and 50 females (also half HR and half C) were kept without access to wheels. Blood samples were taken during peak running on the 6th night of wheel access or no wheel access. Lipids, extracted from plasma, were processed via ultra performance liquid chromatography coupled to tandem mass spectrometry (UPLC/MS/MS). For AEA, we observed a trend for a linetype-by-wheel access interaction ($p=0.06$), with wheel access lowering levels of AEA in HR mice while raising them in C mice; in addition, females tended to have higher levels of AEA than males ($p=0.06$). Considering only the 100 mice with wheel access, the amount of wheel running in the previous 30 minutes before sacrifice was a positive predictor of the amount of plasma AEA ($p<0.01$) and HR mice had significantly lower levels of AEA than C mice ($p=0.01$). For 2-AG, we observed a 3-way interaction between sex, linetype, and wheel access ($p<0.05$); in addition, females always had lower levels than males did ($p<0.05$). Unlike AEA, amount of wheel running did not quantitatively predict plasma levels of 2-AG. Our results support previous studies that show voluntary exercise can alter circulating levels of endocannabinoids and further demonstrate that selective breeding for voluntary exercise can affect regu-

lation of the endocannabinoid system. Supported by NSF IOS-11212732 to TG and NIH R00 DA034009 to NVD.

9.2

TIME OF DAY AND TRAINING STATUS BOTH MEDIATE THE BENEFIT OF CAFFEINE FOR CYCLING PERFORMANCE

James Boyett[1], Gabrielle Giersch[1], Christopher Womack[1], Michael Saunders[1], and Nicholas Luden[1]
[1]Dept. of Kinesiology, James Madison Univ., 261 Bluestone Dr., MSC 2302, Harrisonburg, VA, 22807.

Purpose: This project was designed to determine the effects of time of day and training status on the benefits of caffeine supplementation for cycling performance and peak muscle strength. **Methods:** Twenty trained and untrained subjects completed four trials consisting of 3-km time trials (TT) and isokinetic muscle strength testing. Subjects ingested either 6 mg/kg of caffeine or placebo one hour prior to each trial. The conditions included: morning placebo, morning caffeine, evening placebo, and evening caffeine. Training status was determined by recent training history, and top and bottom tertiles were compared. Magnitude-based inferences were used to evaluate all treatment differences. **Results:** For all subjects, caffeine enhanced 3-km TT performance in the morning (2.3 ± 1.7% 'very likely') and evening (1.4 ± 1.1% 'likely'). However, trained subjects only benefited from caffeine supplementation in the morning (1.0 ± 1.7% 'likely'), whereas untrained subjects rode faster with caffeine in the morning (5.5 ± 4.3% 'likely') and evening (2.9 ± 2.6% 'likely'). Caffeine 'likely' improved 3-km TT performance to a greater extent in untrained subjects than trained in the evening (2.9 ± 2.6% vs. -0.2 ± 2.1%) whereas morning was 'unclear' (5.5 ± 4.3% vs. 1.0 ± 1.7%). Caffeine had little effect on peak muscle strength. The influence of caffeine on most muscle strength measurements was 'likely trivial' or 'unclear'. **Conclusions:** Our observations indicate that trained athletes are more likely to profit from caffeine in the morning than the evening. Further, lesser-trained individuals appear to receive larger gains from caffeine than their trained counterparts.

9.3

EXERCISE TOLERANCE OF STATIN USERS WITH MYOPATHY: AN IMPORTANT ROLE FOR MITOCHONDRIAL FUNCTION

Eline Allard[1], Rebecca Verheggen[1], Maria Hopman[1], and Silvie Timmers[1]
[1]Dept. of Physiology, Radboud Univ. Med. Ctr., 6500HB, Nijmegen, Netherlands.

Cholesterol-lowering statins effectively reduce the risk of major cardiovascular events. Myopathy is the most important adverse event and is associated with exercise intolerance. Recently, we showed that statins have an off-target binding site at the mitochondrial respiratory complex III, leading to disturbances in muscle energy production. Here, we investigated in a cross-sectional approach whether this mechanism explains the muscle pain of statin users with myopathy, and its relation with muscle function and whole-body fitness. Maximal OXPHOS enzyme activities and maximal ATP production rate were determined in muscle biopsies obtained from statin users with and without myopathy, and a group of non-statin users (controls). All subjects performed an incremental cycling test to assess cardiovascular fitness and muscle contractile function and resistance to fatigue was determined during electrically stimulated isometric quadriceps contractions. Mitochondrial complex III activity was significantly lower in statin users with myopathy compared to controls ($p=0.05$), whilst no differences were found for statin users without muscle complaints. This was accompanied with a lower muscle ATP production rate ($p=0.04$). Complex III activity in statin users with myopathy was negatively correlated with the pain rating index ($R=-0.66$, $p=0.05$). Muscle contractile function, assessed by single contractions on different stimulation frequencies, revealed no differences in force rise, or the rate at which force increased or decreased between groups. However, repetitive muscle contractions demonstrated that muscles of myopathic statin users are more susceptible to fatigue as evidenced by the prolonged relaxation time ($p_{time*group} <0.001$) and decrease in maximal force rise over time ($p_{time*group} <0.001$). Maximal exercise performance was similar between groups (VO2peak), although changes were noted in substrate use during exercise. In statin users with myopathy ventilatory threshold 1 ($p=0.02$ compared to controls) and 2 ($p<0.01$ compared to controls) were reached at a lower percentage of VO2peak, indicating a faster switch to anaerobic energy supply. In conclusion, statin users with myopathy have diminished mitochondrial complex III activity, which strongly correlates with pain rating index. This may render them more susceptible to muscle fatigue and may impact on substrate use during aerobic exercise.

9.4

RAPID AND REVERSIBLE EFFECTS OF ESMOLOL ON O_2 EXTRACTION IN EXERCISING MUSCLES

David Proctor[1], Carter Luck[2], Stephan Maman[2], Urs Leuenberger[2], and Matthew Muller[2]
[1]Dept. of Kinesiology, Pennsylvania State Univ., 105 Noll Lab., University Park, PA, 16802, [2]Heart and Vascular Inst., Pennsylvania State Univ. Coll. of Med., 500 University Dr., Hershey, PA, 17033.

Background: The extent to which the leg muscles can augment oxygen (O_2) extraction is an important compensatory adjustment to meeting the O_2 demand of exercise during beta (β)-adrenergic blockade. We used intravenous esmolol, a short-acting cardioselective (β1) blocker, in combination with the high temporal resolution of near infrared spectroscopy (NIRS), to investigate these relationships. We hypothesized that esmolol-induced attenuation of exercise heart rate (HR) augments O_2 extraction in the active muscles of healthy humans, and that these effects are quickly reversible due to the short half-life of this drug. **Methods:** Eight healthy adults (6 men, 2 women, 24-68 yr) performed light and moderately intense bouts of recumbent leg cycling before (PRE), during (β-blocked), and 45 minutes following (POST) intravenous infusion of esmolol HCl. Oxygen uptake (VO_2), HR, systolic blood pressure (SBP), and local oxygen saturation (SmO_2, NIRS Moxy) of the vastus lateralis (VL) and gastrocnemius (G) muscles were continuously monitored during all three conditions. **Results:** β-blockade attenuated the increases in HR and SBP during light (-12±9 bpm and -26±12 mmHg vs. PRE) and moderate (-20±10 bpm and –40±18

mmHg vs. PRE) exercise (all $p<0.01$). End exercise VO_2 was similar across all 3 conditions, as were ratings of perceived effort. Exercise-induced reductions in SmO_2 (indicative of increased muscle O_2 extraction) were intensity dependent (moderate > light) and decreased to a greater extent during the β-blockade condition in both the VL ($p = 0.007$ vs. PRE) and G muscles ($p = 0.02$ vs. PRE). HR, SBP and SmO_2 responses were restored during the POST bouts (all $p>0.27$ versus PRE). Four additional subjects treated with intravenous propranolol exhibited large reductions in VL SmO2 during the β-blockade condition (19±6% lower SmO2 vs PRE, $p=0.007$) and this effect persisted during the POST condition. **Conclusions:** Esmolol-induced attenuation of exercise HR augments active muscle O_2 extraction. These findings reinforce the dynamic link between β1 adrenergic control of HR and active muscle O_2 extraction when systemic demand for blood flow is high. The rapid, reversible, and exercise intensity-dependent effects of esmolol on NIRS estimates of leg O_2 extraction also demonstrate the utility of these combined, minimally invasive methods for studying acute adjustments in cardiac function and peripheral O_2 utilization in exercising humans. **Funding:** NIH UL1 TR000127 and KL2 TR000126 (MDM), Pennsylvania Tobacco CURE funds (MDM), and Health & Human Development seed grant (DNP).

9.5

HIGH INTENSITY EXERCISE PRESERVES MYOCELLULAR SIZE THROUGHOUT DOXORUBICIN TREATMENT

Andrew D'Lugos[1], Cory Cosgrave[2], William Dedmon[2], Broc Astill[2], Shivam Patel[2], Mark Katsma[2], Rayna Gonzales[3], Taben Hale[3], Chad Carroll[2], Siddhartha Angadi[1], and Jared Dickinson[1]
[1]Exercise Sci. and Health Promotion, Arizona State Univ., 425 N. 5th St., Phoenix, AZ, 85004, [2]Physiology, Midwestern Univ., 19555 N. 59th Ave., Glendale, AZ, 85308, [3]Basic Med. Sci., Univ. of Arizona, 425 N. 5th St., Phoe-nix, AZ, 85004.

Anthracyclines are mainstay chemotherapeutic agents proven effecttive at reducing disease recurrence and mortality in breast cancer patients. However, these drugs also have devastating side effects that include skeletal muscle wasting. The purpose of this study was to assess the impact of bi-weekly doxorubicin (DOX) administration on body weight and skeletal muscle fiber size, and secondarily, to assess the ability of high-intensity interval exercise training before and during DOX treatments to attenuate reductions in body weight and fiber size. We hypothesized that DOX treatment would reduce body weight and skeletal muscle size, and that exercise would attenuate this response. Eight-week old ovariectomized female Sprague-Dawley rats were randomized to one of four treatments: Exercise+DOX (Ex-DOX); Ex+Vehicle (Ex-veh), Sedentary+DOX (Sed-DOX); and Sed+veh (Sed-veh). DOX (4mg/kg) or vehicle (saline) intraperitoneal injections were performed bi-weekly for a total of 3 injections (cumulative dose 12mg/kg). Ex animals underwent exercise 5d/week starting one week prior to the first injection and continued throughout study duration. Animals were euthanized ~5d following the last injection, during which the soleus muscle was dissected and prepared for immunohistological analysis. Relative to Sed-Veh, body weight was similarly reduced in Sed-DOX and Ex-DOX ($p<0.05$ vs. Sed-Veh and Ex-Veh). Cross-sectional areas (CSA) of myosin heavy chain (MHC) I and MHCIIa fibers of Sed-DOX were 30% smaller than Sed-Veh ($p<0.05$), whereas CSA of MHCI and MHCIIa were only reduced by 12% in Ex-DOX ($p<0.05$ vs. Sed-Veh). Further, fiber CSAs were larger in Ex-DOX vs. Sed-DOX indicating the preservation of muscle fiber size. These preliminary data suggest that DOX administration may reduce MHCI and MHCIIa fiber CSA, and that independent of changes in animal weight, intense exercise training may provide a therapeutic strategy to preserve skeletal muscle size during chemotherapy treatment. Funding: Intramural funds from Arizona State University and Midwestern University.

9.6

DOES DAILY EXERCISE PREVENT METABOLIC DYSREGULATION DURING UNLOADING?

Meghan Downs, PhD[1], Lori Ploutz-Snyder, PhD[2], Elizabeth Goetchius, M.S.[1], Roxanne Buxton, M.S.[1], Kathleen Randolph, B.S.[3], Christopher Danesi, M.S.[3], Melinda Sheffield-Moore, PhD[3], Randall Urban, M.D.[3], and Lichar Dillon, PhD[3]
[1]Exercise Physiology and Countermeasures, Univ. of Houston, 4800 Calhoun Rd., Houston, TX, 77204, [2]Exercise Physiology and Countermeasures, Universities Space Res. Assn., 3600 Bay Area Blvd., Houston, TX, 77058, [3]Div. of Endocrinology & Metabolism Dept. of Internal Med., Univ. of Texas Med. Branch (UTMB), 301 University Blvd., Galveston, TX, 77555.

Long-term energy imbalance leads to unfavorable changes in body composition and metabolic dysregulation. Relationships between physical inactivity and health are typically evaluated in high-disease-risk individuals; however, the effects in a well-controlled environment in healthy subjects are not well documentted. Our group is particularly interested in understanding the metabolic effects of unloading in astronauts as decreased insulin sensitivity, losses in muscle mass, and cardiovascular fitness are observed after long-duration spaceflight. **Purpose:** To evaluate resting metabolic rate (RMR), body composition, glucose tolerance, and insulin sensitivity during 70-days of bed rest (BR) (CON, N=8), BR with a high-intensity resistance and aerobic exercise countermeasure (BR+EX, N=8), and BR+EX paired with a testosterone supplement (BR+EX+T, N=8). **Methods:** All subjects completed 70-days of strict BR and were provided a World Health Organization weight maintaining diet. Resistance exercise was performed 3×/wk and aerobic exercise was performed 6×/wk. Testosterone enanthate was administered weekly (100 mg, IM) on a 2-week rotation. RMR, iDXA, oral glucose tolerance tests (OGTT), and 2-hour glucose derived CO_2 tests were conducted pre-, mid-, and at the end of BR. Homeostatic model assessment for insulin resistance (HOMA-IR) and Matsuda index of insulin sensitivity (IS) were calculated. Repeated measures ANOVA was used to assess group x time differences in dependent variables ($P<0.05$). **Results:** Body weight, RMR, and IS were maintained in all groups. Fat mass (FM) increased (11.5%) and fat-free mass (FFM) decreased (4.0%) in CON. FM increased (7.6%) in BR+EX. FFM increased in BR+EX+T (4.2%). HOMA-IR increased in CON (40.0%) and decreased in BR+EX+T (35.0%). Breath-measured CO_2 increased in CON (9.0%). **Conclusions:** Prolonged BR results in impaired metabolic efficiency that reaches levels of clinical significance, even

with a controlled weight maintaining diet. The exercise countermeasure appears to mitigate BR-induced metabolic impairments, and the addition of a testosterone supplement may provide further protection. These results highlight the importance of daily physical activity and promotion of FFM for overall health during unloaded conditions (i.e. BR, spaceflight), which is important in regards to preserving the metabolic health of astronauts and the general public given the growing epidemic of sedentary behavior in otherwise healthy middle-aged individuals.

9.7

HIGH INTENSITY EXERCISE PRESERVES SKELETAL MUSCLE MTOR SIGNALING DURING DOXORUBICIN TREATMENT IN OVARIECTOMIZED FEMALE RATS

Jared Dickinson[1], Andrew D'Lugos[1], Tara Mahmood[1], Lara Salvo[1], Cory Cosgrove[2], Logan Dedmon[2], Broc Astill[2], Shivam Patel[2], Mark Katsma[2], Rayna Gonzales[3], Taben Hale[3], Siddhartha Angadi[1], and Chad Carroll[2]

[1]Exercise Sci. and Hlth. Promotion, Arizona State Univ., 425 N. 5th St., Phoenix, AZ, 85004, [2]Physiology, Midwestern Univ., 19555 N. 59th Ave., Glendale, AZ, 85308, [3]Coll. of Med. Phoenix Basic Med. Sci., Univ. of Arizona, 425 N. 5th St., Phoenix, AZ, 85004.

Doxorubicin (DOX) is a chemotherapeutic agent proven effecttive for treatment of breast cancer patients; however, it also has devastating side effects that include skeletal muscle atrophy and dysfunction. The purpose of this study was to determine the ability for high-intensity interval exercise performed prior to and during bi-weekly DOX treatments to attenuate adverse effects of DOX on skeletal muscle. We hypothesized that DOX treatment would reduce mammalian target of rapamycin (mTOR) signaling in skeletal muscle and that exercise would attenuate this response. Eight-week old ovariectomized female Sprague-Dawley rats were randomized to one of four treatments: Exercise+DOX (Ex-DOX); Ex+Vehicle (Ex-Veh), Sedentary+DOX (Sed-DOX); and Sed+Veh (Sed-Veh). DOX (4mg/kg) or Vehicle (saline) intraperitoneal injections were performed bi-weekly for a total of 3 injections (cumulative dose 12mg/kg). Ex animals underwent high intensity (85-95 %VO_2peak) interval exercise (4×4 min bouts) 5d/wk starting 1 week prior to the first injection and continued throughout study duration. Animals were euthanized 5d following the last injection, during which the soleus and gastrocnemius muscles were dissected and prepared for protein analyses via western blot. Phosphorylated levels of $mTOR^{Ser2448}$ were decreased in both the soleus and gastrocnemius of Sed-DOX ($p<0.05$ vs. Sed-Veh), whereas phosphorylation of mTOR was not altered in skeletal muscle of Ex-DOX. Similarly, there was a tendency for reduced phosphorylation of $4E\text{-}BP1^{Thr37/46}$ in the soleus and $Ulk1^{Ser757}$ in the soleus and gastrocnemius in Sed-DOX ($p=0.1$ vs. Sed-Veh), whereas these levels were unaltered in Ex-Dox. These preliminary data suggest that DOX administration may impact mTOR signaling, and that intense exercise may provide a therapeutic strategy to preserve skeletal muscle mTOR activity during chemotherapy treatment.

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10.0 CARBOHYDRATE METABOLISM

10.1

THE EFFECT OF ENDURANCE EXERCISE DURATION, INTENSITY AND FITNESS STATUS ON SKELETAL MUSCLE GLYCOGEN UTILIZATION: A META-ANALYSIS

Jose Areta[1], and Will Hopkins[2]

[1]Dept. of Physical Performance, Norwegian Sch. of Sport Sci., Sognsveien, 220, Oslo, 0863, Norway, [2]Coll. of Sport and Exercise Sci., Victoria Univ., 460 Ballarat Rd., Melbourne, Australia.

Background: Skeletal muscle glycogen is an important energy source for muscle contraction and a key regulator of oxidative phenotype. Manipulation of muscle glycogen is therefore a strategy to improve performance in competitions and training adaptations to endurance exercise. However, assessing muscle glycogen content in the field is impractical, and there are no normative values for glycogen utilization during exercise. **Objective:** To meta-analyze the modifying effects of exercise intensity, exercise duration, baseline glycogen content and fitness on muscle glycogen content. **Methods:** We accessed all publications in PUBMED on direct measurement of muscle glycogen in humans during cycling and running. Glycogen content was expressed as mmol per kg of dry mass. Standard errors for glycogen content were imputed where necessary via prediction of standard errors of measurement. Fixed effects in the meta-regression mixed model included exercise duration (five levels, with means of 5, 23, 53, and 114 min during exercise, and 127 min for time to fatigue), exercise intensity (linear, as percent of VO2max), fitness status (linear, as VO2max in $ml.min^{-1}.kg^{-1}$), and baseline glycogen (linear, in mmol). Intensity, fitness and baseline glycogen were interacted with duration. Random effects accounted for between- and within-study variance. Inferences about change in glycogen were based on acceptable uncertainty (99% confidence intervals) in standardized magnitudes, with thresholds for small, moderate and large changes of 25, 75 and 150 mmol. **Results:** The search yielded 2210 articles, of which 179 were included in the final analysis and 446 exercise sampling-points extracted. A 30% increase of intensity showed positive clear effects: small at 5 min (45 mmol), moderate at 23 and 53 min (88 and 121 mmol), large at 114 min (155 mmol), and trivial but unclear at the point of fatigue. An increase of baseline glycogen of 200 mmol showed positive clear effects: small at 5 and 23 min (44 and 48 mmol), moderate at 23 min (95 mmol) and large at 114 min and at fatigue (161 and 217 mmol). An increase of fitness status of 10 $ml.min^{-1}.kg^{-1}$ showed a trivial effect at 5 and 23 min and at fatigue but a negative (glycolgen sparing) small effect at 53 and 114 min (-36 and -28 mmol). **Conclusions:** This analysis has provided novel useful normative data for the effects of exercise intensity, exercise duration, fitness and baseline glycogen on glycogen utilization.

10.2

A NOVEL METHOD REVEALS A FIBER TYPE SELECTIVE EFFECT OF ACUTE EXERCISE ON GLUCOSE UPTAKE BY SINGLE SKELETAL MUSCLE FIBERS

Mark Pataky[1], Edward Arias[1], Carmen Yu[1], Yilin Nie[1], Kallisse Dent[1], and Gregory Cartee[1]

[1]Sch. of Kinesiology, Univ. of Michigan, 401 Washtenaw Ave., Ann Arbor, MI, 48109.

One exercise bout can increase subsequent insulin-stimulated glucose uptake (GU) by skeletal muscle, a tissue comprised of several metabolically diverse fiber types. The conventional approach for assessing fiber type differences relies on comparing multiple muscles with differing fiber types. Because this approach cannot resolve fiber type differences at the cellular level, we recently developed a novel method to determine both GU and fiber type in a single rat skeletal muscle fiber. Objective: Our primary aim was to determine effects of acute exercise on insulin-independent and insulin-dependent GU by single fibers of different fiber types. Methods: Rats were either sedentary (SED) or exercised (2h swim exercise) with exercised rats studied either immediately post-exercise (IPEX) or 3.5h post-exercise (3.5hPEX). Epitrochlearis muscles were dissected from anesthetized rats and incubated with [^{3}H]-2-deoxyglucose (2DG). Muscles from IPEX and SED rats were incubated without insulin. Muscles from 3.5hPEX and other SED rats were incubated ±100μU/ml insulin. Muscles were then incubated with collagenase, and single fibers were isolated. SDS-PAGE with protein staining was used to identify fiber type based on myosin heavy chain expression. 2DG accumulation was measured by liquid scintillation counting. Results: The major new findings were: 1) 100μU/ml insulin increased GU by single fibers of each fiber type; 2) in the SED group, GU by insulin-stimulated type I and IIA fibers exceeded values for type IIB, IIBX and IIX fibers, and insulin-stimulated values for IIX fibers exceeded IIB fiber values; 3) insulin-independent GU in single fibers of each fiber type was increased IPEX; and 4) insulin-stimulated GU at 3.5hPEX was increased in type I, IIA, IIB and IIBX, but not type IIX fibers. Conclusions: Greater insulin-independent GU IPEX in each fiber type provides strong evidence that each fiber type was recruited. Therefore, it seems unlikely that the lack of greater insulin-stimulated GU in type IIX fibers of 3.5hPEX rats is attributable to IIX fibers not being recruited. Our previous research in whole muscle implicated increased Akt Substrate of 160 kDa (AS160; also called TBC1D4) phosphorylation as a potential mechanism for greater insulin sensitivity post-exercise. Taking together previous and current results, our new working hypothesis is that AS160 phosphorylation is increased in insulin-stimulated type I, IIA, IIB and IIBX fibers, but not IIX fibers at 3.5hPEX.

10.3
PRE-EXERCISE HIGH-FAT/LOW-CARBOHYDRATE DIET FOR 3 DAYS AFFECTS POST-EXERCISE SKELETAL MUSCLE GLYCOGEN REPLETION

Yumiko Takahashi[1], Yutaka Matsunaga[1], Yuki Tamura[1], Shin Terada[1], and Hideo Hatta[1]

[1]Dept. of Sports Sci., Univ. of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo, 153-8902, Japan.

Previous studies suggested that short term high-fat/low-carbohydrate diet decreased glucose disposal after glucose administration. In this study we investigated influences of pre-exercise high-fat/low-carbohydrate diet for 3 days on post-exercise glycogen repletion in skeletal muscle in ICR mice. Mice received either high-fat/low-carbohydrate diet (57% kcal from fat, 23% kcal from carbohydrate, HFD group) or standard lab chow (13% kcal from fat, 60% kcal from carbohydrate, Con group) for 3 days before exercise. Mice performed treadmill running at 25 m/min for 60 min and they were orally administered glucose (2 mg/g body weight) solution at immediately after and 60 min after the exercise. At the end of exercise, there was no significant difference in skeletal muscle glycogen concentration between the two groups. At 120 min after the exercise, however, skeletal glycogen concentration tended to be 34 % lower in the HFD group compared with that of the Con group ($p = 0.05$). The rates of skeletal muscle glycogen accumulation were lower in the HFD group compared with those of the Con group both during the first 60 min and the second 60 min of post-exercise recovery (first 60 min: 1.9 mg/g wet weight [wt] in the HFD group vs. 3.0 mg/g wt in the Con group, second 60 min: 2.6 mg/g wt in the HFD group vs. 3.9 mg/g wt in the Con group). Blood glucose concentration in the HFD group was significantly higher than the Con group at 120 min after the exercise ($p < 0.05$) and no significant difference was observed in plasma insulin concentration. There were no significant between-group differences in phosphorylation state of Akt Thr^{308} and Ser^{473}, AS160 Thr^{642}, glycogen synthase Ser^{641} and in glucose transporter 4 protein level during post-exercise recovery except for higher phosphorylated state of Akt Ser^{473} in HFD group at 60 min after the exercise ($p < 0.05$). Our results suggest that pre-exercise high fat diet attenuates post-exercise glycogen repletion in skeletal muscle without impairing insulin signaling cascade.

10.4
USING A TRIPLE GLUCOSE TRACER TECHNIQUE TO QUANTIFY POSTPRANDIAL GLUCOSE FLUX AFTER ACUTE EXERCISE AND EXERCISE TRAINING

Dale Morrison[1], Clinton Bruce[1], Greg Kowalski[1], and Glenn Wadley[1]

[1]Inst. for Physical Activity and Nutrition, Deakin Univ., 221 Burwood Hwy., Burwood, 3125, Australia.

Background: Much of the scientific knowledge regarding glucose metabolism is inferred from non-physiological measurement techniques that do not accurately represent the dynamic conditions associated with a postprandial state. The 'gold standard' for determining postprandial glucose flux is the triple tracer technique, but so far it is underutilised in human research. Therefore, the aim of this study was to utilize the triple tracer technique to accurately quantify changes to glucose flux under postprandial conditions in response to a single bout of endurance exercise and then 4 weeks of endurance training. **Methods:** Six healthy, lean, untrained males (22.8 ± 0.4 years) underwent the triple tracer technique using stable isotopes [U-13C6], [6,6-2H2] and [1-13C]glucose, at baseline, 20 ± 1hrs after a single bout of endurance exercise and then after 4 weeks of endurance training (71.4 ± 0.1 % VO_2max for 1 hour, 5d/wk). Glucose fluxes involving endogenous glucose production [EGP], glucose rate of appearance [Ra] and glucose rate of disposal [Rd] were calculated as previously described (1). Data are in mean ± SEM. **Results:** Preliminary data indicates that exercise significantly decreased glucose area under the curve (AUC) (1448 ± 5 vs 1243

± 5.8 vs. 1271 ± 3.9, p<.05, baseline vs. acute exercise vs. training, respectively) and peak glucose (8.68 ± 0.62 vs. 7.77 ± 0.59 vs. 6.96 ± 0.44mmol/l, p<.05). However, insulin AUC (3966 ± 22 vs. 2807 ± 9 vs. 2437 ± 9 uU/ml) and peak (43 ± 1 vs. 35 ± 0.7 vs. 26 ± 0.9) only tended to be different. Glucose Ra and Rd were unchanged, while postprandial suppression of EGP was significantly reduced following both acute exercise and exercise training (61.4 ± 0.8 vs. 52.4 ± 1.5 vs. 48.9 ± 2.3% of AUC, p<.05). Peak suppression of EGP was not significantly changed by exercise (3.1 ± 0.26 vs. 3.3 ± 0.2 vs. 3.5 ± 0.2µmol/kg/min). No significant difference between acute exercise and exercise training was observed for any variable. **Conclusion:** The improvement in glucose tolerance seen following exercise training is almost completely due to the effect of the last acute exercise bout and not the summative effect of training. Additionally, under physiological postprandial conditions, the glucoregulatory system is able to achieve the same rate of fluxes following acute exercise and exercise training despite lower prevailing glucose and a tendency for decreased insulin. However, the EGP nadir is more transient following exercise, demonstrating that the system is more quickly able to return toward a steady regulatory state. **References:** 1. Basu R, Di Camillo B, Toffolo G, Basu A, Shah P, Vella A, et al. American Journal of Physiology-Endocrinology And Metabolism. 2003;284(1):E55-E69.

10.5

EFFECTS OF A 4-DAY LOW-CARBOHYDRATE DIET WITH OR WITHOUT POST-MEAL WALKING ON GLUCOSE CONTROL IN TYPE 2 DIABETES

Etienne Myette-Cote[1], Cody Durrer[1], Helena Neurdoff[1], and Jonathan P. Little[1]

[1]Sch. of Hlth. and Exercise Sci., Univ. of British Columbia, 3333 University Way, Kelowna, BC, V1V 1V7, Canada.

Background: Chronic hyperglycemia along with excessive daily glucose fluctuations are linked to increased cardiovascular disease risk. Lifestyle changes are recommended as first-line treatments to improve glucose control in type 2 diabetes. One of the most efficient approaches to lower glucose levels is to consume a low-carbohydrate diet. However, it is unknown if the addition of strategically-timed post-meal exercise could further improve glucose control in this population. **Aim:** To determine if daily post-meal walking, on top of a low-carbohydrate high-fat diet (LCHF+PW), will improve 24-hour glycemic profile to a greater extent than a i) low-carbohydrate high-fat diet (LCHF) alone and a ii) low glycemic index low-fat dietary guidelines diet (DG) in individuals with type 2 diabetes. **Methods:** Eight individuals with T2D (age: 62±9, HbA1c: 6.5±0.7, means±SD) completed three isocaloric 4-day diet conditions in a randomized crossover design. The LCHF+PW diet included three daily 15-min post meal walks at a light-to-moderate intensity. Glucose profiles were assessed by continuous glucose monitoring. Fasting blood samples were obtained before and after each intervention to measure glucose, triglycerides and inflammatory markers. **Results:** Compared to DG (7.0±1.1 mmol/l), both LCHF (6.3±0.9 mmol/l) and LCHF+PW (6.1±0.8 mmol/l) decreased 4-day mean glucose concentrations (p<0.01). Glycemic variability assessed by standard deviation as well as the percentage of time spent above 10 mmol/L were also reduced in LCHF (0.9±0.4 mmmol/l, 0.8±2.3 %) and LCHF+PW (0.9±0.5 mmol/l, 0.3±0.7 %,) compared to DG (1.8±1.2 mmol/l, 8.8±9.5 %; all p<0.05). No significant differences were observed between LCHF and LCHF+PW (p≥0.221). The percentage of time spent <4 mmol/L was similar across all conditions (2.0±5.6, 1.2±1.8, 1.9±2.9 %; p=0.882) and no significant differences between conditions were detected for fasting glucose, triglycerides and white blood cell count. **Conclusions:** Four days of a LCHF diet reduced hyperglycemia and lowered glycemic variability in people with type 2 diabetes. The addition of three daily post meal walks did not further improve short-term glycemic control. Funding source: University of British Columbia internal grant and Medtronic Canada.

10.6

TEN WEEKS OF HIGH INTENSITY INTERVAL TRAINING IN MEN AND WOMEN WITH PRE-DIABETES IS ASSOCIATED WITH IMPROVED GLUCOSE METABOLISM AND ALTERED ADIPOKINE PRODUCTION

Leslie Willis[1], Cris Slentz[1], Kim Huffman[1], Janet Lord[2], William Kraus[1], and David Bartlett[1,2]

[1]Duke Molecular Physiology Inst., Duke Univ., 300 N. Duke St., Durham, NC, 27701, [2]Inst. of Inflammation and Ageing, Univ. of Birmingham Sch. of Med., Birmingham B15 2TT, UK.

Introduction: Increased obesity and reduced physical activity is associated with the prevalence of type-2 diabetes. Adipose tissue contributes to impaired glucose tolerance through persistent production of pro-inflammatory mediators including adipose-specific cytokines such as leptin. Exercise and diet are potent lifestyle modifications that reduce body fat and improve glucose tolerance. These interventions are often time-consuming and have moderate-adherence. High intensity interval training offers a novel avenue to reduce time commitment and potentially improve glucose metabolism in those at risk of diabetes. The aim of this study was to determine if low volume high intensity interval training in those with prediabetes improved glucose metabolism, insulin sensitivity and adipokine production. **Method**: Ten older (Age: 71±5 years; BMI: 29±3 kg/m^2) sedentary participants with prediabetes (HbA1c = 6.1±0.3%) completed 10-weeks of a high intensity interval training program. Training consisted of ten ≥60 second high-intensity intervals (80-90% HRR) separated by similar bouts of low intensity exercise (50-60% HRR) 3 times/week. Glucose tolerance and insulin sensitivity were determined by an oral glucose tolerance test. Adipokine production was assessed by plasma analysis of leptin and adiponectin. **Results**: Significant improvements were observed for relative VO_{2peak} (p=0.004) and absolute VO_{2peak} (p=0.01) with no change in body mass index (p=0.196) or body fat percent (p=0.574). Significant reductions were evident for fasting glucose (p=0.04) and insulin (p=0.05). Glucose and insulin area under the curve reductions suggest that glucose tolerance was improved (p=0.02), while insulin sensitivity was increased (p=0.03). Although there was no change in body fat percentage, there was a 25% reduction in leptin (p=0.017) and no change in adiponectin (p=0.139) resulting in a reduced leptin to adiponec-

tin ratio (p=0.026). **Conclusion:** Ten weeks of low-volume high intensity interval training in older individuals at risk for diabetes significantly improved aerobic fitness, glucose tolerance and insulin sensitivity; also, concentrations of the adipokine, leptin, were reduced. Remarkably, these responses occurred in the absence of significant changes in mass or body composition. Interval-based training offers a novel means of reducing the risk of diabetes in older sedentary men and women. *This work was funded by an EU Marie Curie Outgoing Fellowship Grant (PIOF-GA-2013-629981).*

10.7
FASTING AFFECTS BLOOD LACTATE CONCENTRATIONS DURING HIGH INTENSITY EXERCISE

Kenya Takahashi[1], Yosuke Sato[1], Mai Banjo[1], Yumiko Takahashi[1], and Hideo Hatta[1]
[1]Dept. of Sports Sci., Univ. of Tokyo, 3-8-1, Komaba, Meouro-ku, Tokyo, 153-8902, Japan.

Purpose: Lactate is produced and accumulates in skeletal muscle during exercise depending on muscle glycogen concentration. It can be assumed that intense exercise with fasting decreases lactate production and accumulation due to low muscle glycogen concentration. The purpose of this study was to investigate the effects of fasting on energy substrate concentrations during high intensity exercise. **Methods**: 4-week-old male ICR mice were randomly assigned to control (C, n=5) group, high intensity exercise (E, n=5) group, fasting (F, n=5) group or high intensity exercise with fasting (F+E, n=6) group. Mice were fed ad libitum in all groups and fasted for 18 hours in F group and F+E group before sacrifice. E group and F+E group mice were subjected to treadmill running at a speed of 40 m/min for 2 min. Blood and muscles were harvested immediately after exercise. Energy substrate concentrations were measured. **Results**: Blood lactate concentrations were significantly lower in F+E group than E group (5.5 ± 1.0 vs. 11.2 ± 1.8 mmol/L, mean ± SE). Blood glucose concentrations were also significantly lower in F+E group than E group (4.1 ± 0.5 vs. 7.7 ± 0.5 mmol/L). Blood free fatty acid concentrations were significantly higher in F+E group than E group (0.80 ± 0.18 vs. 0.26 ± 0.04 mEq/L). Mice without fasting showed greater mean decrease of muscle glycogen by the exercise. **Conclusions**: Fasting decreased blood lactate and glucose concentrations and increased blood fatty acid concentrations during high intensity exercise. We conclude that glycogenolysis during high intensity exercise is excessively conducted in glycogen abundant muscle.

10.8
CHRONIC HIGH DIETARY SUCROSE CONSUMPTION INCREASES ENERGY EXPENDITURE INDEPENDENT OF PHYSICAL ACTIVITY OR BODY WEIGHT IN MICE

Erin Stephenson[1], Kathryn Cyrus[2], Joan Han[3,4], and Dave Bridges[5]
[1]Dept. of Pediatrics, Univ. of Tennessee Hlth. Sci. Ctr., 71 S. Manassas St., Ste. 318G, Memphis, TN, 38163, [2]Dept. of Physiology, Univ. of Tennessee Hlth. Sci. Ctr., 894 Union Ave., Ste. 517, Memphis, TN, 38163, [3]Dept. of Pediatrics, Univ. of Tennessee Hlth. Sci. Ctr., 71 S. Manassas St., Ste. 318H, Memphis, TN, 38163, [4]Dept. of Physiology, Univ. of Tennessee Hlth. Sci. Ctr., 71 S. Manassas St., Ste. 318H, Memphis, TN, 38163, [5]Dept. of Nutritional Sci., Univ. of Michigan, 3866 SPH I, 1415 Washington Heights, Ann Arbor, MI, 48109-2029.

Sugar-sweetened beverage (SSB) consumption is the major source of added sugar in the human diet & is strongly associated with the development of obesity. Most studies investigating the effects of dietary sugar use supraphysiological concentrations or are confounded by the addition of high dietary fat. Therefore, whether high-but-physiologically-relevant dietary sugar consumption leads to alterations in energy expenditure (EE) &/or habitual physical activity (PA) is not known. We have used non-invasive body composition analysis, indirect calorimetry & PA monitoring to determine the effects of 12 wk of sucrose consumption in 70 d old male mice. Mice had ad libitum access to standard rodent chow throughout the study. 10% (w/v) sucrose (or water as control) was administered in the drinking water; a concentration similar to many commonly available SSBs. Body composition & food/water intake were measured longitudinally. PA (ambulatory movement) & EE (VO_2) were determined between wk 11 & 12 of sucrose availability.There were no differences in food consumption between the control & sucrose groups; however, sucrose treated mice consumed 34.4% more kCal/d ($p<0.05$) as a result of the additional energy provided by the sucrose. Although body weight did not differ until wk ten (9%, p=0.036), fat mass increased as early as wk five (26.3%, p=0.04) & was 97.9% greater in the sucrose group at the end of 12 wk ($p<0.0001$). There were no differences in fat-free mass at any time point. Average EE was greater in the sucrose mice during both the diurnal & nocturnal phases (13.4%, $p<0.05$). After normalization to fat-free body mass, these differences were retained, indicating that chronic sucrose consumption caused an increase in EE independent of body/fat mass. Both groups had similar respiratory exchange ratios, indicating that energy substrate preference was unaltered by increased carbohydrate availability. No difference in PA was observed during the diurnal phase; however, nocturnal PA was substantially reduced in the sucrose group (-36.7%, $p<0.05$), which is inconsistent with the increased EE observed in these mice. These findings demonstrate that chronic sucrose consumption at concentrations achievable in a typical human diet causes an increase in adiposity & a reduction in habitual PA, while concomitantly increasing EE. Future studies will elucidate the mechanisms responsible for the increase in EE observed with physiologically relevant high dietary sucrose consumption.

11.0 ADIPOSE AND LIPID METABOLISM

11.1
ENHANCED FATTY ACID OXIDATION AND THE RESPONSE TO EXERCISE IN MICE

Stephen Kolwicz Jr. [1], Carliana Halterman[1], Son Nguyen[1], and Samuel Curtis[1]
[1]Mitochondria & Metabolism Ctr., Univ. of Washington, 850 Republican St., N-130, Seattle, WA, 98109.

Background: Mitochondrial uptake of fatty acids has been proposed as one potential factor that could limit endurance exercise capacity. Malonyl CoA, generated by acetyl CoA carboxylase 2

(ACC2), is a potent inhibitor of fatty acid transport into the mitochondria, and subsequently, fatty acid oxidation. In the present study, we generated mice with a systemic deletion of ACC2 (ACC2-null) to test the hypothesis that increased systemic fatty acid oxidation would enhance endurance exercise performance. **Methods:** Male ACC2-null mice and littermate controls (CON; n=4-5 each group) were randomly assigned to an exercise training (EX) protocol on a motorized treadmill (60 min/day, 5 days/wk, 10 wks). A cohort of untrained CON and ACC2-null mice were used as sedentary controls (n=6-7 each group). Mice were subjected to an endurance exercise capacity (EEC) test to exhaustion pre- and post-EX. **Results:** Untrained ACC2-null had similar body weights as CON mice up to 6 months of age. In addition, heart, liver, skeletal muscle, and adipose tissue mass were similar. ACC2-null mice also had similar serum levels of glucose, fatty acids, and triglycerides as CON. When subjected to an EEC test, untrained ACC2-null mice demonstrated a ~30% decrease in total exercise time (78.0 ± 2.9 vs 107.8 ± 9.0 min, $P<0.05$), which was associated with a ~20% reduction of citrate synthase (CS) activity in the soleus but not in liver and heart. Electron microscopy analysis suggested a trend of lower mitochondria density ($P=0.08$) in ACC2-null soleus muscle. However, 10wks of EX abolished the impaired exercise capacity in ACC2-null mice as total exercise time was similar to CON (122.2 ± 4.5 vs 125.1 ± 7.4 min). CS activity in the soleus of trained ACC2-null was increased to levels similar to trained CON. Surprisingly, trained ACC2-null mice had reduced body weight (~7%) and adipose tissue mass (~15%) compared to CON after EX ($P<0.05$). **Conclusion:** Systemic deletion of ACC2 impairs endurance exercise capacity in untrained mice, likely due to a negative effect on skeletal muscle mitochondria. However, chronic exercise training corrects the baseline defect. In young, healthy mice of normal body weight, exercise training combined with ACC2 deletion results in reduced body weight and adipose tissue mass. The present data suggest that inhibition of ACC2 for the treatment of obesity and/or diabetes may not have the desired effects unless combined with chronic exercise training.

11.2
OVEREXPRESSION OF SKELETAL MUSCLE PHOSPHATIDYLETHANOLAMINE METHYLTRANSFERASE DOES NOT AFFECT WHOLE BODY METABOLISM IN MICE

Patrick Ferrara[1], Edward Wentzler[1], Anthony Verkerke[1], Tara Narowski[1], Armondo Balotti[1], and Katsuhiko Funai[1,2]
[1]Dept. of Kinesiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27858, [2]Dept. of Physiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27858.

Phosphatidylcholine (PC) is the most abundant phospholipid that consists in mammalian cellular membranes. Phosphatidylethanolamine methyltransferase (PEMT) synthesizes PC by trimethylation of phosphatidylethanolamine (PE). Previous studies demonstrated that mice with whole-body deletion of PEMT (PEMTKO) are protected from diet-induced obesity concomitant to an increase in whole body energy expenditure. The molecular mechanism for this effect is unknown. Our laboratory recently found that skeletal muscles from these mice exhibit increased resting O_2 consumption, suggesting that skeletal muscle PEMT might alter energy expenditure and the propensity for obesity. Indeed, in mice and humans, high-fat diet feeding promoted an increase in PEMT mRNA level in skeletal muscle. To identify whether an increase in skeletal muscle PEMT is sufficient to decrease energy efficiency and promote obesity, we generated mice with skeletal muscle specific tamoxifen-inducible knock-in of PEMT (PEMT-MKI). Rosa26-targeted knock-in of PEMT resulted in a successful overexpression of PEMT specifically to skeletal muscle (by mRNA and protein). With standard chow or high-fat feeding, control and PEMT-MKI mice did not differ in body weight, body composition, or whole-body energy expenditure. Future studies will investigate whether overexpression of PEMT results in altered O_2 consumption or insulin sensitivity of skeletal muscle. This study was supported by NIH grants DK095774 and DK109888.

11.3
EXERCISE TRAINING ALTERS EXPRESSION OF DEVELOPMENTAL GENES AND ADIPOGENIC POTENTIAL IN ADIPOCYTES AND ADIPOSE-DERIVED STEM CELLS ISOLATED FROM SUBCUTANEOUS AND VISCERAL FAT DEPOTS

Hisashi Kato[1], Hisashi Takakura[1], Mutsuko Hieda[1], Yoshinobu Ohira[1], and Tetsuya Izawa[1]
[1]Fac. of Hlth. and Sports Sci., Doshisha Univ., 1-3 Tatara-Miyakodani, 610-0394, Kyotanabe City, Japan.

Objective: White adipose tissue is classified into subcutaneous (SAT) and visceral (VAT) adipose tissue. SAT and VAT exhibit different intrinsic properties, including the rate of lipolysis and insulin sensitivity, and the excess amount of VAT is associated with insulin resistance and type 2 diabetes. Recent studies indicate that developmental genes are differentially expressed in SAT and VAT, and that some of these genes exhibit changes in expressions which closely correlate with the extent obesity and the pattern of fat distribution. Therefore, well-known beneficial effect of habitual physical exercise, which induces decreases in cell size and lipid content in adipocytes and changes fat distribution, might be associated with alterations in developmental genes in SAT and VAT. However, it remains unclear whether developmental genes are associated with morphological changes in different fat depots in response to regular exercise. Here, the present study aimed to investigate the effect of exercise training (TR) on developmental genes and adipogenic potential of adipose-derived stem cells (ADSCs) in SAT and VAT. Methods: 5-week-old male Wistar rats were divided into two groups: a sedentary control (n = 5) and the TR group (n = 5). The TR rats were subjected to exercise on a treadmill set at a 5-degree incline 5 days per a week for 9 weeks, and the rats were sacrificed 36 h after the last exercise session. Adipocytes and ADSCs were isolated from SAT (inguinal) and VAT (epididymal and retroperitoneal). The mRNA expression levels of developmental genes (i.e., homeobox family and Glypican-4) and bone morphogenetic protein (BMP) family genes were determined using real-time PCR. These genes play a critical role in the commitment of mesenchymal stem/progenitor cells into the adipocyte

lineage in adipocytes and ADSCs. Furthermore, to verify whether exercise training influences adipogenic potential of ADSCs, ADSCs were differentiated into adipocytes, and the mRNA expression levels of developmental, BMP family, and maker genes for adipogenesis were analyzed. Results: The fat depot-specific differences in mRNA expression levels of developmental and BMP family genes were observed in adipocytes and ADSCs isolated from three fat depots. TR induced the changes in the expression levels of some of these genes, i.e., *Hoxc9*, *Hoxc10, Bmp2,* and *Bmp4*. Moreover, TR altered the ability of ADSCs to differentiate into adipocytes in ADSCs isolated from epididymal and retroperitoneal. Interestingly, the expression of *Bmp4* was dramatically enhanced along with differentiation of ADSCs into adipocytes. Conclusion: These data suggest that exercise training alters the expression of developmental genes and adipogenic potential in adipocytes and ADSCs isolated from SAT and VAT.

11.4

IMPACT OF SKELETAL MUSCLE IL-6 ON METABOLIC REGULATION IN ADIPOSE TISSUE DURING PROLONGED EXERCISE

Lærke Bertholdt[1], Anders Gudiksen[1], Camilla L. Schwartz[1], Jakob G. Knudsen[1], and Henriette Pilegaard[1]

[1]Dept. of Biology, Univ. of Copenhagen, Universitetsparken 13, Copenhagen, 2100, Denmark.

Purpose: Interleukin 6 (IL-6) has previously been shown to be released from human skeletal muscle during exercise and has been suggested to regulate metabolism in several tissues including adipose tissue. Therefore the aim was to investigate the role of skeletal muscle IL-6 on lipolysis and substrate regulation in adipose tissue during prolonged exercise. **Methods:** Subcutaneous adipose tissue and trunk blood was obtained from male muscle-specific IL-6 knockout (IL-6 MKO) mice and littermate lox/lox mice (Control) after 10 min, 60 min and 120 min of treadmill running as well as without acute exercise (Rest). **Results:** Plasma glycerol concentrations increased after 10 min of exercise and returned to resting level after 1h of exercise in Control mice, while there was no change during exercise in IL-6 MKO mice. The plasma free fatty acid (FFA) concentrations decreased early during exercise and increased late during exercise in IL-6 MKO mice, but remained unchanged in Control mice. Plasma FFA and glycerol concentrations were lower in IL-6 MKO than Control mice at Rest as well as at Rest and after 10 min of exercise, respectively. In addition, hormone sensitive lipase Ser660 phosphorylation tended to increase at 120 min of exercise in Control mice and perilipin protein was lower in IL-6 MKO mice than Controls at 120 min of exercise. Furthermore, ATGL protein was higher in IL-6 MKO mice than Controls at Rest. Pyruvate dehydrogenase kinase (PDK) 4 mRNA increased similarly in both genotypes at 120 min of exercise and pyruvate dehydrogenase phosphatase 2 mRNA tended to decrease at 120 min of exercise in Controls, while PDK4 protein level and pyruvate dehydrogenase phosphorylation (phosphorylation site 2 and 3) were unchanged during prolonged exercise. **Conclusion:** The present findings indicate that skeletal muscle IL-6 regulates adipose tissue lipolysis at Rest and during prolonged exercise, while regulation of substrate choice in adipose tissue is IL-6 independent at Rest and during prolonged exercise. **Funding:** The study is funded by The Lundbeck Foundation and The Danish Council for Independent Research in the Natural Sciences.

11.5

PHOSPHATIDYLETHANOLAMINE METHYLTRANSFERASE IS REQUIRED FOR MITOCHONDRIAL UNCOUPLING AND CARDIOLIPIN CONTENT IN BROWN ADIPOSE TISSUE

Jordan Johnson[1], Anthony Verkerke[1], Timothy Heden[1], Tara Narowski[1], Armondo Balotti[1], Stephanie Strong[2], Chien-Te Lin[3], and Katsuhiko Funai[1,3]

[1]Dept. of Kinesiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [2]Dept. of Biology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [3]Dept. of Physiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834.

Phosphatidylethanolamine methyltransferase (PEMT) converts phosphatidylethanolamine (PE) to phosphatidylcholine (PC). Mice lacking PEMT (PEMTKO) are resistant to diet-induced obesity and exhibit increased energy expenditure. Mitochondrial proton uncoupling in adipose tissues has been implicated as a site for increased energy expenditure. We previously found no increase in the abundance of uncoupling protein 1 (UCP1) in subcutaneous or visceral adipose tissues from PEMTKO mice. The purpose of this study was to determine if ablation of PEMT would increase mitochondrial uncoupling and energy expenditure in brown adipose tissue (BAT). Surprisingly, mice lacking PEMT exhibited a 93% reduction in UCP1 protein content despite a lack of difference in UCP1 mRNA. Additionally, protein abundance of complexes I, III, and IV of the electron transport system were substantially reduced in PEMTKO mice independent of changes in mRNA levels. In contrast, complex V protein was increased, suggesting that lack of PEMT destabilizes some but not all proteins localized in the inner membrane of mitochondria. Consistent with this idea, the abundance of matrix protein citrate synthase that is not associated with mitochondrial membrane was unaltered with the lack of PEMT. High-resolution experiments in isolated mitochondria revealed that absence of PEMT led to a reduction of oxygen consumption without a change in ATP production, indicating decreased proton uncoupling without compromising ability for ATP resynthesis. Consistent with these observations, GDP, a potent inhibitor of UCP1, robustly reduced BAT respiration from wildtype mice but not in PEMTKO mice. Intriguingly, analysis of the mitochondrial phospholipid composition revealed a 43% reduction in cardiolipin (CL) without having effects on PC or PE. Thus, PEMT deletion may promote UCP1 membrane instability by reducing mitochondrial CL content. The reduction in CL content was likely due to decreased mRNA levels of the CL remodeling enzyme tafazzin, suggesting a possible role for PEMT-derived PC to regulate CL remodeling. In conclusion, PEMT is essential for uncoupled respiration, stability of select mitochondrial membrane proteins, and maintaining CL levels in BAT. This study was supported by NIH grants DK095774 and DK109888.

11.6

THE COMBINATION OF PROLONGED FASTING AND PRIOR EXERCISE INCREASES PEAK FAT OXIDATION AND FATMAX IN HIGHLY TRAINED ATHLETES

Jacob Frandsen[1], Stine Vest[1], Steen Larsen[1], Flemming Dela[1], and Jørn Wulff Helge[1]
[1]Dept. of Biomedical Sci., Univ. of Copenhagen, Munkensvej 6.1tv, Frederiksberg, 2000, Denmark.

Introduction: High plasma free fatty acid availability has been found to be a major factor for increased fat oxidation and glycogen sparing during exercise[1,2,3]. However, the combined effects of prolonged fasting and previous exercise on fat oxidation at rest and during exercise remain to be elucidated.The aim of this study was to investigate to which extent prolonged fasting, and prior exercise would affect peak fat oxidation rate and fatmax. We hypothesized that prolonged fasting and previous exercise would increase peak fat oxidation rate (PFO) and fatmax as a primary consequence of increased plasma free fatty acid availability. Method: In a randomized cross over design 8 highly trained athletes (66.1±2 ml/min/kg, 30±2 yrs.) performed 4 fatmax[4] tests each separated by 4 hours of recovery one day in an overnight fasting state and another day in the fed state with a standardized carbohydrate-rich meal consumed 3-4 hours before each fatmax test. Fat oxidation rate was determined by indirect calorimetry. Venous blood samples were collected at each exercise step throughout the first and fourth test and a basal blood sample was collected before the second and third test. A two-way ANOVA was applied to analyze differences in MFO and fatmax between fasted and fed and between different tests on the same day. Results: PFO were 29%, 55%, 57% and 62% higher in the fasted compared to the fed state on the 1st to 4th fatmax test, respectively. Fatmax occurred at 4%, 16%, 18% and 20% higher relative intensity in the fasted compared to the fed state on the 1st to 4th fatmax test, respectively. In the fasted state PFO was significantly increased on the 3rd and 4th compared to the 1st fatmax test (0.81±0.07g/min, 0.93±0.06g/min vs. 0.66±0.06 g/min), respectively. In the fed state PFO decreases from the 1st to the 2nd and 3rd fatmax test (0.49±0.05g/min vs. 0.41±0.04g/min and 0.45±0.05 g/min), respectively. Conclusion: PFO and fatmax are highly influenced by fasting and prior exercise in highly trained athletes. PFO and fatmax increased in the fasted state, and these effects were not present when fed a high carbohydrate meal 3-h prior exercise thus the increases in PFO and fatmax when fasted were not caused by the previous exercise per se.

11.7

A SINGLE SESSION OF AEROBIC EXERCISE REDUCES MARKERS OF INFLAMMATION IN SUBCUTANEOUS ADIPOSE TISSUE

Douglas W. Van Pelt[1], Lisa M. Guth[1], Konstantinos C. Karabetsos[1], and Jeffrey F. Horowitz[1]
[1]Sch. of Kinesiology, Univ. of Michigan, CCRB, 401 Washtenaw Ave., Ann Arbor, MI, 48109.

Alterations in the inflammatory state, metabolic function, and structure of subcutaneous adipose tissue (SAT) can greatly impact the development of insulin resistance in obesity. Exercise is often prescribed to improve metabolic health in obesity, but the effects of exercise on SAT are not well known. The primary aims of this study was to examine the effects of exercise on mRNA expression of markers of lipid metabolism (*ATGL, HSL, DGAT, GPAT, PPARG, SREBP1c, PLIN1*), inflammation (*TNFA, IL1B, NLRP3, MCP1, CD11C, CD206*), fibrosis (*COL6A1, COL1A1*), and hypoxia/angiogenesis (*HIF1A, VEGF*) in SAT, as well as adipocyte cell size. We recruited overweight-to-obese adults who were either regular exercisers (EX: n=5) or habitually sedentary (SED: n=8). The groups were well-matched for age (27±1 vs. 24±2 y), BMI (29±1 vs. 27±1 kg/m^2), and body composition (30±1 vs 29±1 % body fat), but as expected, cardiorespiratory fitness was greater in EX vs. SED (VO_2peak: 51±3 vs. 42±1 ml/kg FFM/min; p=0.03). Abdominal SAT biopsy samples were obtained before and 1hr after 60min of aerobic exercise (~65% VO_2peak). EX subjects did not exercise for 3 days before the trial. There were no differences in mRNA expression or SAT cell size between SED and EX, so we combined the groups to examine the response to a single session of exercise. In the combined cohort (n=13), we found a significant reduction in mRNA expression of *TNFA, MCP1*, and the marker of "M1" pro-inflammatory macrophage polarization *CD11c* after acute exercise in SAT whole tissue samples ($p \leq 0.01$). We also magnetically sorted CD14+ immune cells from SAT samples and only *TNFA* expression was significantly reduced after acute exercise ($p < 0.01$) in the CD14+ cell fraction. This suggests that the reduction in markers of inflammation we observed in SAT after exercise may be due to an exercise-induced reduction in the abundance of CD14+ cells in the tissue, as well as to changes in the expression of *TNFA* within the resident immune cells. In contrast to the observed changes in inflammatory markers, exercise did not affect markers of lipid metabolism, fibrosis, or hypoxia/angiogenesis in SAT. Together, our data suggest that each session of aerobic exercise initiates reductions in the abundance and inflammatory gene expression of resident immune cells in SAT, and this acute effect of exercise appears to be independent of habitual exercise behavior. Funding: NIH #R01 DK077966, NIH #T32DK007245, NIH #T32DK10135702.

11.8

HUMAN SERUM COLLECTED IMMEDIATELY AFTER EXERCISE DOES NOT ALTER MRNA EXPRESSION RELATED TO FATTY ACID METABOLISM OR INFLAMMATION IN CULTURED 3T3-L1 ADIPOCYTES

Fei Yuan[1], Lisa M. Guth[1], Douglas W. Van Pelt[1], Harkirat S. Jawanda[1], and Jeffrey F. Horowitz[1]
[1]Sch. of Kinesiology, Univ. of Michigan, 401 Washtenaw Ave., Ann Arbor, MI, 48109.

Recent reports indicate acute exercise may trigger important metabolic adaptations in adipose tissue (e.g., regulation of fatty acid storage/release, adipogenesis, inflammation), suggesting that factors released into the systemic circulation during and/or after exercise may initiate adaptive responses in adipocytes. The aim of this study was to determine if incubating adipocytes in serum collected immediately after exercise can induce adaptive responses *in vitro*. Serum was collected from 24 healthy human

subjects before exercise (NO-EX) and immediately after 1 hour of endurance exercise at 65% VO_2peak (EX). Differentiated 3T3-L1 adipocytes were serum-starved for three hours and then treated with media containing 10% NO-EX or EX serum for 2h, 6h, and 24h. The mRNA expression levels of *Pparg*, *Adipoq*, *Hsl*, *Atgl*, *Dgat1*, and *Mcp1* were measured using quantitative real-time RT-PCR. Incubation in EX serum did not significantly alter the mRNA expression of *Pparg*, *Adipoq*, *Hsl*, *Atgl*, *Dgat1*, or *Mcp1* relative to NO-EX serum at any of the three incubation durations (2h, 6h or 24h). *Pparg* and *Mcp1* mRNA were higher at 24h compared with 6h ($p < 0.05$), but no other significant effects of incubation time were observed. Our findings indicate that under these conditions, factors released into the systemic circulation during/immediately after a session of endurance exercise may not affect gene expression of some of the key factors regulating adipocyte fatty acid metabolism and inflammation *in vitro*. Importantly, we cannot rule out the possibility that methodological limitations may have impacted our ability to detect an exercise response. These limitations include: exposure of adipocytes to a relatively low concentration (10%) of exercise serum, assessment of only three incubation time points, mRNA analysis of only a few metabolic and inflammatory markers, and potential species incompatibility (i.e., human serum and mouse-derived 3T3-L1 adipocytes). Nevertheless, our current findings suggest that putative exercise-induced metabolic and inflammatory changes in adipose tissue may be due to mechanisms other than a direct effect of circulating factors released during exercise on adipocyte gene expression.

11.9
SYSTEMIC FATTY ACID MOBILIZATION RATES ARE ELEVATED IN ENDURANCE-TRAINED OBESE/OVERWEIGHT ADULTS, BUT ARE BLUNTED THE DAY AFTER ACUTE EXERCISE

Lisa M. Guth[1], Douglas W. Van Pelt[1], Zhengping Yi[2], and Jeffrey F. Horowitz[1]
[1]Sch. of Kinesiology, Univ. of Michigan, 401 Washtenaw Ave., Ann Arbor, MI, 48109, [2]Dept. of Pharmaceutical Sci., Eugene Applebaum Coll. of Pharmacy/Health Sci., Wayne State Univ., 259 Mack Ave., Detroit, MI, 48201.

Basal fatty acid rate of appearance in plasma (FA Ra) is often very high in obesity and is commonly linked with the development of insulin resistance. However, basal FA Ra has also been reported to be 2- to 3-fold higher in lean endurance athletes than in lean sedentary controls. The effect of exercise on FA Ra in obesity, where FA Ra is already high, is not well characterized. The aims of this study were to determine the effects of habitual and acute exercise on resting FA Ra, lipolytic rate, and gene expression of factors regulating adipose tissue fatty acid release and storage in overweight/obese adults. 8 overweight/obese habitual exercisers (TRAINED; VO_2peak=32±2 ml/kg/min) and 8 overweight/obese sedentary controls (UNTRAINED; VO_2peak=22±2 ml/kg/min; $p<0.01$) participated in this study. The groups did not differ in BMI (31±1 vs. 34±1 kg/m^2), body mass (87±4 vs. 89±4 kg), or body composition (38±3 vs. 43±3% body fat). Basal palmitate Ra (Palm Ra), a measure of FA Ra, and glycerol rate of appearance (Gly Ra), a measure of lipolysis, were assessed using stable isotope tracer methods. Fasting subcutaneous abdominal adipose tissue samples were obtained and mRNA expression of *HSL*, *ATGL*, *DGAT1*, and GPAT were assessed by qRT-PCR. After not exercising for 3 days, TRAINED had ~50% higher basal Palm Ra (4.8±0.5 vs. 3.2±0.4 umol/kg FM/min, $p<0.05$) and Gly Ra (10.8±1.2 vs. 7.5±0.8 umol/kg FM/min, $p<0.05$) compared with UNTRAINED, but whole-body triglyceride reesterification was not different between groups. Adipose tissue *HSL* mRNA expression was higher ($p<0.05$) and *ATGL* and *DGAT1* mRNA expression tended to be higher ($p=0.07$ for both) in TRAINED vs. UNTRAINED. When measured the day after 1h of exercise at 50% VO_2peak, the high basal Palm Ra in TRAINED was blunted (4.3±0.8 umol/kg FM/min, $p<0.05$), and whole-body reesterification declined markedly ($p<0.05$). *HSL* and *ATGL* mRNA expression were also lower in TRAINED the day after exercise ($p<0.05$). Acute exercise did not affect Palm Ra, Gly Ra, reesterification, or gene expression of our markers of lipid metabolism in UNTRAINED. Consistent with previous findings in lean athletes, basal FA Ra and lipolysis were elevated in our trained overweight/obese adults and this was accompanied by elevated lipolytic gene expression. Importantly, a session of exercise in our trained subjects attenuated fatty acid release and markedly reduced whole-body reesterification, potentially lowering the potential for ectopic lipid deposition.

11.10
EFFECTS OF EXERCISE ON ADIPOSE TISSUE RESPONSES TO SHORT-TERM OVEREATING IN HEALTHY ADULTS

Alison C. Ludzki[1], Jenna B. Gillen[1], Lisa M. Guth[1], Konstantinos C. Karabetsos[1], and Jeffrey F. Horowitz[1]
[1]Kinesiology, Univ. of Michigan, 401 Washtenaw Ave., Ann Arbor, MI, 48109.

Adipose tissue inflammation and excessive fatty acid release are central to the development of obesity-related insulin resistance. However, even short-term episodic overeating can contribute to adipose tissue expansion and metabolic abnormalities. In fact, as little as one week of overeating has been found to impair glycemic control and insulin sensitivity. Exercise has been reported to protect against overeating-induced metabolic impairments, but the role of alterations in adipose tissue structure and function in this response is not well characterized. We hypothesized that regular aerobic exercise during one week of overeating would preserve metabolic health as well as adipose tissue inflammation and lipolytic response. Four lean, active adults (23.5 ± 2.2 years; 22.5 ± 1.1 kg/m^2; 21.3 ± 4.6 % body fat) consumed 30% above their daily energy requirements for one week while maintaining their regular exercise habits (≥150 minutes of regularly planned aerobic exercise per week, at least 6 days/week). We measured oral glucose tolerance and collected abdominal subcutaneous adipose tissue samples before and after the one-week overeating intervention. Consistent with previous reports, the overeating intervention did not impair glucose tolerance (3h glucose area under the curve: 15.9 ± 0.3 vs. 14.4 ± 0.4 mM·h). Novel findings from our study indicate that overeating did not increase the protein content of markers of adipose tissue inflammation (i.e. pJNK/JNK, pERK/ERK) or circulating C-reactive protein (4.3 ±

3.1 vs. 3.4 ± 2.4 mg/L). We also measured *ex vivo* lipolysis in isolated mature adipocytes and adipose tissue explants collected before and after overeating and found lipolytic responses to both isoproterenol and insulin to be unchanged after overeating. Our findings expand on existing work to support a protective role of exercise in the metabolic response of adipose tissue to short-term overeating.

11.11

ADIPONECTIN INCUBATION DECREASES SKELETAL MUSCLE GLYCOGEN CONTENT AFTER REVERTING TO A CHOW DIET FOLLOWING DIET INDUCED OBESITY

Cesar Meza[1], Cynthia Montenegro[1], Catalina De La Peña[1], Lannie O'Keefe[2], Shaan Naughton[2], Anna Simcocks[2], Deanne Hryciw[3], Michael Mathai[2], Andrew McAinch[2], and Sudip Bajpeyi[1]
[1]Dept. of Kinesiology, Univ. of Texas at El Paso, 500 W. University Ave., El Paso, TX, 79902, [2]Coll. of Hlth. and Biomedicine, Victoria Univ., Melbourne, VIC 8001, Australia, [3]Dept. of Physiology, Univ. of Melbourne, VIC 3010, Australia.

Consumption of high fat diet (HFD) has been linked to development of insulin resistance, characterized by lower glucose uptake and defects in glycogen storage in skeletal muscle. Adiponectin (Ad) is an adipose-derived cytokine that stimulates glucose uptake, increases fatty acid oxidation, and contributes to the improvement of insulin sensitivity. The purpose of this study was to determine the effects of Ad in concurrence with a HFD on skeletal muscle glycogen content. Male Sprague Dawley rats were fed Western-style HFD (21% fat by weight; 9.76% saturated fat) for 9 weeks to induce obesity, then were continued with the same diet (WD) (n=10) or began a chow diet (CD) (4.8% fat by weight; 0.74% saturated fat) (n=9) for an additional 6 weeks. Right and left hind-leg extensor digitorum longus (EDL) muscles were incubated in an organ bath (Krebs-Henseleit buffer containing 2000 mg/L glucose) with or without 0.1 mg/ml Ad for 30 minutes. Then muscle was frozen and glycogen content was accessed using periodic acid-schiff staining and quantified using imageJ software. There was no significant difference in body weight between animals fed with WD and CD (g±SD; WD: 638.7±38.23 n=10; CD: 575.0±66.15 n=9; p= 0.16). Food consumption was significantly reduced for the WD group compared to CD group (g/d±SD; WD: 19.7±1.26 n=10; CD: 23.8±3.36 n=9; p= 0.0007). In the absence of Ad incubation, glycogen content was similar between two groups (AU±SEM; WD: 4.7±0.11 AU n=6; CD: 4.8±0.13 AU n=5; p= 0.37). However, Ad incubation resulted in a significant decrease in glycogen content in the CD group (4.8±0.13 AU to 4.3±0.12 AU n=6; p= 0.03) and tended to decrease glycogen content in WD (4.7±0.11 AU to4.4±0.09 AU n=5; p= 0.08). Our data suggests that adiponectin incubation results in a significant reduction in glycogen content in animals fed a CD for 6 weeks following a 9 weeks of HFD compared to a less pronounced reduction evident with a HFD for 15 weeks. Acknowledgement: This project was supported by the Allen Foundation and VU/UTEP Collaborative research project grant.

11.12

PROTEIN VS CARBOHYDRATE INTAKE POST-EXERCISE AND THE EFFECT ON WHOLE-BODY FAT OXIDATION

Ulrika Andersson Hall[1,2], Fredrik Edin[2], Stefan Pettersson[2], and Klavs Madsen[1,2]
[1]Section for Sport Sci., Aarhus Univ., Dalgas Ave., 4, Aarhus C, DK-8000, Denmark, [2]Dept. of Food, Nutrition and Sport Sci., Gothenburg Univ., Läroverksgatan 5, Gothenburg, S-405 30, Sweden.

In a recent report we showed that prior exercise followed by fasting recovery increased whole body fat oxidation during a subsequent session by almost 80% in elite endurance athletes*. In the current study, we investigated how post-exercise intake of protein or carbohydrate after a first exercise session affected whole body fat oxidation and selected metabolic parameters during recovery and a subsequent exercise trial. In a cross-over design, twelve moderately trained females (VO_{2max} 45 ± 2 ml/min/kg) performed three identical days of testing after standardized dinners and breakfasts: A control incremental fat oxidation bike test was followed by a 60 min endurance session at 75% VO_{2max}. Immediately post-exercise, subjects ingested drinks containing either 20g whey protein (PRO), 40g maltodextrin (CHO) or placebo (PLA). After 2h rest a second incremental fat oxidation test was performed. Indirect calorimetry and blood sampling was performed throughout bike tests and the rest period. Maximal fat oxidation (MFO) during the control test was 0.28 ± 0.02 g/min, which was increased significantly at the second fat oxidation test following all three post-exercise drinks (PLA 0.57 ± 0.04, PRO 0.52 ± 0.02, and CHO 0.44 ± 0.04 g/min; $P<0.01$). The intensity at which MFO occurs (Fat_{max}) was also increased in all three conditions (PLA 54 ± 1, PRO 55 ± 2, and CHO 50 ± 2 compared to 41 ± 2 % of VO_{2max} for the control test; $P<0.01$). Neither MFO nor Fat_{max} were significantly different between PLA and PRO, whereas CHO was lower than PLA for MFO and PRO for Fat_{max} ($P<0.05$). Resting fat oxidation at 1h post-exercise was lower for CHO compared to PLA and PRO (PLA 0.12 ± 0.01, PRO 0.12 ± 0.01, CHO 0.09 ± 0.01 g/min; $P<0.05$). Both PRO and CHO caused a spike in insulin levels (PLA 4 ± 1, PRO 23 ± 2, CHO 30 ± 2 mIU/L at 1h post-exercise), though this elevation was diminished at the 2h post-exercise mark when the second fat oxidation test started (PLA 7 ± 2, PRO 10 ± 2, CHO 11 ± 4 mIU/L). In conclusion, protein supplementation immediately post-exercise did not affect the 100% increase in whole body fat oxidation seen during a subsequent exercise trial 2 hours later. Neither did it affect resting fat oxidation during the post-exercise period despite increased insulin levels. Carbohydrate intake dampened the increase in fat oxidation during the second test, though a 60% increase was still observed compared to the first test. *Andersson Hall et al. 2016, *APNM* 41(4):430-7.

11.13

HUMAN PREADIPOCYTE FATTY ACID SENSITIVITY CORRELATES WITH IMPROVEMENTS IN INSULIN SENSITIVITY FOLLOWING 12-WEEK EXERCISE TRAINING

Jared Shine[1,2], Joseph White[2,3], Tim Heden[2,4], Barbara Davis[1], Robert Hickner[2,4], and Jacques Robidoux[1,2]
[1]Pharmacology and Toxicology, East Carolina Univ., 600 Moye Blvd., 6s10, Greenville, NC, 27834, [2]ECDOI, East Carolina Diabetes and Obesity Inst., 115 Heart Dr., Greenville, NC, 27834, [3]Bioenergetics and Exercise Sci., East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834, [4]Kinesiology, East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834.

Adipose tissue is an integral part of metabolism in health and disease. Chronic positive energy imbalance is the cause of obesity, but more importantly the cause of adipose tissue and systemic metabolic illness including Type 2 diabetes. A characteristic of the adipose tissue of obese, particularly insulin-resistant obese individuals, is that preadipocyte number and adipogenic potential is decreased. We have shown that incubation of primary human preadipocytes with high, yet physiological, concentrations of FA for 24 hours causes mitochondrial permeability transition (mPT) and cell death. The aim of this study was to determine if initial preadipocyte FA sensitivity predicts the improvement in glycemic control observed following a 12-week exercise program, as well as to test the hypothesis that training improves preadipocyte FA-sensitivity. This may be clinically relevant as a reduced adipogenic potential (less preadipocytes) may lead to elevated serum FA and organ system toxicity; and the effects of exercise are known to improve health and diseases mentioned above, sometimes greater than pharmacologic approaches. Primary preadipocyte isolated from abdominal and gluteal subcutaneous adipose tissue of 24 subjects was isolated before and after training. Exercise sessions were performed 3 times a week and consisted of a 10 minute warm-up (70% heart rate max (HR_{max})) on the treadmill followed by 4 cycles constituted of a 4 minutes high intensity (88-92% HR_{max}) and a 3 minutes low intensity (70% HR_{max}) segment. The number of cells experiencing FA-induced mPT was measured with cobalt-quenched calcein-AM fluorescence while the percent of Live/dead cells was measured with Calcein-AM and Ethidium Homodimer-1 staining via flow cytometry. Results showed that pre-training FA-sensitivity (both mPT and cell death) negatively correlated with the subject's pre-exercise glucose levels and positively with their improvement in insulin sensitivity (HOMA) after training. Post-exercise FA-sensitivity, cell death and mPT, was reduced by 40-58%, and 35-55%, respectively. Improvements in FA sensitivity positively correlated with the reduction in fasting glucose and insulin following training and consequently the improvement in HOMA. These results suggest that preadipocyte sensitivity to FA can predict those individuals that will benefit from lifestyle interventions centered on physical activity. What are the molecular mechanisms underlying these correlations is under study.

11.14
SKELETAL MUSCLE GLYCOGEN CONTENT IS UNAFFECTED BY DIETARY FATTY ACID COMPOSITION

Catalina De La Pena[1], Cesar Meza[1], Cynthia Montenegro[1], Anna Simcocks[2], Shaan Naughton[2], Lannie O'Keefe[2], Deanne Hryciw[3], Micheal Mathai[2], Andrew McAinch[2], and Sudip Bajpeyi[1]
[1]Kinesiology, Univ. of Texas at El Paso, 500 W. University Ave., El Paso, TX, 79936, [2]Coll. of Hlth. and Biomedicine, Victoria Univ., St Albans, Melbourne, VIC 8001, Australia, [3]Physiology, Univ. of Melbourne, Parkville, VIC 3010, Australia.

High fat diet (HFD) has been associated with weight gain, insulin resistance, and a reduced ability to store glycogen in skeletal muscle. The proportions of different fatty acids in diet play an important role in glucose and lipid metabolism. Diets high in linoleic acid, a type of polyunsaturated fatty acid, have been implicated with the development of obesity and type 2 diabetes. The purpose of this study was to determine the effects of high fat diets with alterations in the major dietary fatty acid content (a mixed fat western diet, a polyunsaturated fatty acid (PUFA; predominately linoleic acid) diet or a monounsaturated fatty acid (MUFA; predominately oleic acid) diet) on skeletal muscle glycogen content. Male Sprague Dawley rats were fed a 21% (by weight; 41% total energy) high fat western-style diet for 9 weeks to induce obesity. They were then divided into 3 dietary groups that continued on a 21% HFD for the next 6 weeks with high 1) mixed fat western diet (WD) (9.8% saturated, 7.7% mono; 3.5% poly; n=10); 2) monounsaturated fat (MUFA) (2.8% saturated, 15.8% mono; 2.2% poly; n=10); 3) polyunsaturated fat (PUFA) (3.0% saturated; 2.9%mono; 15.7% poly; n=10). At the end of the dietary intervention, glycogen content was measured in extensor digitorum longus (EDL) muscle via Periodic Acid-Schiff staining using immunohistochemistry technique, and quantified with ImageJ software. After the 6-week dietary intervention there was no difference in body weight or food consumption (Body weight (g± SD) WD: 638.7 ± 38.23 n=10; MUFA: 589.8 ±63.21 n=10; PUFA: 602.6± 54.48 n=10; Food consumption (g/d± SD) WD 19.74±1.26 n=10 ; MUFA: 17.14 ±1.88 n=10; PUFA: 17.72 ± 1.93 n=10). There were no differences in glycogen content among three HFD groups differing in dietary fatty acids. (AU± SEM) WD: 4.66 ± 0.11 AU n=6, MUFA: 4.50 ± 0.07 AU n=7, PUFA: 4.58 ± 0.09 AU n=5; one-way ANOVA p= 0.42). Our data suggest that skeletal muscle glycogen content is unaffected by dietary fatty acid composition (saturated, monounsaturated, polyunsaturated) in a high fat diet. Acknowledgement: This project was supported by the Allen Foundation and VU/UTEP Collaborative research project grant.

11.15
IMPACT OF ENDURANCE EXERCISE TRAINING ON ADIPOCYTE MIRNA EXPRESSION IN OVERWEIGHT MEN

Thomas Tsiloulis[1,2], Joshua Pike[1,2], David Powell[3], Fernando J. Rossello[4,5], Benedict J. Canny[2,6], Ruth C.R. Meex[1,2], and Matthew J. Watt[1,2]
[1]Monash Biomedicine Discovery Inst., Metabolism and Obesity Program, Monash Univ., Wellington Rd. & Blackburn Rd., Clayton, Australia, [2]Dept. of Physiology, Monash Univ., Wellington Rd. & Blackburn Rd., Clayton, Australia, [3]Monash Bioinformatics Platform, Fac. of Biomedical and Psychological Sci., Monash Univ., Wellington Rd. & Blackburn Rd., Clayton, Australia, [4]Australian Regenerative Med. Inst., Monash Univ., Wellington Rd. & Blackburn Rd., Clayton, Australia, [5]Dept. of Anatomy and Developmental Biology, Monash Univ., Wellington Rd. & Blackburn Rd., Clayton, Australia, [6]Sch. of Med.,

Fac. of Hlth., Univ. of Tasmania, Churchill Ave., Hobart, Australia.

Adipocytes are major regulators of metabolism and dysregulated adipocyte function in obesity is linked to the metabolic syndrome. Endurance-exercise training improves adipocyte function; however, the molecular mechanisms that regulate the chronic adaptive responses are incompletely described. MicroRNAs (miRNAs) influence adipocyte differentiation and metabolism, yet their role in exercise-induced adipocyte phenotypes is unknown. We used next generation sequencing (NGS) to profile miRNA expression of adipocytes isolated from subcutaneous abdominal (ABD) and gluteofemoral (GF) adipose tissue of overweight men before and after six weeks of endurance-exercise training. Differentially expressed miRNAs were over-expressed or silenced in 3T3-L1 adipocytes and lipid metabolism examined. NGS identified 526 miRNAs in adipocytes and there were no statistical differences in miRNA expression when comparing the pre- and post-training samples for both ABD and GF adipocytes. miR-10b expression was increased in ABD compared with GF, while miR-204, miR-3613 and miR-4532 were more highly expressed in GF compared with ABD adipocytes. Blocking miR-10b in adipocytes suppressed ß-adrenergic lipolysis but had a minor effect on lipid metabolism in general. Unlike their critical role in adipogenesis, stable changes in miRNA expression do not play a prominent role in the regulation of adipocyte function in response to endurance-exercise training. **Financial Support:** This work was supported by a research grant from the National Health and Medical Research Council (NHMRC) of Australia (ID: APP1098972). TT is supported by the Australian Postgraduate Award (Monash University), and the Paula and Jack Hansky PhD Scholarship. MJW is supported by a Senior Research Fellowship from the NHMRC (ID: APP1077703).

11.16
ADIPONECTIN IS MORE EFFECTIVE IN SPARING GLYCOGEN CONTENT WITH HIGH FAT DIET IN DIETARY MONOUNSATURATED FAT COMPARED TO DIETS HIGH IN SATURATED AND POLYUNSATURATED FAT

Cynthia Montenegro[1], Catalina De La Pena[1], Cesar Meza[1], Shaan Naughton[2], Anna Simcocks[2], Lannie O'Keefe[2], Deanne Hryciw[3], Michael Mathai[2], Andrew McAinch[2], and Sudip Bajpeyi[1]
[1]Kinesiology, Univ. of Texas at El Paso, 500 W. University Ave., El Paso, TX, 79902, [2]Coll. of Hlth. and Biomedicine, Victoria Univ., St Albans, Melbourne, VIC 8001, Australia, [3]Physiology, Univ. of Melbourne, Parkville, VIC 3010, Australia.

High fat diet (HFD) is associated with the development of insulin resistance, which is characterized by a lower glucose uptake and glycogen synthesis capacity in skeletal muscle. Consumption of linoleic acid, a type of polyunsaturated fatty acid (PUFA), has been associated with obesity and type 2 diabetes. Adiponectin (Ad), on the other hand, is an adipokine that promotes glucose uptake and fatty acid oxidation. The purpose of this study was to determine the effects of Ad on skeletal muscle glycogen content in animals fed with HFD but alteration in dietary fatty acids (mixed fat western diet, predominately linoleic acid containing PUFA diet or predominately oleic acid containing monounsaturated fatty acid (MUFA) diet). Male Sprague Dawley rats were fed a Western-style (21% fat by weight, 41% by energy) HFD for 9 weeks in order to induce obesity. Then they were divided into 3 groups for an additional 6 weeks consuming either of the following HFDs: a) mixed fat Western diet (WD) (21% fat; 9.8% saturated fat; 7.7% MUFA, 3.5% PUFA; n=10), b) HFD consisting of high MUFA (21%fat; 15.76% MUFA; 1.8% PUFA; n=10), or c) HFD consisting of high PUFA (21%fat; 2.72% MUFA; 15.65% PUFA; n=5). Right and left hind-leg extensor digitorum longus (EDL) muscles were incubated in an organ bath (Krebs-Henseleit buffer containing 2000 mg/L glucose) with or without 0.1 mg/ml Ad for 30 minutes. Glycogen content was measured in the EDL muscle by using periodic acid-schiff staining using immunohistochemistry technique, and quantified with imageJ software. After the 6-week dietary intervention, there was no difference in body weight (Body weight (g±SD) WD: 638.7 ± 38.23 n=10; MUFA: 589.8 ± 63.21 n=10; PUFA: 602.6 ± 54.48 n=10; Food consumption (g/d±SD) WD: 19.74 ± 1.26 n=10; MUFA: 17.14 ± 1.88 n=10; PUFA: 17.72 ± 1.93 n=10). The Ad incubation resulted in a significant decrease in muscle glycogen content in animals fed with PUFA ((AU±SEM) 4.58 ± 0.09 to 4.22 ± 0.04 AU n=5; p=0.04), tended to decrease with WD (4.66 ± 0.1 to 4.39 ± 0.11 AU n=6; p=0.07), and tended to increase with MUFA (4.50 ± 0.1 to 4.70 ± 0.11 AU n=7; p=0.08). When change (%) in glycogen content was compared, an increase in glycogen content after MUFA was significantly different compared to a decrease in WD (p=0.02) and PUFA (p=0.009) ((%±SEM) WD: -5.41 ± 3.70% decrease, MUFA: 4.66 ± 1.61% increase; PUFA: -7.74 ± 1.37% decrease; one way ANOVA p=0.0058). In summary, adiponectin incubation results in better preservation/increase in glycogen content in animals fed with HFD rich in dietary MUFA and a decrease in glycogen content in animals fed with HFD rich in mixed fat WD or PUFA. Acknowledgement: This project was supported by the Allen Foundation and VU/UTEP Collaborative research project grant.

11.17
MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION CAPACITY IN HUMAN ADIPOSE TISSUE AND ADAPTATIONS WITH EXERCISE TRAINING

Joseph White[1,2], Tim Heden[1,2], Rick Alleman[2], Jared Shine[2,3], Jacques Robidoux[2,3], and Robert Hickner[1,2]
[1]Kinesiology, East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834, [2]East Carolina Diabetes and Obesity Inst., East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834, [3]Pharmacology and Toxicology, East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834.

The distribution of body fat is an important factor for the metabolic outcomes associated with obesity although the mechanisms determining depot-specific lipid accumulation are not well understood. Upper but not lower body fat accumulation correlates with obesity-associated metabolic abnormalities including dyslipidemias and systemic insulin resistance. Lipogenesis is correlated to mitochondrial content however investigations of mitochondrial function in human subcutaneous adi-

pose tissue (SCAT) are scarce. Physical activity is a therapy that has been shown to affect depot-specific lipid accumulation without significant weight loss correlating to improvements in metabolic profiles. We measured mitochondrial oxidative phosphorylation (OXPHOS) capacity in abdominal and gluteal SCAT from overweight and obese men and women at baseline and after 12wks of exercise training. Exercise sessions were performed 3x/wk on a treadmill and included a 10min warm-up at 70% heart rate max (HR_{max}) followed by 4 intervals at 88-92% HR_{max} for 4min interspersed with 3min recovery periods at 70% HR_{max}. VO_{2peak} increased significantly in response to the exercise training intervention. At baseline, state 2 complex II-linked respiration was significantly higher in abdominal compared to gluteal SCAT, while state 3 complex II and complex I & II-linked respiration was similar between depots. Interestingly, complex II activity in abdominal and gluteal SCAT represented the majority of the OXPHOS capacity, confirmed by the addition of mitochondrial complex II inhibitor malonate. After the exercise training intervention there was a trend for an increase in state 2 complex II-linked, state 3 complex II-linked and I & II-linked, and complex II respiration in the gluteal SCAT while the abdominal SCAT respiratory rates remained unchanged. Collectively, these results highlight depot-specific differences in SCAT OXPHOS capacity that may be modifiable with exercise training.

12.0 GENOMICS, METABOLOMICS, AND PROTEOMICS

12.1
SHORT–TERM HEAT STRESS STIMULATES GLYCOGEN AND PROTEIN METABOLISM IN RAT SKELETAL MUSCLE

Ayumi Goto[1,2], Tatsuro Egawa[1], Keiichi Sekine[1], Ichika Sakon[1], Rieko Oshima[1], Satoshi Tsuda[1], and Tatsuya Hayashi[1]
[1]Grad. Sch. of Human and Environmental Studies, Kyoto Univ., Yoshidanihonmatsucho, Sakyo-ku, Kyoto, Japan, [2]Sportology Ctr., Grad. Sch. of Med., Juntendo Univ., 2-1-1 Hongo, Bunkyo-ku, Tokyo, Japan.

Objective: Skeletal muscle is the major organ responsible for whole-body glucose metabolism and utilization. Heat stress (HS) has been implicated in the regulation of whole-body glucose homeostasis. Recently, we have demonstrated that short-term HS (for 10 and 30 min) in vitro activates insulin-independent glucose transport, at least in part by stimulating 5' -AMP-activated protein kinase (AMPK) via decreased energy status in rat skeletal muscle (Goto A, et al. Physiol Rep. 3: e12601, 2015). However, as far as we know, there have been no reports about the effect of short-term HS on glycogen and protein metabolism in skeletal muscle. Methods: Experimental protocols were approved by the Kyoto University Graduate School of Human and Environmental Studies, and followed the Guiding Principles for the Care and Use of Animals in the Field of Physiological Science (The Physiological Society of Japan, 2015). Male Sprague-Dawley rats weighing 150 g were killed by cervical dislocation without anesthesia, and epitrochlearis muscles were isolated. Muscle was then incubated in the absence or presence of HS (42°C, 10 or 30 min) in alpha minimum essential medium containing 50 mU/mL insulin. Results: HS for 10 min activated both AMPKα1 and AMPKα2. HS increased 3-*O*-methyl-d-glucose (3MG) transport, and the stimulatory effect of 3MG transport was inhibited by dorsomorphin (AMPK inhibitor). HS decreased glycogen content and activated glycogen synthesis without affecting the phosphorylation of glycogen synthase kinase 3β or glycogen synthase. HS tended to decrease protein synthesis, and correspondingly, HS decreased the phosphorylation of p70 ribosomal protein S6 kinase and 4E-binding protein 1. On the other hand, HS did not affect the RNA expression of muscle-specific ubiquitin ligases: muscle atrophy F-box/atrogin-1 and muscle ring finger 1, or of the autophagy-related markers: microtubule-associated protein 1 light chain 3 and p62. Conclusion: Short-term HS increased AMPK activity rapidly, and activated insulin-independent glucose transport. Short-term HS also decreased glycogen content and activated glycogen synthesis. On the other hand, Short-term HS suppressed signaling molecules leading to protein synthesis. Short-term HS might be a physiologically relevant stimulus that promotes the glucose transport/glycogen synthesis axis and inhibit protein synthesis, at least in part by activating AMPK in skeletal muscle.

12.2
SKELETAL MUSCLE MICROBIOPSY TECHNIQUE AND DEUTERATED WATER USED TO DETECT SKELETAL MUSCLE PROTEIN FRACTIONAL SYNTHESIS RATE DURING TESTOSTERONE THERAPY IN OLDER MEN

Lucy Piner[1], Kim Huffman[1], Lorraine Elliott-Penry[1], Mahalakshmi Shankaran[2], William Evans[3,4], Marc Hellerstein[3], Susan Andrews[5], Ann Walker[5], Ram Miller[5], Richard Clark[5], and William Kraus[1]
[1]Sch. of Med., Duke Molecular Physiology Inst., Duke Univ., 3475 Erwin Rd., Durham, NC, 27705, [2]Proteomics, KineMed, Inc., 5980 Horton St., Ste. 470, Emeryville, CA, 94608, [3]Nutritional Sci., Univ. of California, Berkeley, 309 Morgan Hall, Berkeley, CA, 94702-3104, [4]Sch. of Med./Geriatrics, Duke Univ., 3501 Busse Bldg., Box 3003, Durham, NC, 27710, [5]R&D, GlaxoSmithKline, USA-Research Triangle Park, 5 Moore Dr., Research Triangle Park, NC, 27709-3398.

Biomarkers of muscle protein synthesis responsive to anabolic stimuli would be useful for studies of pharmacological or physiologic stimuli. To test if detection of such tissue or circulating biomarkers is feasible, we used a small-bore skeletal muscle biopsy technique (microbiopsy) with simultaneous serial plasma sampling in older male healthy volunteers randomized to either placebo or testosterone therapy for three weeks. We examined association of muscle protein fractional synthesis rates (FSRs) with change in strength; and with co-temporal assessments of two proteins (carbonic anhydrase 3 and creatine kinase M type) in plasma, believed >95% derived from skeletal muscle and to represent leakage from muscle. Subjects were men, aged 60-75 y, healthy, ambulatory, with body weight ≥50 kg, BMI 20 to 34 kg/m^2 (inclusive), and renal clearance ≥45 mL/min. Deuterated water (^2H_2O) was administered orally for 3 weeks prior to and during 3 weekly intramuscular injections of testosterone (13 men) or placebo (4 men). FSRs were determined by LC/MS/MS-measurements of mass isotopomer labeling. Analy-

sis of variance was used to estimate within and between treatment differences in the fraction of newly synthesized protein and in change from baseline in muscle. Differences in least squares means, Bonferroni adjusted p-values and 95% confidence intervals for the differences were determined. Of the 17 candidate proteins pre-selected for assessment in muscle, alpha-skeletal actin (decrease) and beta-myosin heavy chain (increase) demonstrated significant changes from baseline to Day 21 within the testosterone group; whereas skeletal muscle troponin-C in muscle demonstrated a significant difference in change from baseline between testosterone and placebo treated subjects. Changes in skeletal muscle troponin-C, beta-enolase, carbonic anhydrase 3 and myosin light chain 1/3 (faster) were correlated with change in strength (1-RM). FSRs of the two plasma proteins increased co-temporally with muscle proteins; however, they were poorly correlated. Plasma values were ~ 50% greater in plasma than in muscle; perhaps reflecting generalized muscle protein synthesis responses as compared to effects on the biopsied muscle. In sum, the microbiopsy technique provided enough sample to perform muscle protein FSRs using a deuterated water procedure. This approach may provide a promising technique to monitor anabolic effects in muscle in response to pharmacologic and physiologic interventions.

12.3

ACUTE EXERCISE EXACERBATES MUSCLE CERAMIDE LEVELS IN DIABETIC AND OBESE HUMANS

Joseph Brozinick[1], Hai Hoang Bui[1], Phil Sanders[1], Ming-Shang Kuo[1], Bryan Bergman[2], Leigh Perreault[2], and Devon Hunerdosse[2]

[1]Diabetes, Eli Lilly and Co., Lilly Corp. Ctr./DC 0545, Indianapolis, IN, 46285, [2]Div. of Endocrinology, Diabetes, and Metabolism, Univ. of Colorado, Anschutz Med. Campus P.O. Box 6511, MS 8106, CO 80045, Aurora, CO, 80045.

It has been hypothesized that the intake of a Western diet enriched in saturated fat drives skeletal muscle insulin resistance via the generation/accumulation of particular lipid species in this tissue. While there are differing hypotheses as to the identity of this lipid, many recent studies have focused on the sphingolipid ceramide. Moreover, the effects of acute exercise on muscle ceramide levels has not been examined in diseased humans. Here we investigate ceramide levels in human serum and muscle biopsies from athletes (A), obese non-diabetics (OND), and individuals with type 2 diabetes (T2D) during rest, acute exercise (1.5 h at 50% $VO2_{max}$) or recovery after exercise, and relate levels of these lipids to insulin sensitivity. Serum levels of the sphingolipids C18:0 ceramide and dihydroceramide were highly elevated in obese and T2D serum samples, and had the strongest correlations with the insulin sensitivity index (Si), and this relationship was not altered by exercise. Similarly, muscles from OND and T2D showed no change in total sphingolipids, but during rest had higher levels of the same C18:0 sphingolipids observed in serum. In contrast to what was observed in the serum, acute exercise significantly exacerbated the elevations in ceramide levels in muscles from OND and T2D as compared to A and these levels remained elevated during recovery. In contrast to the muscle ceramide data, muscle levels of DAG's at rest were highly elevated in A as compared to OND and T2D, while acute exercise elevated muscle DAG's in both OND and T2D, but not A. Examination of muscle gene expression revealed a number of differently expressed genes between A and T2D subjects, however the expression of genes in the de-novo sphingolipid synthesis pathway were unaltered. Finally, analysis of muscle inflammatory status indicated an activation of inflammatory pathways that correlated with muscle C18:0 ceramide levels. These data suggest stearate containing ceramides play unique roles in promoting insulin resistance in skeletal muscle, and may also drive diabetic sarcopenia.

12.4 Withdrawn.

12.5

GENETIC VARIATION OF BOTH THE BETA-2 ADRENERGIC RECEPTOR AND PHENYLETHANOLAMINE-N-METHYLTRANSFERASE HAVE A COMBINED EFFECT ON AIRWAY FUNCTION DURING EXERCISE IN HEALTHY HUMANS

Elizabeth Peitzman[1], Eric Snyder[1], Micha Johnson[1], and Bruce Johnson[2]

[1]Kinesiolgy, Univ. of Minnesota, Cooke Hall, 1900 University Ave., SE, Minneapolis, MN, 55455, [3]Cardiovascular Diseases, Mayo Clinic, 200 First St., SW, Rochester, MN, 55905.

Introduction: Change in airway tone during exercise is important for opening up the airways to meet the gas exchange demands of exercise. Epinephrine is the main agonist for the β_2 adrenergic receptors (ADRB2), the stimulation of which leads to bronchonoredilation. Phenylethanolamine-N-methyltransferase (PNMT) is an enzyme that is responsible for the conversion of norepinephrine to epinephrine (EPI). Several genotypes of both PNMT and ADRB2 have been shown to be functionally important in EPI release and β_2 receptor function, respectively. We sought to determine the combined effects of PNMT and ADRB2 genotypes on airway function with exercise in healthy humans. We hypothesized that subjects with functional haplotypes of PNMT (1*7, 2*1, 2*2, and 2*3) and the ADRB2 (Gly16Gly) would have higher forced expiratory flows (FEF), and maximum mid-expiratory flow (MMF), when compared to the least functional genotypes of these genes (2*7 and Arg16Arg, for PNMT and ADRB2, respectively). Methods: Subjects performed steady-state exercise for 9 minutes on a cycle ergometer at 75% of maximum effort. At rest and at peak exercise arterial catecholamines were sampled via indwelling catheter and airway function (FEF at 25 and 50% of the forced vital capacity, and MMF) was assessed. Results: At rest, there were no differences in airway function between the 2*7/Arg16Arg genotype (n=8) and the non-2*7/Gly16Gly genotype (n=24). With heavy exercise, the 2*7/Arg16Arg genotype had lower FEF25, FEF50, MMF (FEF25= 8.2.5±0.45 vs. 9.6±0.28 l/sec, FEF50= 5.3±0.31 vs. 5.5±0.21 l/sec, MMF= 4.7±0.29 vs. 5.6±0.19). There were no differences in the %change in airway function from rest to heavy exercise between the groups. However, we found differences in %change from rest to recovery from exercise (at 5 and 10 minutes) according to genotype. The non-2*7/GlyGly genotype had more sustained bronchodilation when compared to the non-2*7/ArgArg genotype

(MMF=4.1±0.2 vs 4.9±0.2%) for ArgArg and GlyGly of the non-2*7 PNMT gentotype. In contrast, within the 2*7 genotype of PNMT (which has previously demonstrated lower EPI synthesis with exercise), there was no difference in change in airway function from rest according to ADRB2 genotype, likely because of less EPI and, therefore, smaller differences in receptor desensitization. Conclusion: These findings demonstrate genetic interaction of two systems key in regulating airway tone highlighting the importance of multigenetic studies on exercise response.

13.0 EPIGENETICS

13.1
MATERNAL EXPOSURE TO WESTERN DIET AFFECTS BODY COMPOSITION BUT NOT ADULT ACTIVITY LEVELS IN MICE BRED FOR HIGH VOLUNTARY EXERCISE

Layla Hiramatsu[1], Will Agnew-Svoboda[2], Mikkal Blick[3], Gerald Claghorn[1], Jarren Kay[1], Ralph Lacerda de Albuquerque[1], Jennifer Singleton[1], Zoe Thompson[2], James Colbath[4], Brett Ho[4], Brittany Ho[4], Gabriela Sanchez[4], Danny Thai[4], and Theodore Garland, Jr.[1]

[1]Evolution, Ecology, and Organismal Biology, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521, [2]Neuroscience, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521, [3]Genetics, Genomics and Bioinformatics, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521, [4]Biology, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521.

Lack of physical activity contributes to many human diseases, including overweight and obesity. To help disentangle the numerous genetic and environmental factors that influence adult activity levels, we used an ongoing selection experiment with 4 replicate lines of mice bred for high voluntary wheel running (HR: generation 73) and 4 replicate, non-selected control lines (C). From 2 weeks prior to mating until their pups could feed on solid food (~14 days of age), 100 dams (50 HR, 50 C) were fed a "Western" diet (WD, Harlan Teklad TD.88137, high in fat and sucrose) and another 100 dams were fed standard diet (SD). Of the resulting pups, 100 males (50 WD, 50 SD) were considered focal mice and received various tests from weaning into adulthood: food consumption, body composition, elevated plus maze, maximal aerobic capacity (VO_2max) during forced exercise, 6 days of wheel access, home-cage activity, and organ masses. Nested ANCOVA was used with line nested within linetype (HR or C), with body mass and/or age as covariates. Adjusted for dam mass, litter size at weaning was larger for HR but not significantly affected by maternal WD. Mean pup mass was smaller for HR and increased by maternal WD. Home-cage activity of young focal males tended to be increased by maternal WD. Young-adult lean and fat masses were increased by maternal WD, but food consumption was unaffected. Behavior in an elevated plus maze, often used to indicate anxiety, and VO_2max were unaffected by maternal WD, but HR had higher VO_2max than C mice, as reported previously. Adult body, lean, and fat masses were increased by maternal WD. No aspect of adult wheel running (total distance, duration, average running speed) or home-cage activity was statistically affected by maternal WD. The amount of fat lost after 6 days of wheel running was greater for mice with maternal WD, though changes in total and lean masses were unaffected and did not differ between HR and C. Heart ventricle mass was increased by maternal WD in both HR and C mice, but fat pad, liver, spleen, and brain masses were unaffected. As reported previously, HR mice had larger brains than C mice. Grand-offspring were unaffected by grand-maternal WD for adult body mass and wheel running. Analyses of circulating hormone levels and other traits are ongoing. Supported by NSF grant IOS-1121273 to TG.

13.2
MARINE CORPS MARTIAL ARTS PROGRAM DOES NOT CAUSE GLOBAL DNA METHYLATION CHANGES IN FEMALE MARINES

Jake Deckert[1], Jaimie Ward[1], Jacob Siedlik[2], Evan Barnes[1], Evan Landes[1], John Vardiman[3], and Philip Gallagher[1]

[1]Hlth. Sport & Exercise Sci., Univ. of Kansas, Robinson Ctr., 1301 Sunnyside Ave., Lawrence, KS, 66045-2567, [2]Exercise Sci. and Pre-Health Professions, Creighton Univ., Kiewit Fitness Ctr., 2500 California Plaza, Omaha, NE, 68178, [3]Nutrition, Kansas State Univ., Justin Hall, 1324 Lovers Ln., Manhattan, KS, 66506.

Exercise is known to modify the expression of mRNA and protein levels of many different genes regulating mitochondrial function and fuel usage. There is growing evidence that suggests that changes to the epigenome are linked to these exercise-induced changes in gene expression. DNA methylation is an epigenetic modification that is generally associated with gene silencing and decreased gene expression. However, there is limited research, especially in humans on DNA methylation, and the results vary between age, sex, tissue and type of exercise. We examined the global DNA methylation changes in whole blood after an acute bout of U.S Marine Corps Arts Training (MCMAP). Further, we examined the effects of repeated bouts of MCMAP training on DNA methylation over a six week period. Ten, female marines underwent 60 minutes of MCMAP training consisting of 30 minutes of Combative Conditioning and 30 minutes of Combative Arts. Venous blood samples were taken at rest, immediately after training end and 1 hour post-training for three different visits over the six week period. Global DNA methylation changes were analyzed after an acute bout of MCMAP training. Resting blood samples from the three different visits were used to analyze the changes in global DNA methylation after repeated bouts of MCMAP training. There was very little variation observed when examining either acute or chronic changes in global DNA methylation in response to training. Our analyses indicated a small increase in global methylation within the one-hour recovery period post-training. While this change is likely not biologically relevant, an examination of methylation responses to higher intensity training is warranted.

13.3
A NEW RRBS APPLICATION TO ASSESS DNA METHYLATION IN HUMAN SLOW- AND FAST-TWITCH SKELETAL MUSCLE FIBERS WITH LOW-DNA INPUT

Gwenaelle Begue[1], Ulrika Raue[1], Bozena Jemiolo[1], and Scott Trappe[1]
[1]Human Performance Lab., Ball State Univ., 2000 W. University Ave., Muncie, IN, 47306.

DNA methylation plays a major role in the control of gene expression and in defining cell types. Reduced Representation Bisulfite Sequencing (RRBS) is a technique used to study genome-wide DNA methylation at a single-base resolution (CpG). However, the DNA input requirements are challenging when working with small pools of tissue-specific cell type. Here, we describe RRBS data quality on low-DNA input from human slow-twitch (MHC I) and fast-twitch (MHC IIa) skeletal muscle fibers. This investigation examined: 1) DNA amount required from human muscle fibers (20-40 fibers) for a successful RRBS library construction, and 2) sequencing data quality obtained from low-DNA input of fiber-type specific samples. Individual muscle fibers were separated from vastus lateralis muscle bundles (~5-6 mm length) under a light microscope, using fine tweezers. The fiber type (MHC) was determined using SDS-PAGE, and DNA extraction of pooled single muscle fibers (~20-40 fibers) was performed using the QIAamp® DNA Micro kit (Qiagen). Library construction and sequencing (50bp paired-end read) were then conducted using the Zymo Research RRBS platform (Methyl-MidiSeq™). We show that: 1) an amount of DNA as low as 15 ng from human muscle fibers was sufficient for high-quality library construction, and 2) high-quality sequencing data can be obtained using 32 ng of DNA from type-specific muscle fibers. Typical mapping ratios (~47%) and bisulfite conversion rates (~97%) were obtained. Approximately 17 million of unique CpG-sites were assessed, which represent 30% of the total number of CpG-sites in the human genome (56 million), and 3-5 times more CpG-sites than previous RRBS protocols on human cells and tissues. Coverage of CpG islands, promoters, exons, introns, and enhancers was similar or higher than previously reported in the literature for human samples. In summary, the RRBS technique can be successfully applied to low-DNA input for the investigation of DNA methylation in human muscle fibers. This approach provides a unique platform for future human studies to gain new knowledge into fiber-type specific skeletal muscle epigenetic regulation with health, aging, athletics, and disease. Sponsored by NIH grant R01 AG-038576.

13.4
DNA METHYLATION AND GENE EXPRESSION IN HUMAN SLOW- AND FAST-TWITCH SKELETAL MUSCLE FIBERS: AN EXPLORATORY ANALYSIS

Gwenaelle Begue[1], Ulrika Raue[1], Bozena Jemiolo[1], and Scott Trappe[1]
[1]Human Performance Lab., Ball State Univ., 2000 W. University Ave., Muncie, IN, 47306.

DNA methylation plays a major role in the control of gene expression and in defining cell types. Recently, we demonstrated high-quality fiber-type specific (MHC I, MHC IIa) sequencing methylation data using an RRBS protocol on low-DNA input from human skeletal muscle. Here we report**:** 1) the global DNA methylation profiles of skeletal muscle fibers, and 2) MHC I and MHC IIa DNA methylation and how it relates to gene expression of select genes in active young men. Individual muscle fibers were separated from vastus lateralis muscle bundles (~5-6 mm length) under a light microscope, using fine tweezers. The fiber type (MHC) was determined using SDS-PAGE before fiber-type specific DNA and RNA extractions. Library construction and sequencing were then performed using the Zymo Research RRBS (Methyl-MidiSeq™) platform and the Cofactor Genomics RNA-Sequencing (RNA-Seq) service. The global muscle fiber methylation profile obtained in this study shows low methylation levels in gene promoters and CpG islands but high methylation levels in gene bodies, representative of non-malignant/young healthy cells. We identified 143,160 differentially methylated sites across 14,046 genes. The integration of the DNA methylation and RNA-Seq data revealed that the fiber-type specific DNA methylation of select genes relates to the gene expression of these genes. When the gene was hypermethylated, the gene expression was low, and vice-versa. These data provide initial insight into basal DNA methylation pattern differences between MHC I and MHC IIa muscle fibers in healthy young men. These findings are complemented by the RNA-Seq data, and collectively shed light on the relationship between fiber-type specific gene DNA methylation and expression. Future studies could be extended to hybrids (MHC I/IIa, MHC IIa/x) and super-fast (MHC IIx) fibers, particularly prevalent with disease or disuse, in order to better understand the DNA methylation dynamic of various muscle wasting pathologies. Furthermore, fiber-type specific methylome studies can increase the understanding of how exercise leads to muscle phenotype changes in various age group and population. Sponsored by NIH grant R01 AG-038576.

13.5
MATERNAL EXERCISE ALTERS OFFSPRING ADIPOGENESIS

Leryn Reynolds[1], Josh Preston[1], Lindsay Carter[1], and Kevin Pearson[1]
[1]Pharmacology and Nutritional Sci., Univ. of Kentucky, 900 S. Limestone, C.T. Wethington Bldg., Rm. 571, Lexington, KY, 40536.

Introduction: Previous studies demonstrate that maternal exercise lowers offspring risk of obesity. However, the mechanisms involved in this risk reduction are not entirely known. Thus, the purpose of this study was to examine if markers involved in the regulation of adipogenesis were altered in murine embryonic fibroblasts (MEFs) from dams who had access to voluntary wheel running (EX) or were sedentary during pregnancy (SED). **Methods:** MEFs (EX, n=7 and SED, n=5) were collected at day 14 of gestation, cultured, and subsequently plated to 12 well plates. 48 hours post confluency, RNA was isolated from each set of cells. A second set of cells was induced with an adipogenic cocktail (media containing: 10% fetal bovine serum, penicillin streptomycin, 1 μM dexamethasone, 0.5 mM 3-isobutyl-1-methylxanthine, 10 μg/mL insulin and 1.0 μM rosiglitazone) for 3 days. Then, for an additional 7 days the cells were maintained in media containing 10% fetal bovine serum, penicillin streptomycin, 10 μg/mL insulin and 1.0 μM rosiglitazone before RNA was isolated. mRNA expression of adipogenic markers, cheme-

rin, fatty acid binding protein 4 (FABP4), and adiponectin were measured. Further, the set of cells induced with the adipogenic cocktail were stained with oil red o to assess the amount of lipid in each well. **Results:** FABP4 and adiponectin mRNA expression increased in both the SED and EX MEFs following adipogenesis ($p<0.05$), however, this was not different between the two groups. Chemerin mRNA expression was significantly elevated in the SED MEFs compared to the EX MEFs ($p<0.05$), these changes were evident 48 hours post confluency and following 10 days of the adipogenic cocktail ($p<0.05$). Further, oil red o extraction revealed increased staining in SED MEFs compared to EX MEFs indicating greater quantities of lipid ($p<0.05$). **Conclusion:** Preliminary studies suggest that maternal exercise during gestation results in early adaptations in utero in offspring which play a role in adipocyte differentiation. Chemerin, an adipokine which regulates adipocyte differentiation, may be a mechanism by which maternal exercise reduces later risk of obesity in offspring. This study was supported by a National Institutes of Health R01 DK090460 (KJP).

13.6
EIGHT WEEK EXERCISE TRAINING ALTERS THE GLOBAL DNA METHYLATION PATTERNS IN HUMAN SKELETAL MUSCLE

Samantha Day[1], Richard Coletta[2], Luis Garcia[2], Tonya Benjamin[3], Lori Roust[3], Elena De Filippis[3], Lawrence Mandarino[4], and Dawn Coletta[5]

[1]Sch. of Life Sci., Arizona State Univ., 427 E. Tyler Mall, Tempe, AZ, 85281, [2]Sch. for the Sci. of Hlth. Care Delivery, Arizona State Univ., 500 N. 3rd St., Phoenix, AZ, 85004, [3]Endocrinology Dept., Mayo Clinic, 13400 E. Shea Blvd., Scottsdale, AZ, 85259, [4]Div. of Endocrinology, Diabetes and Metabolism in the Dept. of Med., Univ. of Arizona, 1501 N. Campbell Ave., Tucson, AZ, 85724, [5]Sch. of Med. Sch. of Nutrition and Hlth. Promotion, Arizona State Univ., 550 N. 3rd St., Phoenix, AZ, 85004.

The effect of exercise training on epigenetic factors, such as DNA methylation in insulin resistant muscle has not yet been fully established. Therefore, the aim of this study was to determine whether an 8-week exercise training regimen in obese insulin resistant participants alters global DNA methylation patterns. Basal muscle biopsies were obtained from five obese (3M/2F; age 41.8±3.3; body mass index 32.3±0.8 kg/m^2) participants pre and post exercise training. Four lean (2M/2F; age 36.3±3.4 years; body mass index 23.8±0.6 kg/m^2) participants served as controls. Training increased peak aerobic capacity (VO_2peak) from 20.2±1.9 to 24.3±2.7 mL/kg/min in the obese subjects. We performed reduced representation bisulfite sequencing on the DNA isolated from the vastus lateralis muscle biopsies. We set out to determine whether exercise training returns the methylation profile of post exercise skeletal muscle toward that of lean controls. Of the millions of sites captured using this technology, we identified 72 significant methylation sites that post exercise were normalized to levels similar to those observed in the lean controls.The methylation site (Chr. 1:119532387) that was most increased in the obese compared to the lean was located in the T-Box 15 (TBX15) gene and went from 41.1% to 77.1% (adjusted $P<0.05$). Exercise training decreased TXB15 methylation to 47.0% in the obese. Conversely, the methylation site (Chr.17:46800675) that was most decreased in obesity was Prostate Cancer Susceptibility Candidate (PRAC) compared to the lean from 37.5% to 1.4% (adjusted $P<0.05$). Exercise training increased PRAC methylation to 28.2% in the obese. Our results provide evidence that exercise can alter DNA methylation in obese human skeletal muscle towards methylation observed in lean.

14.0 GENDER DIFFERENCES

14.1
RELATIONSHIP BETWEEN BODY COMPOSITION AND MENSTRUAL/PREMENSTRUAL SYMPTOMS IN JAPANESE YOUNG WOMEN

Kanako Ohno[1], Hisashi Naito[1], and Shuichi Machida[1]

[1]Grad. Sch. of Hlth. and Sports Sci., Juntendo Univ., 1-1 Hirakagakuendai, Inzai, Japan.

Background: It has been suggested that several factors, such as body mass index (BMI), are associated with menstrual/premenstrual symptoms, including both physical and psychological symptoms. However, there is no information regarding interplay between body composition and menstrual/premenstrual symptoms. The aim of this study is to investigate the relationship between body composition and menstrual/premenstrual symptoms in Japanese young women. **Methods:** A total of 39 young women (aged 19–25 years) voluntarily participated in the study. Participants completed a translated Moos Menstrual Distress Questionnaire during their menstrual and premenstrual phases. Body composition, including body fat mass and skeletal muscle mass, was determined using Inbody 730 (Biospace), which utilizes bioelectrical impedance analysis. The Pearson correlation coefficient was used for data analysis. **Results:** Body fat mass was significantly positively correlated with physical symptoms in the menstrual ($r = 0.377$, $P = 0.018$) and premenstrual ($r = 0.390$, $P = 0.014$) phases. On the other hand, no significant relationship was observed between skeletal muscle mass and menstrual/premenstrual symptoms. BMI was also not associated with menstrual/premenstrual symptoms. **Conclusions:** The data demonstrated that higher body fat mass was associated with an increase in physical symptoms during the menstrual and premenstrual phases.

14.2
HYPOVOLEMIC MEN AND WOMEN REGULATE CEREBRAL BLOOD FLOW DIFFERENTLY FOLLOWING EXPOSURE TO ARTIFICIAL GRAVITY

Michelle Favre[1,2], Michael Falvo[1,2], Joyce Evans[3], and Jorge Serrador[1,2]

[1]Pharmacology, Physiology, and Neuroscience, Rutgers Univ., 185 S. Orange Ave., Newark, NJ, 07103, [2]War Related Illness and Injury Study Ctr., Vet. Affairs New Jersey Hlth. Care Sys., 385 Tremont Ave., E. Orange, NJ, 07018, [3]Biomedical Eng., Univ. of Kentucky, 143 Graham Ave., Lexington, KY, 40506.

Exposure to artificial gravity (AG) has been identified as an effective countermeasure to increase orthostatic tolerance in bedrested men. We have previously reported that acute exposure to AG also improved orthostatic tolerance limit (OTL) in both men

and women during hypovolemia compared to head-down bed rest (HDBR). However, in that work we did not examine the effect of AG on cerebral blood flow velocity (CBFV) during OTL tests. This work represents the CBFV response in the previously reported subjects during OTL tests following hypovolemia with or without AG exposure. Nine men (37.7 ± 4.0 years) and seven women (29.6 ± 2.2 years) participated in the study. The study consisted of a low salt diet for 24 hours, followed by furosemide infusion, 90 minutes of AG exposure or 90 minutes of -6° HDBR, and an OTL test. The OTL test consisted of a 10 minute 70° head up tilt test followed by 3 minute intervals of 10mmHg reductions in pressure using lower body negative pressure until the onset of presyncope. Continuous measurements of CBFV, blood pressure, heart rate, and end-tidal CO_2 were taken during the OTL tests. The two test days (artificial gravity and HDBR) were randomized and separated by 21 days. Results indicate a 30% increase in OTL in men compared to a 22% increase in OTL in women during acute AG exposure compared to HDBR. Examining if CBFV was different between the AG day, with increased OTL, and the HDBR day, we found a significant difference in the response between men and women. Men did not show any difference in CBFV just prior to presyncope (AG: 72.9 ± 3.6 %; HDBR: 73.4 ± 4.2 %) and no difference in end tidal CO_2 (AG: 31.8 ± 1.3 mmHg; HDBR: 31.9 ± 1.3 mmHg). In contrast, women had significantly higher CBFV following AG exposure just prior to presyncope (81.9± 4.0%) compared to the HDBR (71.2± 4.8%), while end tidal CO_2 was not different (AG: 31.8 ± 1.5 mmHg; HDBR: 32.4 ± 1.5 mmHg). These findings suggest that in men, reductions in CBFV to ~70% resulted in the development of presyncope, regardless of AG exposure. In women, CBFV remained elevated following AG exposure. This suggests that AG exposure improves CBFV in women, and that there must be a different limiting factor for OTL in hypovolemic women that remains to be elucidated. This study suggests that AG may be an effective countermeasure to improve CBFV and OTL in hypovolemic women and men. This research was funded by the KY NASA EPSCoR grant and the Dept of Veteran Affairs.

14.3
DIFFERENCES IN EXERCISE CAPACITY IN ADULTS BORN PRETERM APPEAR TO BE DRIVEN BY MALES AND NOT FEMALES

Laura Tetri[1], Kristin Haraldsdottir[1], Emily Farrell[1], Mari Palta[2], David Pegelow[1], and Marlowe Eldridge[1]

[1]Pediatrics, Univ. of Wisconsin, Madison, 600 Highland Ave., Madison, WI, 53792, [2]Biostatistics and Med. Informatics, Univ. of Wisconsin, Madison, 600 Highland Ave., Madison, WI, 53792.

Background: Preterm birth affects approximately 12% of children born in the United States. Many of these infants grow up to be active and healthy appearing individuals. However, multiple studies have shown differences in exercise capacity and metabolic changes during exercise. While sex differences are widely acknowledged in the early outcomes in the neonatal intensive care unit in infants born prematurely, sex differences have not been widely studied in these children as they grow into young adults. **Objective:** This study attempts to identify sex differences during exercise in young adults born preterm. **Methods:** Adults born preterm (preterm) and age matched term-born controls (control) (n=4 males, 8 females) with an average age of 21 to 22 years old performed incremental graded exercise on a cycle ergometer to volitional exhaustion. During this time, arterial blood was drawn at every stage, and metabolic data was collected. Maximal absolute oxygen consumption (VO_2), maximal power output, and arterial blood gases were analyzed using a two-way ANOVA to compare groups and sex. **Results:** We have previously shown a reduced power output in preterm young adults (Farrell et al, 2015, Annals ATS). Post-hoc analysis of this data shows that the difference in power output is driven by a lower power output in preterm males (24% lower), compared to control males (interaction $p<0.05$). Furthermore, the preterm males had a lower maximal VO_2 (L/min) compared to male controls (23% lower); there were no differences between the female groups (interaction $p=0.005$). At peak power output, there was a trend towards an interaction between sex and group in arterial pH, with the preterm males having a lower pH compared to male controls (0.05 lower), but no difference in females (interaction $p=0.08$). There was also a trend towards an interaction between sex and group in arterial bicarbonate levels ($p=0.09$) with a lower bicarbonate in preterm males compared to control males (4.1 mEq/L lower). There were no differences in arterial PCO_2. The preterm males had a higher respiratory rate at peak power than control males (35% higher), and no difference existed between the female groups (interaction $p=0.04$). **Conclusions:** Farrell et al report significant limitations in exercise capacity in adults born preterm. These limitations appear to be driven by alterations in exercise capacity and metabolic response of preterm males, with no changes identified in preterm females.

15.0 MOLECULAR TRANSDUCERS

15.1
DEFINING NUTRIENT-SENSITIVE PATHWAYS OF MTOR ACTIVATION IN HUMAN SKELETAL MUSCLE

Nathan Hodson[1], Jess Dent[1], Daniel Craig[1], Michael McLeod[1], James Murray[2], D. Lee Hamilton[3], Leigh Breen[1], and Andy Philp[1]

[1]Sch. of Sport, Exercise and Rehabilitation Sci., Univ. of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, [2]Sch. of Biochemistry and Immunology, Trinity Coll., Dublin, Pearse St., Dublin, Ireland, [3]Hlth. and Exercise Sci. Res. Grp., Sch. of Sport, Univ. of Stirling, Stirling, FK9 4LA, UK.

The mechanistic target of rapamycin (mTOR) is a key regulator of protein balance in skeletal muscle, sensing alterations in amino acid availability and mechanical loading to increase skeletal muscle protein synthesis. Recent evidence suggests that interaction of mTOR with the lysosome is essential for optimal nutrient-stimulated signalling. Therefore, the current study aimed to examine whether amino-acid/carbohydrate feeding stimulates mTOR interaction with the lysosome in human skeletal muscle. Eight young, healthy, male participants volunteered to take part in this study. Muscle biopsies and blood samples were collected in the fasted state and 1h and 3h post consumption of a protein-carbohydrate beverage (Gatorade Recover®,

Gatorade, IL, USA) providing 20/44/1g of protein/carbohydrate/fat respectively. Immunofluorescence approaches were used to study mTOR localisation and protein complex formtion, whilst kinase activity assays and immunoblotting were used as surrogate markers of mTOR activity. mTOR and LAMP2 (lysosomal marker) were observed to colocalise at all time-points, indicating that mTOR is in constant association with the lysosome ($p>.05$). We observed a 17% increase in mTOR localisation with the plasma membrane 1h following beverage consumption ($p=.026$), which returned to baseline values 3h post-consumption. In parallel, we observed an ~10-fold increase in S6K1 and AKT kinase activity 1h post exercise. To assess mechanisms of nutrient mediated activation of mTOR, we investigated the activity of mitogen-activated protein 4 kinase 3 (MAP4K3) and vacuolar protein sorting 34 (VPS34), two purported amino acid sensors in skeletal muscle. Whilst no increases in MAP4K3 phosphorylation or VPS34 activity were observed at any timepoint, in contrast, we observed an 11% increase in VPS34 association with mTOR at the 1h timepoint ($p=.045$). In conclusion, our data suggests that mTOR-lysosomal complex translocation to the cell periphery occurs in human skeletal muscle following AA/CHO ingestion, in parallel to increased mTOR activity. This would suggest that the temporal localisation of mTOR is fundamentally important for enhancing translational processes in skeletal muscle following an anabolic stimulus.

15.2

THEORETICAL AND MOLECULAR RESOLUTION OF THE LINK BETWEEN LOW EXERCISE CAPACITY AND DISEASE

Lauren Gerard Koch[1], Steven L. Britton[1], Sung-Jun Park[2], and Jay H. Chung[2]
[1]Anesthesiology, Univ. of Michigan, 2021 Biomedical Sci. Res. Bldg., 109 Zina Pitcher Pl., Ann Arbor, MI, 48109-2200, [2]Lab. of Obesity and Aging Res., Natl. Heart Lung and Blood Inst., Bldg. 10-7D14, 10 Center Dr., Bethesda, MD, 20892.

The association between low exercise capacity and high morbidity and mortality is statistically strong yet unresolved mechanistically. By connecting clinical observation with a theoretical base, we hypothesized that: variation in capacity for energy transfer metabolism is the central mechanistic determinant between disease and health (energy transfer hypothesis: ETH). As a predictive test of this hypothesis, we show that two-way selective breeding of genetically heterogenous rats for low and high intrinsic treadmill running capacity (used as a surrogate for energy transfer) also produces rats that differ for disease risks. The lines are termed Low Capacity Runners (LCR) and High Capacity Runners (HCR) and after 36 generations of selection differ by over 8-fold in running capacity. Consistent with the *ETH*, the LCR score high for developing metabolic syndrome, neurodegeneration, cognitive impairment, fatty liver disease, susceptibility to cancer, and reduced longevity. We use concepts from Ilya Prigogine, Hans Krebs, and Peter Mitchell to formulate a theoretical explanation for the *ETH*: 1) non-equilibrium thermodynamic energy dissipation mechanisms drove evolution to attain living structures with higher complexity for enhanced capacity for energy transfer (order from disorder), and 2) the rise in atmospheric oxygen and its accompanying high energetic nature was permissive for the emergence of multi-cellular complexity. These ideas promote the view that energy transfer is the central feature of evolution and suggest that disease is also associated with this pattern. Recent work provides mechanistic molecular specification in accord with the *ETH* that is confirmed in LCR-HCR rats, mice, and monkeys. We find that DNA-dependent protein kinase (DNA-PK) is a driver of the aging-associated decline in metabolism and fitness. Aging increases DNA-PK activity, decreasing the ability of HSP90α to chaperone clients such as AMP-activated protein kinase (AMPK). DNA-PK activity was 3-fold lower and p-HSP90α was ~60% lower in HCR compared LCR rats. Inhibiting DNA-PK, both genetically or with a small molecule inhibitor, prevents the weight gain, decline of mitochondrial function and physical fitness in mice, and protects against type-2 diabetes in obese mice. We conclude that DNA-PK activates a "metabolic brake" starting at middle age, which makes staying lean and physically fit difficult at older age and increases susceptibility to metabolic diseases. (NIH P40OD021331)

15.3

EXERCISE-TRAINING INCREASES BASAL AUTOPHAGY-RELATED GENE EXPRESSION IN MURINE ARTERIAL ENDOTHELIAL CELLS

J. S. Kim[1], L. P. Bharath[1], J. Allsop[1], T. Bean[1], T. Bonn[1], G. Hestwood[1], D. Nelson[1], M. Drummond[1], P. V. A. Babu[1], T. E. Graham[1], and J. D. Symons[1]
[1]Nutrition and Integrative Physiology; Endocrinology, Metabolism, and Diabetes, Univ. of Utah, 15 N. 2030 E., Salt Lake City, UT, 84112.

Autophagy is a conserved process whereby cells remove or recycle damaged or dysfunctional organelles in response to nutriaent or environmental stress. Our preliminary results indicate that indices of autophagy and eNOS activation increase ($p<0.05$) in bovine aortic endothelial cells (BAECs) exposed to 180-min x 20 dyne•cm^2 shear stress, and in arteries from mice that complete 60-min of treadmill-running. It is unknown whether the chronic stress of exercise-training increases autophagy-related (Atg) gene expression in arterial endothelial cells (ECs) and media + adventitia (M+A) under basal conditions. 5-month old male C57Bl6 mice were treadmill-trained (ETR, n=6, 32±1 g) or remained sedentary (SED, n=5, 32±1 g) 6 days per week. After 10-weeks, total workload [i.e., body weight (kg) • time (min) • speed (m/min) • treadmill grade (%)] completed during a maximal exercise test was greater ($p<0.05$) in ETR (3.63±0.48 kgm) vs. SED animals (1.08± 0.22 kgm). 24 h later the soleus muscle, iliac, and carotid arteries were obtained. The respiratory control ratio (RCR, state III to state IV respiration) was greater ($p<0.05$) in soleus from ETR (2.04±0.14) vs. SED mice (1.31±0.16). The iliac and carotid arteries were perfused with QIAzol lysis reagent. The effluent containing ECs and the remaining vessel containing M+A were collected. mRNA expression was quantified by real-time RT-PCR using SYBR green fluorescence. Cycle threshold (Ct) values were normalized to the housekeeping gene 18S. Purity of the EC and M+A fractions was confirmed by measuring PECAM-1 and α-SMA expression respectively. mRNA expression increased 1.8 - 4.1-fold ($p<0.05$) for beclin-1,

LC3-II, Atg3, Atg5, Atg7, Atg12, and Atg16, and decreased 2-fold ($p<0.05$) for p62, in iliac artery ECs from ETR vs. SED mice. Of the autophagy-related genes assessed, training did not influence mRNA expression in M+A from iliac arteries, or in ECs or M+A from carotid arteries. Ongoing studies are addressing whether exercise-training increases basal expression of autophagy-related proteins in arteries of aged mice. This is relevant clinically because we and others have shown depressed vascular autophagy in arteries from aged vs. adult mice that exhibit concurrent vascular dysfunction.

15.4

EXERCISE SERUM INCREASES GLUT4 CONTENT IN HUMAN PRIMARY ADIPOCYTES

Marcelo Flores-Opazo[1], Arthe Raajendiran[2], Matthew Watt[2], and Mark Hargreaves[1]

[1]Physiology, Univ. of Melbourne, Grattan St., Melbourne, Australia, [2]Physiology, Monash Univ., Wellington Rd., Clayton, Australia.

Contracting skeletal muscle releases biologically active proteins, nucleic acids and metabolites during exercise (coined "exerkines") that may mediate some of the systemic benefits of regular exercise. We have previously reported that four weeks of exercise training increases glucose transporter GLUT4 protein content in adipose tissue from patients with type 2 diabetes (Hussey et al., 2011). The present study was undertaken to examine the hypothesis that circulating factors may mediate this response. Cells were isolated from the stromal vascular fraction of subcutaneous abdominal adipose tissue obtained by percutaneous needle biopsy from two male subjects (31 & 35 yrs, 71 & 94 kg, BMI: 25 & 27 $kg.m^{-2}$). These cells were cultured in DMEM/Nutrient Mixture F-12 supplemented with GlutaMAX™ and chemically differentiated to mature adipocytes as indicated by lipid loading. Mature cells were insulin-starved for 48 hr and then incubated for 48 hr in media containing 10% serum obtained either at rest or after exercise. Eight, healthy male subjects (age: 21.4 ± 0.6 yr, body mass: 71 ± 4 kg, BMI: 22 ± 1 $kg.m^{-2}$, VO_2 peak: 43 ± 2 $ml.kg^{-1}.min^{-1}$) exercised for 60 min at ~70% VO_2 peak. Venous blood samples were obtained before and during the last one min of exercise and the serum was frozen for later incubations. Adipose cells harvested after 48 hr incubation with serum were analysed for GLUT4 content by Western blotting. In a separate experiment, cells were harvested after 6, 12 and 24 hr of incubation and analysed for GLUT4 gene expression by real time qPCR. Exercise serum from 5/8 subjects increased GLUT4 protein in adipose cells and, on average, there was a small (~15%), but significant ($P<0.05$), increase in GLUT4 protein content compared with cells treated with resting serum. There was no effect of exercise serum on GLUT4 mRNA after 6 and 24 hr, but a ~3-fold increase ($P<0.05$) after 12 hr. Our results suggest that circulating factor(s) may mediate the effects of exercise on adipose tissue GLUT4 expression.

Reference: Hussey, S.E., S.L. McGee, A. Garnham, J.M. Wentworth, A.E. Jeukendrup & M. Hargreaves (2011). Diabetes Obes. Metab. 13: 959-962. Supported by Diabetes Australia Research Program.

16.0 MITOCHONDRIAL FUNCTION

16.1

A SINGLE BOUT OF AEROBIC EXERCISE INCREASES CITRATE SYNTHASE SPECIFIC ACTIVITY AND ATP PRODUCTION RATE IN ISOLATED MITOCHONDRIA FROM HUMAN SKELETAL MUSCLE

Katon Kras[1,2], Wayne Willis[2,3], Eleana De Filippis[2], Lori Roust[2], Nyssa Hoffman[1,2], and Christos Katsanos[1,2]

[1]Nutrient Metabolism Lab., Sch. of Life Sci., Arizona State Univ., 427 E Tyler Mall, Tempe, AZ, 85281, [2]Mayo Clinic in Arizona, 13208 E. Shea Blvd., Scottsdale, AZ, 85259, [3]Coll. of Hlth. Solutions, Arizona State Univ., 500 N. 3rd St., Phoenix, AZ, 85004.

Exercise training increases the myocellular content of mitochondria (MITO) and oxidative capacity of skeletal muscle. However, the effects of an acute bout of exercise on MITO function are less clear. Across the mitochondrial reticulum, MITO located near the periphery, termed subsarcolemmal MITO (SS MITO), have been shown to be more adaptable to exercise intervention than MITO located deep within the myofibrils, termed intermyofibrillar MITO (IMF MITO). On the other hand, the IMF MITO have been implicated more directly in the ATP production supporting the mechanical work of the skeletal muscle. We hypothesized the following changes in MITO function following a single bout of aerobic exercise: SS MITO will exhibit greater changes in non-ATP production-related enzyme activity, whereas the IMF MITO will exhibit greater changes in MITO ATP production rate (MAPR). Biopsies were obtained from vastus lateralis muscle before (PRE) and three hours after (POST) 45 min of exercise at 75% of VO_{2max} from 9 sedentary subjects (5 males/4 females; age = 32±6 years; body mass index = 30±4 kg/m^2; body fat = 29±5 %). SS and IMF MITO were isolated using standard differential centrifugation techniques. Citrate synthase (CS) activity was determined spectrophotometrically and MAPR (using Malate + Pyruvate + Glutamate + Succinate as oxidative substrates) was assayed using luciferase. Exercise increased whole muscle CS activity by 29% (PRE 6.5±0.8 vs POST 8.4±0.8 µmol/min/g wet muscle; $P<0.05$). CS specific activity increased in both SS MITO (38%) and IMF MITO (27%) following exercise ($P<0.05$): SS MITO PRE and POST exercise CS specific activity was 754±79 and 1036±110 nmol/min/mg MITO protein, respectively; IMF PRE and POST exercise CS specific activity was 558±66 and 710±100 nmol/min/mg MITO protein, respectively. Similarly, MAPR increased in both SS MITO (55%) and IMF MITO (92%) following exercise ($P<0.05$): SS MITO PRE and POST exercise MAPR was 371±54 and 575±46 nmol ATP/min/mg MITO protein, respectively; IMF PRE and POST exercise MAPR was 290±43 and 558±107 nmol ATP/min/mg MITO protein. Notably, the exercise-induced increase in MAPR observed in IMF MITO (i.e., 92%) was significantly higher compared to the increase in MAPR observed in SS MITO (i.e., 55%; $P<0.05$). These results show that SS MITO and IMF MITO respond to a single bout of aerobic exercise by increasing both the specific activity of CS and MAPR. Moreover, the effects of acute exercise on MAPR are more evident in the IMF MITO when compared to SS MITO.

16.2

PHYSICAL ACTIVITY REDUCES THE RISK OF TYPE 2 DIABETES ASSOCIATED WITH M.1382A>C POLYMORPHISM ENCODING 12S RRNA AND MITOCHONDRIA DERIVED MOTS-C

Noriyuki Fuku[1], Hirofumi Zempo[1], Yuichiro Nishida[2], Yasuki Higaki[3], Hisashi Naito[1], Megumi Hara[2], and Keitaro Tanaka[2]
[1]Grad. Sch. of Hlth. and Sports Sci., Juntendo Univ., 1-1 Hirakagakuendai, Inzai City, Chiba, 270-1695, Japan, [2]Fac. of Med., Saga Univ., 5-1-1 Nabeshima, Saga, 849-8501, Japan, [3]Fac. of Sports and Hlth. Sci., Fukuoka Univ., 8-19-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan.

Introduction: Type 2 diabetes mellitus (T2DM) results from the interaction between environmental and genetic factors. The Japanese population is noted to have a higher prevalence of T2DM than its European counterparts with the same body mass index. This may be explained in part by the differing generic backgrounds among ethnicities. Recently, Lee et al. (Cell Metabolism, 2015) reported that the mitochondria-derived peptide MOTS-c (mitochondrial open-reading-frame of the twelve s rRNA–c) enhances insulin action in mice skeletal muscles. MOTS-c is composed of 16 amino acid residues. More recently, we reported an east-Asian specific m.1382 A>C polymorphism that causes amino acid replacement from Lys (K) to Gln (Q) at the 14th amino-acid residue of MOTS-c (Fuku et al., Aging Cell, 2015). Therefore, we hypothesized that the m.1382A>C polymorphism might influence the prevalence of T2DM in the Japanese population through altered insulin action in the skeletal muscle of the east Asian-specific K14Q in MOTS-c. **Purpose**: The aim of the present study was to determine the effect of the m.1382A>C polymorphism and/or MOTS-c K14Q on T2DM in the Japanese population. **Methods**: In total, 12,069 community-dwelling Japanese individuals (5078 men and 6991 women), aged between 40 and 69 years, participated in the present study. The m.1382A>C polymorphism was analyzed by Luminex methods. In addition, participants were measured for physical activity using an accelerometer. **Results**: The prevalence of T2DM in men (11.0%) was found to be higher than that in women (4.6%). An association was observed between the m.1382A>C polymorphism and T2DM prevalence in men, where subjects with the C allele showed higher prevalence of T2DM compared to those with the A allele ($P = 0.20$), even though there was no such association in women. Because moderate to vigorous intensity physical activity (MVPA) is known to influence incidence of T2DM, we analyzed MVPA and the m.1382A>C genotype in combination. In the lowest tertile of MVPA, subjects with the C allele showed significantly higher prevalence of T2DM than in those with the A allele among men (C allele: 18.5%, A allele: 11.2%; $P < 0.01$). **Conclusions**: Higher physical activity reduces the risk of T2DM associated with the m.1382A>C polymorphism encoding 12S rRNA and mitochondria-derived MOTS-c, in men but not in women.

16.3

PGC-1A AND B NOT REQUIRED FOR EXERCISE-INDUCED OXIDATIVE CAPACITY IN ADULT SKELETAL MUSCLE

Yawen Tang[1], Christopher Ballmann[1], Zachary Bush[1], and Glenn C. Rowe[1]
[1]Div. of Cardiovascular Dis., Dept. of Med., Univ. of Alabama at Birmingham, 1918 University Blvd., MCLM 280, Birmingham, AL, 35294.

Exercise has been shown to be the best known intervention in the treatment for many diseases. Many of the benefits of exercise are thought to be mediated by adaptions induced in skeletal muscle. The PGC-1 family of transcriptional coactivators have emerged has being key mediators of the exercise response and are considered to be essential for many of the adaptions seen in skeletal muscle. However, their contribution has not been fully evaluated in adult skeletal muscle. We therefore utilized an inducible muscle-specific deletion of PGC-1α and β (iMyo-PGC-1DKO) to assess the contribution of PGC-1s in the exercise training response. We first determined whether deletion of both PGC-1α and β affected muscle strength in these animals. Using a grip strength assay, we did not observe any differences in muscle strength in the iMyo-PGC-1DKO animals. We next sought to determine the endurance based exercise capacity in these animals. Untrained iMyo-PGC-1DKO animals exhibited a time dependent decrease in exercise performance 8 weeks post deletion similar to what was observed in the previously reported congenital PGC-1 double knockouts (Myo-PGC-1DKO). However, with 4 weeks of voluntary training the iMyo-PGC-1DKOs were able to exhibit an increase in exercise performance and oxidative capacity. This increase was associated with an increase in electron transport complex (ETC) expression and activity in the absence of PGC-1α and β expression. Moreover, we observed a block in exercise induced-mitochondrial biogenesis suggesting a possible role for PGC-1β in the exercise response. Taken together these data suggests that PGC-1α and β expression are not required for training induced exercise performance, highlighting the contribution of PGC-1 independent mechanisms.

16.4

THE ROLE OF IL15/IL15RA SIGNALING IN MUSCLE OXIDATIVE METABOLISM

Emanuele Loro[1], Erin L. Seifert[2], David W. Frederick[3], Manoj K. Mishra[1], Joseph A. Baur[3], and Tejvir S. Khurana[1]
[1]Physiology, Univ. of Pennsylvania, 750 Clinical Res. Bldg. (CRB), 415 Curie Blvd., Philadelphia, PA, 19104, [2]Pathology, Anatomy, and Cell Biology and MitoCare Ctr., Thomas Jefferson Univ., 1020 Locust St., 527A JAH, Philadelphia, PA, 19107, [3]Dept. of Physiology and Inst. for Diabetes, Obesity and Metabolism, Univ. of Pennsylvania, Smilow Ctr. for Translational Res., 3400 Civic Ctr. Blvd., Philadelphia, PA, 19104.

Although interleukin 15 (IL-15) and its receptor α (IL15Ra) are best known as mediators of pro-inflammatory signaling, the association of *IL15Ra* SNPs with muscle response to resistance training and elite endurance athletic performance suggests a novel role for these molecules as determinants of muscle function and energy metabolism. More recently however, we and others have demonstrated that blocking IL15 signaling in mice by knocking-out the *Il15ra* gene increases spontaneous activity, improves fatigue resistance in glycolytic muscles, and protects from diet-induced obesity, at least in part via improved oxidative metabolism. Mechanistically, the lack of IL15Ra enhanced

AMPK phosphorylation after *ex vivo* stimulation, increasing mitochondrial fatty acids uptake for beta oxidation. Intriguingly, these beneficial adaptations occur despite the fact that mice ubiquitously lacking IL15Ra have disrupted circadian rhythms, a known risk factor for metabolic diseases. Here, we use a whole body *Il15ra* knockout mouse model to investigate the consequences of IL15Ra loss on mitochondrial structure and function in muscle. Ultrastructural analysis of mitochondria in EDL crossections indicated that Il15ra$^{-/-}$ fibers had increased mitochondria content and area as well as higher cristae density. The increase in cristae density in Il15ra$^{-/-}$ mitochondria was consistent with higher cardiolipin and OPA1 levels, and suggestive of an adaptative response to increased energy demand. Immunostaining for myosin isoforms on extensor digitorum longus (EDL) sections showed that the changes in mitochondrial content and structure did not result in a fiber-type switch. Functionally, oxygen consumption of isolated muscle mitochondria was similar between genotypes, suggesting that any improvement in respiratory capacity in vivo is likely due to a change in mitochondrial mass and/or substrate delivery. To study the crosstalk between IL15/IL15Ra signaling and mitochondrial oxidative metabolism, we have generated and are characterizing a C_2C_{12} line in which IL15Ra was mutated by CRISPR. Overall, the effects of IL15/IL15Ra signaling blockade on muscle oxidative metabolism suggest that these molecules may be targeted to improve overall metabolism and exercise capacity, with both medical and performance enhancing outcomes. Supported by ITMAT (University of Pennsylvania).

16.5

ABSENCE OF MITOCHONDRIAL PHOSPHATIDYLETHANOLAMINE SYNTHESIS IMPAIRS SKELETAL MUSCLE RESPIRATION AND PROMOTES RAPID DEATH

Timothy Heden[1], Edward Wentzler[1], Tara Narowski[1], Randall Renegar[2], Jeffery Brault[1,3,4], and Katsuhiko Funai[1,4]

[1]Dept. of Kinesiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [2]Dept. of Anatomy and Cell Biology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [3]Dept. of Biochemistry and Molecular Biology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [4]Dept. of Physiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834.

The strongest predictor of all-cause mortality is aerobic capacity, which is largely dependent on skeletal muscle mitochondrial respiration. A plethora of data has described the impact of mitochondrial proteins on skeletal muscle respiration, but less is known of mitochondrial phospholipids. The most abundant phospholipid synthesized within mitochondria is phosphatidylethanolamine (PE), which is synthesized by the enzyme phosphatidylserine decarboxylase (PSD) that resides within the inner mitochondrial membrane. In C57BL6/J mice, 5-wks of treadmill training increased skeletal muscle PSD gene expression and isolated mitochondrial PE, whereas an 8-wk high-fat diet (HFD, 45% fat) did not alter muscle PSD gene expression but decreased mitochondrial PE. These data suggest different alterations in mitochondrial PE may mediate differences in the metabolic phenotype of skeletal muscle from exercise trained and HFD fed mice. To better understand how muscle mitochondrial PE synthesis impacts respiration and metabolism, PSD expression was decreased in skeletal muscle *in vitro* and *in vivo*. In C2C12 myotubes, a lentivirus-mediated knockdown of PSD decreased mitochondrial PE, complex II mediated respiration, fatty acid oxidation, and succinate-induced H_2O_2 emission. Mitochondrial biogenesis, fusion, or insulin signaling were not affected with PSD knockdown, but light chain 3B II protein abundance increased, suggesting increased autophagosome content. Mice with tamoxifen-inducible skeletal muscle specific knockout of PSD (PSD-MKO) have decreased whole-body oxygen consumption and muscle mitochondrial respiration in permeabilized fibers. Muscle mitochondrial content or resting ATP/ADP levels are not altered, but these mice have abnormally enlarged mitochondria with disorganized cristae formation. Unexpectedly, PSD-MKO mice lose nearly a quarter of their lean mass and die within 6 weeks of PSD knockout. In contrast, mice with heterozygous deletion of muscle PSD (PSD-MHet) and fed a standard chow diet are apparently healthy and compared to control mice have similar exercise endurance, whole body oxygen consumption, glucose tolerance, and insulin sensitivity. After an 8-wk HFD, PSD-MHet mice have decreased insulin sensitivity compared to control littermates. These findings highlight a novel role for mitochondrial PE synthesis in regulating skeletal muscle oxidative capacity, insulin sensitivity, and mortality. Funding Sources: NIH DK095774, DK109888, and AHA 16POST30980047.

16.6

OVEREXPRESSION OF SKELETAL MUSCLE PHOSPHATIDYLSERINE DECARBOXYLASE INCREASES RESPIRATORY CAPACITY AND ATTENUATES H_2O_2 PRODUCTION IN TAFAZZIN DEFICIENCY

Jordan Johnson[1], Timothy Heden[1], Armondo Balotti[1], Edward Wentzler[1], Tara Narowski[1], and Katsuhiko Funai[1,2]

[1]Dept. of Kinesiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [2]Dept. of Physiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834.

Barth Syndrome is an X-linked recessive disorder characterized by mutations in the tafazzin (TAZ) gene, a key enzyme in the biosynthesis of the mitochondrial phospholipid cardiolipin (CL). The loss of TAZ function causes aberrant CL synthesis, resulting in increased H_2O_2 production, reduced mitochondrial respiratory function, and cardiac and skeletal muscle myopathy. Recent work in lower organisms has demonstrated that mitochondrial phosphatidylethanolamine (PE) has overlapping functions with CL. Mitochondria with elevated PE content exhibit increased respiratory capacity and ATP production in mouse liver. The purpose of this study was to determine if elevated mitochondrial PE can mitigate the deleterious effects of TAZ deficiency. Here we show that overexpressing phosphatidylserine decarboxylase (PSD), the PE-synthetic enzyme resident in the inner mitochondrial membrane, enhances respiratory capacity in C2C12 myotubes, concomitant with the upregulation of genes

involved in mitochondrial biogenesis. Mice with a tamoxifen-inducible skeletal muscle-specific knock-in of PSD (PSD-MKI) were generated to study the effects of PSD overexpression *in vivo*. High-resolution respirometry experiments revealed trends for increased complex dependent respiration and ATP production, independent of changes in electron transport system complex protein abundance in PSD-MKI mice. To study the effects of PSD overexpression in the context of TAZ deficiency, PSD was overexpressed in C2C12 myotubes following a lentivirus mediated knockdown of TAZ. PSD overexpression in TAZ deficient myotubes decreased succinate stimulated H_2O_2 emission and production by 36% and 45% respectively. These results demonstrate that elevated PSD levels may prevent mitochondrial abnormalities associated with Barth Syndrome. Future studies include assessment of protective effect of PSD overexpression in TAZ knockdown mice, a murine model of Barth Syndrome. This study was supported by NIH grants DK095774 and DK109888.

16.7
SKELETAL MUSCLE-SPECIFIC DELETION OF P53 DOES NOT IMPAIR MITOCHONDRIAL CONTENT OR ENZYME ACTIVITY

Ben Stocks[1], Steven Bullard[2], Christopher Adams[2], and Andrew Philp[1]
[1]Sch. of Sport, Exercise and Rehabilitation Sci., Univ. of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, [2]Int. Med., Univ. of Iowa, Carver Coll. of Med., Iowa City, IA, 52242.

Tumour suppressor protein 53 (p53) has been implicated in the regulation of mitochondrial biogenesis in skeletal muscle, with whole-body knockout mice displaying impairments in basal mitochondrial content, respiratory capacity and enzyme activity (2, 3). To determine the muscle fibre-specific role of p53, we examined mitochondrial protein content and enzyme activity in twelve-week-old male muscle fibre-specific p53 knockout mice (p53 mKO) and floxed littermate controls (WT) (1). All animal procedures were approved by the Institutional Animal Care and Use Committee of the University of Iowa in accordance with American Physiological Society guidelines. Protein content was determined in gastrocnemius, quadriceps and triceps muscle samples via immunoblotting, whilst an enzyme activity assay was performed for citrate synthase (CS). p53 mKO and WT mice displayed similar protein content of mitochondrial proteins (CS, COX I, COX II, COX IV, COX V and mitofillin) in all muscles examined. In addition, the protein content of enzymes regulating fatty acid metabolism (b-HAD, MCAD, LCAD, VLCAD), carbohydrate metabolism (HK2, PDH, GLUT4), energy sensing (AMPKa2), transcription (NRF1, PGC-1a and TFAM) and mitochondrial fusion (MFN2) were comparable in p53 mKO and WT mice ($p > 0.05$). The activity of CS was also similar in the triceps of p53 mKO and WT mice ($p > 0.05$). Together, these data suggest that muscle-specific deletion of p53 does not reduce the protein content of mitochondrial enzymes involved in oxidative phosphorylation, fatty acid and carbohydrate metabolism or regulators of mitochondrial biogenesis. This abstract was supported in part through a BBSRC Midlands Integrative Biosciences Training Programme studentship to BS and a BBSRC New Investigator Award to AP. References: 1. Fox DK, Ebert SM, Bongers KS, Dyle MC, Bullard SA, Dierdorff JM, Kunkel SD, and Adams CM. P53 and ATF4 mediate distinct and additive pathways to skeletal muscle atrophy during limb immobilization. *Am J Physiol - Endocrinol Metab* 307: E245-E261, 2014. 2. Park J-Y, Wang P-y, Matsumoto T, Sung HJ, Ma W, Choi JW, Anderson SA, Leary SC, Balaban RS, Kang J-G, and Hwang PM. P53 improves aerobic exercise capacity and augments skeletal muscle mitochondrial DNA content. *Circ Res* 105: 705-712, 2009. 3. Saleem A, Adhihetty PJ, and Hood DA. Role of p53 in mitochondrial biogenesis and apoptosis in skeletal muscle. *Physiol Genomics* 37: 58-66, 2009.

16.8
MECHANISTIC FLEXIBILITY OF MITOCHONDRIAL COMPLEX I AND ITS ASSOCIATED H_2O_2 EMITTING POTENTIAL

Maria J. Torres[1,2], P. Darrell Neufer[1,2,3], and Tonya N. Zeczycki[2,4]
[1]Kinesiology, East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834, [2]East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [3]Physiology, East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834, [4]Biochemistry and Molecular Biology, East Carolina Univ., 600 Moye Blvd., Greenville, NC, 27834.

Mutations in mitochondrial complex I (CI) give rise to ~50% of mitochondrial disorders affecting energy metabolism, and often result in exercise intolerance. In addition, CI comprises a major site of reactive oxygen species (i.e. H_2O_2), and dysregulated production of H_2O_2 has been linked to numerous pathological conditions including insulin resistance. CI catalyzes the oxidation of NADH coupled with the reduction of coenzyme Q (CoQ) in two seemingly independent steps, with the active sites located 90 Å apart and linked by a series of 8 redox FeS-clusters, but the mechanism governing the coordination of these two reactions remains controversial. Previous enzymological studies have fallen short in addressing the regulation of H_2O_2 production within the context of physiology, and broader physiological studies of CI activity often lack the mechanistic rationale imperative to effective therapeutic design. Therefore, the aim of the present study is to determine the kinetic mechanism of CI activity and regulation of H_2O_2 emitting potential in isolated mitochondria under physiological conditions associated with over nutrition and low metabolic demand (i.e. sedentarism). Using stopped-flow techniques, we determined the pre-steady and steady-state kinetics of NADH oxidation and the reduction of the CoQ analog, decyl-ubiquinone (DCU). Initial rate dependence on [NADH] and [DCU] exhibited Michaelis-Menten type kinetics. Secondary plots revealed that NADH oxidation can occur prior to DCU reduction at low [NADH] (<25μM), but both half-redox reactions occur simultaneously at high [NADH] (≥25μM). In parallel, the measurement of H_2O_2 emitting potential revealed a sigmoidal dependence of JH_2O_2 with [NADH] ($r^2 = 0.975$). In order to simulate conditions of high reducing pressure on the Q-pool *in vitro* (which increase mitochondrial ROS production), [DCU] was progressively reduced (25 - 0.25μM). This led to an up-ward shift of the sigmoidal curve at sub-saturating [DCU] (≤1μM), with unchanged JH_2O_2 at [NADH] < 1μM, but a markedly higher maximal JH_2O_2 emitting capacity

(+33%, $p<0.001$) at [NADH] >10μM; suggesting that the ability of CI to cope with increases in NADH supply is compromised by the reduced availability of oxidized quinone. Our working model of CI activity is that the series of 8 redox sensitive FeS-clusters comprise an "electron capacitor", capable of sensing NADH levels and thus modulating the enzyme's mechanism *via* the degree of coupling of the two half-redox reactions, and its associated ΔH_2O_2. We propose CI as a potential major sensor of metabolic reducing pressure in the electron transport system that responds via H_2O_2 emission, potentially to help maintain cellular redox homeostasis. Deciphering the kinetic signature of electron transfer by CI will provide novel insights into CI role as a source of H_2O_2 in physiological/pathological conditions. Funding: NIH DK096907, and ECU Office of Research and Grad. Studies.

16.9

EFFECTS OF ACUTE AEROBIC EXERCISE ON MITOCHONDRIAL MORPHOLOGY IN ENDURANCE-TRAINED RATS

Daiki Nakano[1], Kana Takagi[1], and Shuichi Machida[1]
[1]Grad. Sch. of Hlth. and Sports Sci., Juntendo Univ., Hiragagakuendai 1-1, Inzai, 285-0928, Japan.

Mitochondria in mammalian cells remodel their structural shapes via dynamic events of fusion (maintaining functional mitochondria) and fission (removing dysfunctional mitochondria) to adapt to external exercise-associated stimuli and functional needs. Hence, we postulated that the dynamic events occurring in the mitochondria in response to acute exercise differ for trained and sedentary muscle cells (i.e., those with or without prior mitochondrial adaptations, respectively). Twelve female Sprague–Dawley rats (4 weeks old) were assigned to either endurance training (80% $VO_{2\,max}$, 120 min•day^{-1}, and 5 days/week^{-1}) or sedentary control environment for 8 weeks. After 8 weeks, the two groups were further divided as follows: (1) endurance training only (T), (2) endurance training followed by acute treadmill exercise (T + Ex), (3) sedentary only (S), and (4) sedentary followed by acute treadmill exercise (S + Ex). The acute treadmill exercise (S + Ex and T + Ex) involved a treadmill run at 60% $VO_{2\,max}$ for 120 min. Upon completion of each intervention, the soleus muscle was dissected. Approximately 1,600 intermyofibrillar (IMF) mitochondria were analyzed by transmission electron microscopy. We estimated the shapes and sizes of sampled mitochondria using ImageJ software based on measurements of surface area, perimeter, aspect ratio (AR), form factor (FF), circularity, and roundness. After 8 weeks of intervention, $VO_{2\,max}$ was greater for the trained rats (T and T + Ex) by 20% than for the sedentary rats (S and S + Ex). For the trained rats, mitochondrial fragmentation (an indication of fission) was absent, whereas indications of fusion were present after performing acute exercise (T vs. T + Ex), i.e., increased AR (+9%) and decreased roundness (−8%). In contrast, mitochondrial fragmentation became apparent as a result of the acute exercise by the sedentary rats (S vs. S + Ex comparison), with decreased surface area (−36%), perimeter (−39%), AR (−31%), and FF (−41%), as well as increased circularity (+47%) and roundness (+38%). In conclusion, mitochondrial adaptations of trained muscle cells in response to exercise stimuli may be more related to fusion, whereas sedentary muscle cells may accelerate fission for the adaptations.

16.10

PALMITOYL-COA INDUCES MITOCHONDRIAL UNCOUPLING IN RAT MYOFIBRES EXPOSED TO HEAT STRESS

Alexandra Malgoyre[1], Pierre Emmanuel Tardo Dino[1,2], Julianne Touron[1,3], Nathalie Koulmann[1,4]
[1]Environnements Operationnels, Inst. de Res. Biomedicale des Armees, BP73, Bretigny sur Orge, 91223, France, [2]EDISS 205, Univ. Claude Bernard Lyon 1, Campus de la Doua, Villeurbanne, France, [3]UFR STAPS, Univ. d'Evry, D93A, EVRY, France, [4]Chaire de Res., Ecole du Val de Grâce, Rue Saint Jacques, Paris, France.

Introduction: Heat is a crucial factor to take into account for athletes involved in competitions in hot countries. Besides hydration, substrates utilization also contributes to exercise performance in heat. While glucose dependence has already been described, probably depending on both alteration in systemic hormones and local heat effect on skeletal muscle, the effect of heat on fatty acid oxidation remains largely unknown. **Purpose**: We wanted to study the effect of heat on carbohydrates and fatty acids oxidation by skeletal muscles. **Methods:** Oxygen consumption was monitored in duplicate using progressive increase of concentrations of physiological substrates, pyruvate (carbohydrate) or palmitoyl-CoA (a long chain fatty acid, LCFA), by *in situ* mitochondria respiration of permeabilized fibres from rat soleus muscle (n=8) exposed either to 35°C or to 40°C. Maximal oxygen consumption was measured with glutamate and succinate (Vmax), Pyr (Pyr-Vmax) and PCoA (PCoA-Vmax) for each rat. Km for substrate was calculated with a Michaelis-Menten's model. Results were normalized by the weight of dry fibres, and specific substrate values were also expressed in percent of Vmax. Means were compared by paired T-test. **Results:** Basal O2 consumption (V0) measured in non-phosphorylated conditions did not differ between the two temperatures whatever the substrate. Vmax was not altered at 40°C (9.97± 0.16 μmol^{-1}.min^{-1}.g^{-1}) vs 35°C (8.72 ± 0.29 μmol^{-1}.min^{-1}.g^{-1}). Pyr-Vmax was similar at 35°C and 40°C and represented 88 ± 3 % and 86 ± 2 % of Vmax, respectively. PCoA-Vmax did not differ at 35°C and 40°C although relative values appeared lower at 40°C (42 ± 1 %) than at 35°C (52 ± 2 %). Pyr acceptor control ratio (ACR) corresponding to the V0-Vmax ratio, was similar at 35°C and 40°C, whereas PCoA-ACR significantly decreased from 2.92 ± 0.09 at 35°C to 2.15 ± 0.05 at 40°C ($p<0.05$), becoming different from Pyr-ACR at 40°C only ($p<0.005$). Km for these two substrates was not modified by heat exposure. **Conclusion:** Maximal oxidative capacities of mitochondria are maintained despite of temperature elevation. The decrease of ACR observed at 40°C for PCoA only, suggests a heat-induced mitochondrial uncoupling occurring with LCFA oxidation. Mechanisms underlying this uncoupling effect of LCFA remain to be found. One consequence could be a higher heat production during muscle contraction and addresses the issue of safety of lipid ingestion before exercise in the heat.

16.11

ADENINE NUCLEOTIDE TRANSLOCASE (ANT) CONTROL OF OXIDATIVE FLUX IN HUMAN SKELETAL MUSCLE MITOCHONDRIA: INFLUENCE OF LYSINE ACETYLATION

Wayne Willis[1], Elizabeth Willis[2], Jamie Hudgens[3], Jean Finlayson[4], Paul Langlais[5], and Larry Mandarino[4]

[1]Ctr. for Metabolic Biology, Arizona State Univ., Shea Blvd. and 134th St., Scottsdale, AZ, 85259, [2]Physiology, Univ. of Arizona, 1501 N. Campbell Ave., Tucson, AZ, 85724, [3]Sch. of Life Sci., Arizona State Univ., 427 E. Tyler Mall, Tempe, AZ, 85281, [4]Med., Univ. of Arizona, 1501 N. Campbell Ave., Tucson, AZ, 85724, [5]Ctr. for Metabolic Biology, Mayo Clinic Arizona, Shea Blvd. and 134th St., Scottsdale, AZ, 85259.

Cytosolic [ADP] activates mitochondria (MITO) to synthesize ATP, but may concomitantly inhibit ATP-utilizing processes. Thus, MITO sensitivity to ADP stimulation may critically affect myocyte ATP turnover and functional performance. We have recently shown that all-atom molecular dynamic modeling of ANT function predicts a 20-fold decrease in ADP^{3-} binding affinity when ANT lysine23 is acetylated (K23Ac), and also that acute exercise deacetylates human skeletal muscle ANT K23Ac. The purposes of this study were to determine ANT abundance and flux control strength in isolated human skeletal muscle MITO, and then to assess apparent ADP affinity (as K_MADP for respiration) and its relationship to K23Ac. Overnight fasted, healthy lean participants (n=9) had vastus lateralis biopsies to isolate MITO, which were assessed using respirometry with 10 mM succinate plus 10 mM glutamate as fuels. Maximal (state 3) O_2 consumption ($nmolO_2$ min^{-1} $mgprotein^{-1}$, Jo), resting (state 4) Jo, respiratory control ratio (state 3/state 4), and phosphorylation ratio (ADP/O) were 353±48, 40.8±4.5, 10.7±0.7 and 2.42±0.05, respectively. Titrating out Jo with stepwise additions of carboxyatractyloside (CAT), a specific inhibitor of ANT, indicated a MITO ANT abundance of 0.97±0.14 nmol/mg. CAT titrations when [ADP] was clamped at 21 μM showed that ANT accounted for 82±6% of oxidative flux control. In contrast, no flux control resided at ANT (1±1%) when the same titration was carried out at saturating (2 mM) [ADP]. The ANT turnover rates were 11.9±0.5 s^{-1} and 27.5±1.7 s^{-1} at the lower and higher [ADP], respectively. The apparent K_MADP for respiration was 32.4±1.8 μM (range 21.8-39.0 μM) and correlated (R^2=0.554, P=0.022) with K23Ac abundance, which was quantified using targeted proteomic analysis. We conclude that 1) ANT is the primary locus of control of the oxidative flux of human skeletal muscle MITO exposed to ADP levels characteristic of resting-to-mildly-working muscle and 2) lysine acetylation of ANT influences MITO sensitivity to the ADP respiratory signal. Supported by: R01 DK47936 NIDDK.

16.12

A SINGLE BOUT OF HEAT STRESS TREATMENT INCREASES MITOCHONDRIAL-ASSOCIATED GENE EXPRESSION IN MOUSE SKELETAL MUSCLE

Yuki Tamura[1], Yu Kitaoka[2], Arata Tsutaki[1], Koichi Nakazato[1], and Hideo Hatta[2]

[1]Dept. of Exercise Physiology, Nippon Sport Sci. Univ., 7-1-1, Fukasawa, Setagaya, Tokyo, 158-8508, Japan, [2]Dept. of Sports Sci., Univ. of Tokyo, 3-8-1, Komaba, Meguro, Tokyo, 153-8902, Japan.

Recent our studies have shown that daily heat stress treatment increases mitochondrial content in mouse skeletal muscle. However, its underlying mechanisms remain unclear. To extend our basic knowledge, we therefore examined whether acute heat stress drives mitochondrial gene transcription in mouse gastrocnemius muscle. A single bout of heat stress treatment (mice placed in a chamber with hot environment; 40°C, 30 min) upregulated mRNA expression of mitochondrial-associated genes encoded by both nDNA (CS: +21.7%, ALAS: +24.8%, Tfam: +21.7% and Cyt c: +22.5%) and mtDNA (COX II: +38.5%, ND1: +29.1% and ND4: +40.4%) at 3-hr after the treatment. We also found that three hours after heat stress, protein abundance of PGC-1α was increased both in nuclear (+46.4%) and mitochondria (+34.9%) fraction without any changes in whole-cell lysate. Taken together, heat stress treatment promotes transcription of mitochondrial-associated genes, which would be induced by concomitant translocation of PGC-1α to nuclear and mitochondria.

16.13

INTERLEUKIN-15 IMPROVES SKELETAL MUSCLES GLUCOSE UPTAKE AND MITOCHONDRIAL FUNCTION IN ASSOCIATION WITH AMPK ACTIVATION

Lucien Nadeau[1,2], Marc Foretz[3,4], Pascal Haddad[1,5], Barbara G. Anderson[6,7], LeBris Quinn[6,7], and Céline Aguer[1,2]

[1]Inst. de Res. de l'Hôpital Montfort, 713 Montreal Rd., Ottawa, ON, K1K 0T2, Canada, [2]Biochemistry, Microbiology and Immunology, Fac. of Med., Univ. of Ottawa, 451 Smyth Rd., Ottawa, ON, K1H 8M5, Canada, [3]INSERM U1016, Inst. Cochin, 24 rue du Faubourg Saint Jacques, Paris, 75014, France, [4]CNRS UMR8104, Univ. Paris Descartes, 24 rue du Faubourg Saint-Jacques, Paris, 75014, France, [5]Fac. of Sci., Univ. of Ottawa, 75 Laurier Ave., E., Ottawa, ON, K1N 6N5, Canada, [6]Div. of Gerontology and Geriatric Med., Dept. of Med., Univ. of Washington, 1959 NE Pacific St., Seattle, WA, 98195, [7]Geriatric Res., Education, and Clinical Ctr., 1660 S. Columbian Way, Seattle, WA, 98108.

During contraction, skeletal muscle secretes myokines that act on distant tissues to mediate the beneficial effect of exercise on general health. Some myokines also act locally in skeletal muscle in an autocrine/paracrine fashion to facilitate adaptations to physical exercise. One of these myokines, interleukin-15 (IL-15), is known to reduce adiposity, to enhance whole-body insulin sensitivity, and to upregulate fatty acid oxidation and pro-oxidative transcription factors in skeletal muscle. The aim of our study was to determine by which mechanism IL-15 increases energy metabolism in skeletal muscle. Acute IL-15 exposure (3h) in L6 myotubes increased resting oxygen consumption rate and basal glucose uptake by 20-30%. Chronic IL-15 exposure (48h) increased resting and maximal oxygen consumption rates by 40%. Preliminary results show a trend for an increase in the expression of mitochondrial respiratory chain complexes suggesting that chronic IL-15 treatment increases mitochondrial

biogenesis. The effect of IL-15 on skeletal muscle energy metabolism seems to involve the AMPK pathway since IL-15 increased the phosphorylation of AMPK and its downstream target acetyl-CoA carboxylase (ACC) in a time and dose-dependent manner. This effect was not related to any alteration in ADP or ATP levels. Current experiments are designed (1) to determine whether mice overexpressing IL-15 in skeletal muscle show increased AMPK pathway activation, and (2) to confirm the role of the AMPK pathway in IL-15 mechanism of action by using primary myotubes derived from AMPKα1/2 knockout mice. By increasing skeletal muscle mitochondrial function and glucose utilization, IL-15 may prove to be an interesting target to treat metabolic diseases such as obesity and type 2 diabetes.

16.14

THE MITOCHONDRIAL RETICULUM OF THE HEART

Brian Glancy[1], Lisa M. Hartnell[2], Christian A. Combs[3], Armel Fenmou[4], Junhui Sun[5], Elizabeth Murphy[5], Sriram Subramaniam[2], and Robert S. Balaban[4]

[1]NHLBI, NIAMS, NIH, 10 Center Dr., Rm. B1D416, Bethesda, MD, 20892, [2]NCI, NIH, 9000 Rockville Pike, Bethesda, MD, 20892, [3]NHLBI, NIH, 10 Center Dr., Rm. 6N309, Bethesda, MD, 20892, [4]NHLBI, NIH, 10 Center Dr., Rm. B1D416, Bethesda, MD, 20892, [5]NHLBI, NIH, 10 Center Dr., Rm. 8N206, Bethesda, MD, 20892.

The heart has one of the highest and most consistent energy demands in the body. Cellular energy distribution within the constantly working heart has long been considered to occur through the creatine kinase and myoglobin facilitated diffusion pathways. However, we recently reported structural and function evidence suggesting that energy may be rapidly distributed primarily by electrical conduction through a large, grid-like network in skeletal muscle cells. We undertook this study to determine whether a similarly conductive mitochondrial energy distribution network is present in cardiac cells. Large field of view (~45 x 20 x 12 μm), high resolution (15 nm), 3D structures of the heart were acquired by focused ion beam scanning electron microscopy (FIB-SEM) of perfusion fixed murine left ventricles. 3D electron tomography was used to evaluate smaller regions (~2 x 2 x 0.25 μm) with increased resolution (~2 nm). Individual mitochondrial morphologies and physical mitochondrial network connectivity were assessed by manual tracing of mitochondrial structures in 3D. Functional, electrical mitochondrial network connectivity was determined in live, isolated cardiomyocytes by using a photoactivated mitochondrial uncoupler to depolarize mitochondria in the center of the cell while observing the mitochondrial membrane potential (TMRM) response in the rest of the cell. The heart mitochondrial reticulum is comprised of several subnetworks of tens to hundreds of adjacent mitochondria primarily arranged in rows down the long axis of the cell. These subnetworks provide the links between the paravascular, paranuclear, and intrafibrillar mitochondrial pools within the cell. Inner and outer membranes of adjacent mitochondria form specialized intermitochondrial junctions characterized by abundant mitochondria-to-mitochondria contact sites. Consistent with this network structure, uncoupling of mitochondria in the center of the cell results in a rapid, coordinated depolarization of the mitochondrial membrane potential preferentially down the long axis of the cell. These results demonstrate a heart mitochondrial reticulum capable of rapid energy distribution throughout the cell and suggest that the primary mechanism is electrical conduction of the mitochondrial membrane potential across intermitochondrial junctions.

16.15

EVIDENCE OF MEMBRANE POTENTIAL-DEPENDENT AND INDEPENDENT REDOX CIRCUITS LINKING FATTY-ACID OXIDATION ENZYMES AND THE ANTIOXIDANT PROTEIN NETWORK IN SKELETAL MUSCLE MITOCHONDRIA

Cody Smith[1], Chien-Te Lin[2], Kelsey H. Fisher-Wellman[3], Deborah M. Muoio[3], and P. Darrell Neufer[1,2]

[1]Physiology, East Carolina Univ., 4th Fl., 115 Heart Dr., Greenville, NC, 27834, [2]Diabetes and Obesity Inst., East Carolina Univ., 4th Fl., 115 Heart Dr., Greenville, NC, 27834, [3]Duke Molecular Physiology Inst., Duke Univ., 300 N. Duke St., Durham, NC, 27701.

Mitochondrial H_2O_2 emission rate (JH_2O_2) is a function of the rate of H_2O_2 production balanced by the reducing efficiency of the matrix-contained antioxidant protein network. NADPH is the source of electrons for the system and is maintained at a high concentration by activity of the membrane potential ($\Delta\Psi_m$)-dependent nicotinamide nucleotide transhydrogenase (NNT) protein. Therefore, when JH_2O_2 production is high, flux through the antioxidant system may represent a significant source of energetic demand within the mitochondria. The present study investigated this relationship in skeletal muscle mitochondria by testing whether increased flux through fatty-acid oxidation (FAO) is associated with an increased oxidant burden and thus, an increased energetic demand by the NNT-linked antioxidant protein network. Flux through FAO was controlled by additions of carnitine, which facilitates fatty acid transport into the mitochondria and minimizes product inhibition (acetyl-CoA) via CrAT activity. Increased flux through FAO (314±20 vs 41±4.5 pmol O_2/sec/mg) increased JH_2O_2 emission (152%) and production (264%) compared to low FAO-flux ($p<0.05$), yet the % H_2O_2 buffered by the antioxidant system was the same for both FAO-fluxes (~70-80%). The % H_2O_2 buffered was also unaffected when the JH_2O_2 production was isolated to specific sites within the mitochondria, so long as the JH_2O_2 production did not exceed the availability of NADPH required by the antioxidant system. Evidence of potentially redundant, $\Delta\Psi_m$-independent mechanisms of NADPH production were also observed. Consistent with the original hypothesis, elevated FAO-flux increased energetic demand (measured by H^+ conductance, 25%) by the antioxidant protein network, whereas the presence of catalase limited net H_2O_2 production and decreased (15%) the net energy demand of the NADPH antioxidant system. In mice lacking NNT (C57Bl/6J), the rate of FAO-induced H_2O_2 emission was elevated (104%) while the energetic demand was decreased (22%), as expected due to lack of the $\Delta\Psi_m$-dependent NNT protein. Taken together, these data suggest that the antioxidant protein network includes both $\Delta\Psi_m$-dependent and independent mechanisms of NADPH production that enables high efficiency

in reducing FAO-induced H_2O_2 production. The redox circuit(s) linking FAO-derived H_2O_2 production with the $\Delta\Psi_m$-dependent NNT arm of the antioxidant system represents a significant energetic demand in muscle mitochondria. In the context of exercise and dietary challenges, these redox circuits function to preserve both mitochondrial energetic state and intracellular redox homeostasis. NIH DK096907.

16.16

CARDIAC ISCHEMIA RESULTS IN DECREASED INTERMEDIATE MITOCHONDRIAL RESPIRATION RATES AND IMPAIRS EVERY STEP OF THE OXIDATION PHOSPHORYLATION PATHWAY

Sarah Kuzmiak-Glancy[1], Brian Glancy[2], and Matthew Kay[1]
[1]Biomedical Eng., George Washington Univ., 800 22nd St. NW, Washington, DC, 20052, [2]Natl. Heart, Lung, and Blood Inst., Natl. Inst. of Hlth., Bldg. 10 Rm. B1D416, Bethesda, MD, 20814.

Introduction: Despite numerous investigations examining the effects of ischemia on the ability of cardiac mitochondria to produce ATP, it is still unclear how mitochondrial respiration is impacted across a range of oxygen consumption rates, nor is it known how ischemia affects each component of mitochondrial energy transduction pathway. The present study examined mitochondrial function at respiration rates between resting and maximal as well as utilized force-flow analysis to determine the effect of ischemia on each step of the oxidative phosphorylation pathway. Methods: Mitochondria were isolated from rat hearts subjected to either 60 minutes of control coronary flow or 60 minutes of no flow ischemia. Mitochondrial driving forces (extramitochondrial phosphorylation potential, mitochondrial membrane potential, and NADH redox status) and flux (oxygen consumption and reactive oxygen species (ROS) production rates) were determined. Force-flow analysis was used to determine the interaction between energetic driving forces and flux to calculate the effective activity of each step within the oxidative phosphorylation pathway. Results: Ischemia reduced mitochondrial oxygen consumption rates at high phosphorylation potentials (300 ± 27 vs 161 ± 13 nmol O2/nmol cytochrome a/min) but had much less of an effect at low phosphorylation potentials (76 ± 10 vs 55 ± 5 nmol O2/nmol cytochrome a/min), however ischemia diminished mitochondrial membrane potential (~11 mV) across all phosphorylation potentials. Force-flow analysis revealed ischemia resulted in a more severe decrease in the conductance of the electron transport chain (ETC) (2.6 fold) than the decrease in the conductance of the combined activity of ATP synthase and the adenine nucleotide translocase (2 fold). It was also determined that ROS production was higher at lower respiration rates and was linearly related to driving force down the ETC (from redox potential to mitochondrial membrane potential) in both control and ischemic mitochondria, however ROS production rates were 2.3-fold higher in ischemic mitochondria. Conclusions: The decreases mitochondrial ATP production capabilities caused by ischemia are distributed throughout the oxidative phosphorylation energy production pathway and high mitochondrial respiration rates are the most severely inhibited. Neither reductions in ETC or ATP synthase activity alone are responsible for ischemia-induced impairments, and to improve respiration at higher workloads, the function of the entire pathway must be improved.

16.17

EFFECTS OF FASTING AND WHEEL RUNNING ON *IN VIVO* HEPATIC AUTOPHAGY THROUGH THE USE OF THE AUTOPHAGY INHIBITOR LEUPEPTIN

Colin McCoin[1,2], E. Matthew Morris[1,2], Julie Allen[1,2], and John Thyfault[1,2]
[1]Molecular and Integrative Physiology, Kansas Univ. Med. Ctr., 3901 Rainbow Blvd., Mail Stop 3043, Kansas City, KS, 66160, [2]Res. Service, Kansas City VA Med. Ctr., 4801 Linwood Blvd., Kansas City, MO, 64128.

Cellular autophagy is a tightly regulated process that controls the degradation and recycling of organelles and cellular material. Mitochondrial autophagy, or mitophagy, is the process specifically involving the regulation of mitochondrial salvaging. In general, autophagy is activated by fasting and exercise and impaired by obesity. We tested the effects of 4 days of voluntary wheel running (VWR) or overnight fasting compared to the sedentary/fed condition in C57BL/6J mice treated with leupeptin or saline to determine hepatic autophagy flux between these conditions. Leupeptin is a cysteine, serine and threonine protease inhibitor that prevents lysosomal degradation and results in an accumulation of a lipidated form of the protein microtubule-associated protein 1A/B light-chain 3 (LC3-II). LC3-II is a critical autophagic protein required for autophagosome formation and induction of autophagy that can be used as a surrogate marker of autophagic flux based on the degree of accumulation. Mice were injected with leupeptin at both 16 hours and 4 hours prior to sacrifice to ensure adequate levels of inhibition. Our results suggest that overnight fasting in mice (~16 hours) resulted in approximately 2-fold greater LC3-II levels than both VWR and sedentary control mice, which had comparable accumulation. These results suggest that fasting more robustly increases hepatic autophagy than short term VWR. Future studies aim to examine the effects and mechanisms of fasting and higher intensity exercise to induce alterations in hepatic autophagy flux with an ultimate goal of assessing mitophagy via utilization of mitochondrial proteins under these conditions.

16.18

DIFFERENTIAL ENRICHMENT OF SUBSARCOLEMMAL MITOCHONDRIA WITH INDIVIDUAL PROTEINS BETWEEN LEAN AND OBESE, INSULIN-RESISTANT SUBJECTS

Christos Katsanos[1], Katon Kras[2], Paul Langlais[3], Wayne Willis[2], Lawrence Mandarino[2], Eleanna De Filippis[4], and Lori Roust[4]
[1]Ctr. for Metabolic and Vascular Biology, Arizona State Univ./Mayo Clinic in Arizona, Mayo Clinic Collaborative Res. Bldg., Rm. 2-223, 13208 E. Shea Blvd., Scottsdale, AZ, 85259, [2]Ctr. for Metabolic and Vascular Biology, Arizona State Univ./Mayo Clinic in Arizona, Mayo Clinic Collaborative Res. Bldg., 13208 E. Shea Blvd., Scottsdale, AZ, 85259, [3]Dept. of Biochemistry, Mayo Clinic in Arizona, Mayo Clinic Collaborative Res. Bldg., 13208 E. Shea Blvd., Scottsdale, AZ, 85259,

[4]Dept. of Endocrinology, Mayo Clinic in Arizona, Mayo Clinic Collaborative Res. Bldg., 13208 E. Shea Blvd., Scottsdale, AZ, 85259.

Mitochondria located beneath the sarcolemma are more responsive to metabolic changes and appear to be affected particularly by the metabolic environment associated with obesity. We investigated whether enrichment of these mitochondria with individual proteins differs between lean and obese, insulin-resistant subjects. Sub-sarcolemmal mitochondria were isolated using standard differential centrifugation techniques, from sedentary lean (n=6) and obese (n=6) subjects (age: 41±9 vs 34±9 years, mean±SE, $P > 0.05$; BMI: 22±2 vs 36±3 kg/m^2, $P < 0.05$; insulin resistance Matsuda index: 11±1 vs 3±1, $P < 0.05$). Label-free quantitative proteomics was performed on proteins in the isolated mitochondrial suspension. Spectra corresponding to the relative abundance of proteins in the mitochondrial suspension were processed using Progenesis QI software. Of the 469 mitochondrial proteins identified, the following represented lower percent relative to the average mitochondrial protein spectra in obese vs lean ($P < 0.05$): BDH (regulates ketolysis; 4.9±1.0 vs 9.3±0.5 %), RT36 (enhances mitochondrial protein synthesis; 22.1±1.7 vs 31.0±1.7 %), ODO2 (catalyzes conversion of 2-oxoglutarate to succinyl-CoA; 151.8±2.4 vs 189.1±10.0 %) and HINT2 (enhances mitochondrial lipid metabolism and lessens hyperacetylation of mitochondrial proteins; 7.6±0.9 vs 10.7±0.9 %). The following represented higher percent relative to the average mitochondrial protein spectra in obese vs lean ($P < 0.05$): KCRS (enhances energy transfer from ATP to creatine; 1038.0±63.7 vs 846.5±44.9 %) and MAOM (catalyzes the metabolism of malate to pyruvate; 4.5±0.8 vs 2.2±0.1 %). These findings describe distinct differences in individual proteins regulating sub-sarcolemmal energy metabolism in obesity, associated possibly with differential capacity for both lipid/energy metabolism and mitochondrial protein synthesis in skeletal muscle.

17.0 REDOX BIOLOGY

17.1
NRF2 DEFICIENCY AGGRAVATES DENERVATION-INDUCED OXIDATIVE STRESS BUT NOT ATROPHY IN SKELETAL MUSCLE

Yu Kitaoka[1], Kohei Takeda[2], Yuki Tamura[1], Shin Fujimaki[2], Tohru Takemasa[2], and Hideo Hatta[1]

[1]Dept. of Sports Sci., Univ. of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo, 153-8902, Japan, [2]Grad. Sch. of Comprehensive Human Sci., Univ. of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8572, Japan.

Oxidative stress-induced mitochondrial dysfunction is associated with age-related and disuse-induced skeletal muscle atrophy. However, the direct relationship between oxidative stress and muscle fiber atrophy has not been fully elucidated. In this study, we examined whether deficiency of nuclear factor erythroid 2-related factor 2 (Nrf2), which is known as a master regulator of antioxidant transcription, promotes denervation-induced muscle atrophy. Nrf2 knockout (KO) mice and C57BL/6J wild-type (WT) mice were unilaterally denervated by severing the sciatic nerve of left hindlimb, with the right hindlimb serving as the sham-operated control. Following 2 weeks of denervation, gastrocnemius muscles were extracted for subsequent mRNA expression and whole muscle protein analyses. We found that the expression of Nrf2 and its target antioxidant genes were up-regulated at 2 weeks after denervation in WT mice. The response of these antioxidant genes was attenuated in Nrf2 KO mice. Nrf2 KO mice had elevated 4-hydroxynonenal (4-HNE) in skeletal muscle. Protein levels of mitochondrial oxidative phosphorylation were declined in the denervated muscle of Nrf2 KO mice. Denervation decreased muscle mass of both WT and Nrf2 KO mice, however, there was no difference between these two groups. Nrf2 deficiency did not affect denervation-induced autophagy and satellite cell activation. These findings suggest that Nrf2 deficiency aggravates denervation-induced oxidative stress, but not the loss of skeletal muscle mass.

17.2
TRANS-PLASMA MEMBRANE ELECTRON TRANSPORT AND ASCORBATE EFFLUX IN SKELETAL MUSCLE CELLS

Amanda M. Kaverman[1], Rohan M. Prasad[1], and Jonathan S. Fisher[1]

[1]Dept. of Biology, St. Louis Univ., 3507 Laclede Ave., St. Louis, MO, 63103.

Ascorbate plays a key antioxidant role in protection of cells from damage by reactive oxygen species, which have been implicated in causing metabolic dysfunction such as insulin resistance. It has been shown in hepatocytes that ascorbate is exported as an antioxidant and taken back into the cell as its oxidized form, dehydroascorbic acid (DHA), whereupon the DHA is reduced back into ascorbate. As 40% of the body's ascorbate is present in muscle cells, ascorbate export by muscle could potentially be a major source of extracellular antioxidant. Thus, we hypothesized that muscle cells export ascorbate and that glucose transporters (GLUTs, which also transport DHA) would play a supporting role in ascorbate cycling. In order to measure trans-plasma membrane electron transport (tPMET), we assayed the ability of cultured muscle cells and isolated extensor digitorum longus (EDL) and soleus (SOL) to reduce two different extracellular, membrane-impermeable electron acceptors, water soluble tetrazolium salt 1 (WST-1) and dichlorophenolindophenol (DPIP). Ascorbate oxidase (AO) was utilized in order to determine which portion of WST-1 and DPIP reduction was dependent on ascorbate efflux. We found that cultured C2C12 and L6 myoblasts, C2C12 myotubes, EDL, and SOL can reduce extracellular electron acceptors, and a substantial portion of this was dependent on ascorbate. In myoblasts, the GLUT1 inhibitors phloretin, fasentin, and STF-31 along with the general inhibitor of GLUT-mediated transport cytochalasin B suppressed tPMET, while the GLUT4 inhibitor indinavir had no effect. Phloretin also decreased the AO-sensitive portion of tPMET. The AMP-activated protein kinase activator 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) suppressed both tPMET and ascorbate efflux from myoblasts. Our data suggests that muscle cells are capable of ascorbate cycling, with ascorbate efflux followed by GLUT1-mediated DHA uptake. The AICAR effect on tPMET and ascorbate efflux is consistent with the energy-conserving actions described for AMPK. Our data suggest a model in which resting muscle exports electrons and

antioxidant to the extracellular environment, while sensing of metabolic stress suppresses these energetically costly processes. This project is funded by the National Institute of Diabetes and Digestive and Kidney Diseases grant R15DK102122.

17.3

PEROXIDASE ACTIVITY OF MYOGLOBIN

Mark Mannino[1], Rishi Patel [2], Blythe Janowiak [2], and Jonathan Fisher [2]

[1]Dept. of Biology, St. Louis Univ., 3507 Laclede Ave., St. Louis, MO, 63103, [2]Biology, St. Louis Univ., 3507 Laclede Ave., Dept. of Biology, St. Louis, MO, 63103.

Although there is extensive evidence roles of myoglobin (Mb) in oxygen storage and diffusion in skeletal muscle and heart, Mb has also been implicated in cellular antioxidant defense. Upon releasing its oxygen, Mb can be oxidized to peroxidase-active metMb which can then react with hydrogen peroxide to produce a highly reactive oxoferryl heme iron (IV=O). Although the oxoferryl heme of Mb is a strong oxidant and has been proposed to contribute to oxidative damage, it is possible that rapid reduction of Mb (IV=O) to metMb by reducing substrates allows for the major effect of Mb peroxidase activity to act as an antioxidant as opposed to an oxidant. We hypothesized that Mb can act as a peroxidase using a variety of reducing substrates. Using spectrophotometric techniques, our data show that horse skeletal muscle Mb has peroxidase activity using 2,2'-azinobis [3-ethylbenzothiazoline-6-sulfonic acid] (ABTS) and 3,3',5,5'-tetramethylbenzidine (TMB) as reducing substrates, as well as the biological substrates NADH/NADPH, vitamin E analog trolox C, ascorbate, L-tyrosine, lipoic acid and glutathione. The reaction of Mb with H_2O_2 was shown to follow Michaelis-Menten kinetics and was inhibited by addition of sodium cyanide as well as sodium azide. The reaction was pH dependent, showing increased activity with decreasing pH within the biologically relevant range of 6.1-7.4. In addition, we found that metMb reacts with hypochlorite in a heme-dependent fashion. However, physiological concentrations of hypochlorite did not appreciably affect Mb peroxidase activity, implying that Mb might play a role in hypochlorite detoxification. Together, these data provide evidence that Mb peroxidase activity might be an important antioxidant mechanism, especially in contracting muscle where decreased pH due to lactic acid fermentation and high concentrations of NADH could increase its effect. This project is funded by the National Institute of Diabetes and Digestive and Kidney Diseases grant R15DK102122.

17.4

CHANGES IN ENERGY STATE ACUTELY ALTER REDOX STATE AND INSULIN SENSITIVITY IN HEALTHY HUMANS

Chien-Te Lin[1,2], Laura A. Gilliam[1,2], Terence E. Ryan[1,2], Maria J. Torres[1,3], Cody D. Smith[1,2], Patty M. Brophy[1], Angela H. Clark[1], Robert C. Hickner[1,2,3], and P. Darrell Neufer[1,2,3]

[1]East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [2]Physiology, East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [3]Kinesiology, East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834.

We recently found in rodents that both acute and chronic energy oversupply induced by high fat diet (HFD) increased skeletal muscle mitochondrial H_2O_2 emitting potential (mE_{H2O2}) and decreased insulin sensitivity (SI). Such HFD-induced deleterious effects were attenuated by a simultaneous mild increase in energy expenditure. In order to determine the impact of acute- and short-term chronic changes in energy status on mitochondrial function, redox state and SI in humans, ten healthy sedentary young male subjects (24.9±1.9 yr, BMI=25.2±0.7, SI=4.73±0.41) consumed a 60% HFD for 18 days, with a mild exercise intervention (1h at 50% HR_{max} twice/day) from days 13 to 17. Intravenous glucose tolerance tests and several parameters of mitochondrial function and cellular redox state measured from skeletal muscle biopsies were performed in both fasted (overnight) and fed states (8h after HFD meal) on days 0, 6, 12, and 18. In permeabilized muscle fiber bundles, mitochondrial respiratory capacity was unaltered by HFD or exercise. In response to each acute HFD meal on day 0, 6, and 12, there was an increase in peroxiredoxin-2 decamer formation (+71%) and mE_{H2O2} (+45%), and a decrease in GSH/GSSG ratios (-6%) and SI (-34%). Overnight fasting returned peroxiredoxin-2 decamer, mE_{H2O2} and SI to baseline levels, but did not restore the shift in GSH/GSSG ratio. Finally, piror exercise intervention blunted the changes observed in GSH/GSSG, peroxiredoxin-2 decamer, mE_{H2O2} and SI when challenged with a HFD meal on day 18. SI correlated with mE_{H2O2} across all metabolic states (R^2=0.09, $P<0.05$). These data provide evidence that SI fluctuates in response to acute changes in whole body energy state during HFD feeding/fasting cycles, and that governance of mE_{H2O2} may be a primary factor regulating SI in skeletal muscle. Supported by NIH DK074825.

18.0 MUSCLE FUNCTION AND ADAPTATION

18.1

A LONG-TERM HIGH FAT DIET CAUSES MUSCLE DYSFUNCTION IN MOUSE FAST-TWITCH SKELETAL MUSCLE.

Hiroaki Eshima[1], Yoshifumi Tamura [1], Saori Kakehi[1], Ryuzo Kawamori[2], and Hirotaka Watada[1]

[1]Endocrinology, Univ. of Juntendo, 2 Chome-1-1 Hongo, Bunkyo, Tokyo 113-0033, Tokyo, Japan, [2]Sportology Ctr., Univ. of Juntendo, 2 Chome-1-1 Hongo, Bunkyo, Tokyo 113-0033, Tokyo, Japan.

In the present study we investigate the effect of long-term high fat diet on contractile function and morphology in skeletal muscle. Male C57BL/6J mice were fed a high fat diet (HFD; 60% kcal: fat) for 4 weeks (4wk HFD) and 12 (12wk HFD) weeks. Isolated fast-twitch extensor digitorum longus (EDL) was measured muscle force by electrical stimulation, morphology and contraction-related protein analysis. 12wk HFD decreased muscle tetanic force compared than control, but not 4wk HFD. Morphology analysis, muscle fiber type shifts to oxidative fibers, mitochondrial oxidative enzyme activity and intramyocellular lipid (IMCL) levels were increased in only 12wk HFD. No changes in the expression of calcium handling-related protein levels were evident HFD models, whereas troponin T isoform protein levels was decreased in 12wk HFD, but not 4wk HFD. These findings indicate that long-term HFD induces muscle dysfunction in fast-twitch dominant muscle fiber, but not short-term high-fat feeding. The latter was associated with a changes of con-

tractile-related protein levels, oxidative metabolic and accumulation of IMCL levels.

18.2

THE EFFECT OF CHRONIC RESISTANCE TRAINING ON MYONUCLEAR ABUNDANCE IN OLETF RAT SKELETAL MUSCLE

Satoru Ato[1], Kohei Kido[1], Koji Sato[2], and Satoshi Fujita[1]
[1]Fac. of Sport and Hlth. Sci., Ritsumeikan Univ., Nojihigashi1-1-1, Kusatsu, Japan, [2]Fac. of Human Development, Kobe Univ., Nada Tsurukabuto 3-11, Kobe, Japan.

Introduction: Skeletal muscle fiber (single cell of a muscle) contains multiple number of nucleus. Resistance training or overload induces muscle hypertrophy and new myonuclear accretion in human and rodents. Previous studies have suggested that level of myounuclear accretion is responsible for the magnitude of exercise-induced muscle hypertrophy. Moreover, conditional depletion of satellite cell (i.e. source of new myonucleus) attenuates load-induced muscle hypertrophy in rodents. These evidences suggest that myonuclear accretion is involved in training-induced hypertrophic response. Previous report indicates that type 2 diabetes mellitus (T2DM) attenuates muscle hypertrophy induced by functional overload. Moreover, satellite cell response to cytokine from T2DM patients has shown to be impaired. Consequently, the impairment of satellite cell function in T2DM might suppress resistance training-induced myonuclear accretion and muscle hypertrophy. However, it is not understood whether myonuclear number is increased by resistance training in T2DM. Therefore, purpose of this study was to investigate the effect of 18 bouts of resistance training on myonuclear number in skeletal muscle of Otsuka Long-Evans Tokushima Fatty (OLETF; T2DM model) rat. Methods: Six-week male OLEFT rats were acclimated for 14 weeks. We recognized that rats develop T2DM (fasting blood glucose was more than 126 mg/dl) at 20 weeks of age. Six-week resistance training (18 bouts) was exerted 3 sessions per week (e.g. Monday, Wednesday, Friday). Resistance exercise (3s contraction x 10 times / set, 3 sets, 3 min rest between sets) was performed by percutaneous electrical stimulation on right hind limb muscle (100Hz, 30V, left leg was saved as control). A week after final session, rats were sacrificed and gastrocnemius muscle was taken after an over night fast. Muscle samples were weighted and incubate with 4% PFA in PBS more than 48h. Fixed muscle were incubate in 40% NaOH for 2h, and obtained single fiber. Fiber was stain with DAPI and myonuclear number and fiber size were counted under fluorescence microscope. Results: Trained gastrocnemius muscle (right leg) wet weight was significantly higher than control leg (left leg). Myonuclear number / mm fiber was significantly higher as compared with control leg ($p<0.05$). Myonuclear domain (μm^3 /myonuclear number) was not different between trained and control legs. Conclusions: While 6-week resistance training did not change myonuclear domain, muscle mass and myonuclear number of T2DM model rats were significantly increased.

18.3

RELATIONSHIP BETWEEN TRAINING FREQUENCY AND MUSCLE PROTEIN SYNTHESIS IN RESISTANCE EXERCISE ELICITED BY ELECTRICAL STIMULATION

Junya Takegaki[1], Riki Ogasawara[2], Arata Tsutaki[3], Ryo Takagi[1], Koichi Nakazato[3], and Naokata Ishii[1]
[1]Dept. of Life Sci., Univ. of Tokyo, 3-8-1 Komaba, Meguro-ku, 153-8902, Japan, [2]Dept. of Life Sci. and Applied Chemistry, Nagoya Inst. of Technology, Gokiso-cho, Showa-ku, 466-8555, Japan, [3]Dept. of Hlth. and Sport Med. Sci., Nippon Sport Sci. Univ., 7-1-1 Fukasawa, Setagaya-ku, 158-8508, Japan.

Introduction: Resistance training induces muscle hypertrophy through the accumulation of muscle protein. The training effect has been thought to depend on training intensity, volume, and recovery time. However, the effect of recovery time between the sessions of resistance exercises on muscle protein synthesis is unclear. Purpose: To see changes in protein synthesis and relating factors by changing the recovery time between sessions of resistance exercise with equal exercise volume. Methods: Male C57BL/6J mice (n=18) were randomly assigned into three groups: resistance-trained with 3 bouts at intervals of 72h (72H), 24h (24H) and 8h (8H), respectively. The resistance exercise consisted of 50 repetitions of maximal isometric contraction of the tibialis anterior muscle. The right tibialis anterior muscle was used as trained muscle, and the left was used as internal control. The muscle contraction was induced by transcutaneous electrical stimulation of deep fibular nerve under anesthesia. Muscle samples were collected 6h after the final exercise session, and kept frozen until analysis. Fifteen minutes prior to the muscle sampling, mice were injected with 0.04 μmol/g puromycin. Results: Puromycin-incorporated proteins, i.e., newly synthesized proteins in ribosomes, increased in 72H, but not in 24H and 8H. The phosphorylation of Akt (Ser473) was observed in 24H and 8H, and that in 8H was significantly higher than in 24H. The phosphorylation of p70S6K (Thr389) was observed in all exercised groups, and 8H and 24H showed significantly higher level than 72H. The phosphorylation of rpS6 (Ser240/244) was observed in all exercised groups, and was higher in 24H and 8H than in 72H. The content of carbonylated protein was significantly increased only in 8H. Conclusion: The present results suggest that consecutive bouts of resistance training at 8h interval do not effectively cause an increase in protein synthesis, even though activate Akt-mTOR signaling pathway. Increase in oxidative stress would be one of the possible causes for this.

18.4

NUCLEAR AND CYTOPLASMIC MUSCLE-BLIND-LIKE 1 IN MOUSE SKELETAL MUSCLE IN RESPONSE TO AGING AND UNLOADING WITH OR WITHOUT RELOADING

Ayane Nakamura[1,2], Rika Ito[1,3], Naomi Ikegaya[1], Masaki Higa[1], Shingo Yokoyama[1], Yoshitaka Ohno[1], Takao Sugiura[4], Yoshinobu Ohira[5], Toshitada Yoshioka[6], Leslie, M. Baehr[7], Sue C. Bodine[7], and Katsumasa Goto[1]
[1]Dept. Physiol., Grad. Sch. Hlth. Sci., Toyohashi Sozo Univ., Matsushita, Toyohashi, Japan, [2]Dept. Rehabil., Nishio Municipal Hosp., Kamiawahara, Nishio, Japan, [3]Dept. Exer. Physiol., Grad. Sch. Sci. Technol. Innovation, Yamaguchi Univ., Yoshida, Yamaguchi, Japan, [4]Fac. Edu., Yamaguchi Univ., Yoshida, Yamaguchi, Japan, [5]Fac. Hlth. Sports Sci., Grad. Sch. Hlth.

Sports Sci., Doshisha Univ., Miyakodani, Kyotanabe, Japan, [6]Dept. Physiol., Hirosaki Gakuin Univ., Minori, Hirosaki, Japan, [7]Dept. Neurobiol., Physiol. Behavior, Univ. California, Davis, 4303 Tupper Hall One Shields Ave., Davis, CA, 95616.

Muscleblind-like1 (MBNL1) is an alternative splicing factor involved in postnatal development of heart and skeletal muscles in humans and mice, and its dysfunction is considered to play a crucial role in the onset and development of myotonic dystrophy (DM). Recently, it has been shown that MBNL1 may be a key factor in age-associated skeletal muscle atrophy, namely sarcopenia. Even though it is suggested that the nuclear accumulation of MBNL1 may be a cause of muscle atrophy in DM patients, age-related changes in nuclear MBNL1 is still unclear. The purpose of this study was to investigate the changes in the nuclear fraction of MBNL1 in mouse skeletal muscle in response to aging and unloading with or without reloading. All experimental procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health (Bethesda, MD, USA) and were approved by the Animal Use Committee of Toyohashi SOZO University. Both 10-, 50- and 100-week-old male C57BL/6J mice were divided into unloaded and control groups. Mice in unloaded group were subjected to 2-week hindlimb suspension. Immediately after the 2-week hindlimb suspension, ambulation recovery was allowed for some mice in the unloaded group. Plantaris (PLA) and Medial Gastrocnemius (MG) muscles were dissected from both hindlimbs at baseline (control group), and at 0 and 2 weeks after 2-week hindlimb suspension. Age-associated reduction of muscle weight in PLA was higher than in MG. Response of the nuclear and cytoplasmic contents of MBNL1 in PLA to aging was different from that in MG. Although there was a distinct difference in the responses of muscle weight to 2-week hindlimb suspension with or without reloading between PLA and MG, nuclear MBNL1 in both muscles in 10-week-old mice decreased following the 2-week suspension. However, nuclear MBNL1 in MG increased following reloading, but not in PLA. MBNL1 may play a role as a mediator of skeletal muscle mass in response to aging, as well as, unloading. This study was supported, in part, by Grants-in-Aid for challenging Exploratory Research (26560372), and Grants-in-Aid for Scientific Research (C, 26350818) from the Japan Society for the Promotion of Science, the Uehara Memorial Foundation, the Naito Foundation, Graduate School of Health Sciences, Toyohashi SOZO University, Descente Sports Foundation, and All Japan Coffee Association.

18.5
TRAINING STATUS AND PDH REGULATION IN HUMAN SKELETAL MUSCLE DURING EXERCISE

Anders Gudiksen[1], Lærke Bertholt[1], Tomasz Stankiewicz[1], Jonas Tybirk[2], Peter Plomgaard[3], Jens Bangsbo[2], and Henriette Pilegaard[1]

[1]Dept. of Biology, Univ. of Copenhagen, Universitetsparken 13, Copenhagen, 2100, Denmark, [2]Dept. of Nutrition, Exercise and Sports, Univ. of Copenhagen, Universitetsparken, 13, Copenhagen, 2100, Denmark, [3]Dept. of Clinical Biochemistry, Rigshospitalet, Univ. of Copenhagen, Blegdamsvej 9, Copenhagen, 2100, Denmark.

Background: The ability of skeletal muscle (SkM) to shift between lipid and carbohydrate (CHO) oxidation, defined as metabolic flexibility, is essential during metabolic challenges like exercise. Exercise training has been shown to increase maximal capacity for both lipid and carbohydrate oxidation and induce a shift towards higher reliance on lipid utilization and glycogen sparing in SkM. Pyruvate dehydrogenase (PDH) is the gateway enzyme for CHO derived intermediates into the TCA cycle and may play a central role in regulating substrate use during exercise and with exercise training. However, the impact of PDH on metabolic flexibility and the detailed regulation of PDH during exercise are not fully elucidated. The aim of the present study was therefore to investigate the impact of training status on metabolic flexibility and regulation of PDH in SkM during incremental exercise. **Methods:** Nine untrained (UT) (VO_2max<45 $ml \cdot min^{-1} \cdot kg^{-1}$) and ten trained (T) ($VO_2max$>55 $ml \cdot min^{-1} \cdot kg^{-1}$) young male subjects performed an incremental exercise bout on a magnetically braked cycle ergometer: 40 min at 50% VO_2max, 10 min at 65% VO_2max, and finally 80% VO_2max until exhaustion. Biopsies were taken from m. vastus lateralis prior to exercise (PRE), after 30 min, 41 min, and at exhaustion (EXH). RER was measured in 5 min intervals leading up to each biopsy. Blood samples were obtained regularly throughout the exercise bout. **Results** RER was lower in T than UT at 50%, and 65% VO_2max. Plasma free fatty acids increased similarly in T and UT with exercise. Plasma glucose was generally higher in T than UT while muscle glucose was similar in UT and T except at EXH where higher in T than UT. Plasma and muscle lactate levels were higher in UT than T except at EXH where plasma lactate was similar in T and UT. Muscle glycogen was lower in UT than T at 50%, and 65% VO_2max but similar at EXH. PDHa activity was similar at PRE and increased similarly in T and UT at 50%, and 65% VO_2max, but was higher in T than UT at EXH. **Conclusion** Similar SkM PDHa activity at given relative submaximal exercise intensities was associated with lower RER, less glycogen use, and seemingly lower lactate production in T than UT indicating increased lipid utilization with exercise training. Together this demonstrates an enhanced level of substrate control evident at the level of PDH in SkM with increased training status.

18.6
A NOVEL METHOD TO QUANTIFY RESTING AND CONTRACTION-STIMULATED O_2 CONSUMPTION IN ISOLATED MOUSE SKELETAL MUSCLE

Patrick Ferrara[1], Anthony Verkerke[1], Armondo Balotti[1], Tara Narowski[1], Espen Spangenburg[2], and Katsuhiko Funai[1,2]

[1]Dept. of Kinesiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27858, [2]Dept. of Physiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27858.

The purpose of this study was to develop a novel method to measure skeletal muscle O_2 consumption at rest and following a bout of isometric contractions in whole mouse muscle *ex vivo*. Extensor digitorum longus (EDL) muscles were dissected from

C57BL/6J mice and incubated in O_2-saturated Krebs-Hanseleit buffer (- $CaCl_2$) at a resting tension of ~ 40 mN. After testing contractile viability with a pulse stimulation, the muscle incubation bath (1.9 mL volume) system that includes an O_2 probe was sealed. After the 5-min probe equilibration period, EDL muscles from one limb were subjected to the measurement of resting O_2 consumption, and the contralateral EDL muscles were used for the measurement of O_2 consumption during electrically-stimulated contraction. For the resting protocol, muscles were suspended in a sealed bath at resting tension for 5 min with constant O_2 readout. The O_2 disappearance from the system was plotted for each muscle and lines of best fit were created. The slope was used to determine rates of O_2 disappearance which was converted to μMole O_2 and normalized to wet weight of each muscle. For the contraction protocol, EDL muscles underwent ten electrically-stimulated isometric contractions (0.1 ms pulse width, 100 Hz pulse frequency, 1 s train, 4 s between trains) with recordings of O_2 immediately before and up to 30 min after the completion of electrical stimulation. We found a large portion of O_2 consumption occurred after the electrical stimulation was complete, but this increase in the rate of O_2 consumption was reversed to the resting level by 5 min post-contraction. Total O_2 consumption in the first 5 min post-contraction was then divided by the force-time integral (FTI: area under the curve of force generated by contracting muscle) to derive mechanical energy efficiency of contracting skeletal muscle. This method provides a novel platform to assess bioenergetics of resting and contracting skeletal muscles in small animals. This study was supported by NIH grants DK095774 and DK109888.

18.7

REDUCED NON-BICARBONATE SKELETAL MUSCLE BUFFERING CAPACITY IN MICE WITH THE MINI-MUSCLE PHENOTYPE

Jarren Kay[1], Zoe Thompson[2], Erick Contreras[1], Jocelyn Ramirez[1], and Theodore Garland[1]
[1]Biology, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92507, [2]Neuroscience, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92507.

During exercise, muscle pH decreases due to by-products of muscle contraction and replenishment of high-energy phosphate stores. Many mechanisms exist by which muscle acidosis may impair muscle function, including decreased maximum force, decreased Ca^{2+} sensitivity, decreased Ca^{2+} reuptake and release by the sarcoplasmic reticulum, and increases in K^+ conductance via the ATP-dependent K^+ channel. More recently, evidence has been presented that calls into question the theory that acidosis or lactate causes muscle fatigue and, moreover, suggests that acidosis can be beneficial to exercising muscles. Specifically, current thought suggests that acidosis may be protective against K^+-induced force paralysis and can increase oxygen delivery to tissues via the Bohr Effect. Further, lactate can sometimes act as a fuel source, via conversion to ATP. Sedentary humans and endurance athletes generally have lower skeletal muscle buffering capacity than do athletes that perform burst activity. Interestingly, although endurance cyclists have lower buffering capacity than other athletes that perform more short-term, high-intensity exercises, high-intensity training by endurance cyclists can increase the buffering capacity of their skeletal muscle. We hypothesized that High Runner (HR) lines of mice from an artificial selection experiment that breeds for high voluntary wheel running would have elevated muscle buffering capacity as compared with their non-selected control counterparts. Mice of both linetypes were split into two groups, those without access to running wheels and those given access to wheels for 6 days (as used in the routine selection protocol). We predicted that wheel access would reduce muscle buffering capacity because wheel running is similar to endurance exercise, especially in the HR lines. We also expected a subset of the HR mice with the "mini-muscle" phenotype to have even lower buffering capacity because of their greatly reduced numbers of type IIb muscle fibers (and low sprinting ability). We tested buffering capacity of thigh muscles following Castellini and Somero (1981, J *Comp Physiol* 143:191–98). We found no difference between HR and C mice, and no training effect. However, as predicted, mice expressing the mini-muscle phenotype had significantly reduced buffering capacity compared with other mice. In addition, females had lower buffering capacity than males. Supported by NSF IOS-11212732 to TG.

18.8

CAN AGED SKELETAL MUSCLE INFLAMMATION SUSCEPTIBILITY BE MODULATED WITH DAILY CONSUMPTION OF AN ANTI-INFLAMMATORY FOOD?

Vincent Georgescu[1], Christopher Demczar[1], Christian Behrens[2], Steven McAnulty[1], Lisa McAnulty[2], and Edward Merritt[1]
[1]Hlth. & Exercise Sci., Appalachian State Univ., 111 Rivers St., PO Box 32071, Boone, NC 28608, [2]Nutrition & Healthcare Management, Appalachian State Univ., 261 Locust St., Boone, NC 28608.

Evidence suggests that muscles of old (vs. young) respond to stress with heightened pro-inflammatory signaling that disrupts the regenerative process. This could ultimately lead to a decline in muscle mass. With high levels of antioxidants and anti-inflammatory effects, blueberries (BB) are an ideal natural food to potentially regulate aged muscle inflammation susceptibility. The **purpose** of this study was: 1) To determine the effects of 6 weeks of BB supplementation on the systemic and local muscle inflammatory profile of older adults; and 2) To measure the inflammatory response of the muscle following a regenerative stimulus with or without BB supplementation. We **hypothesized** that 6-weeks of BB supplementation would lower the basal inflammatory profile of aged muscle and subsequently attenuate the heightened inflammatory response observed after a stressful bout of resistance exercise. **Methods:** Healthy men and women over 60 years old (n=22) were recruited for the study. Baseline blood and muscle profiles of inflammation signaling pathways known to affect muscle mass (IL-6, TNFα) were established prior to 6-weeks of daily consumption of blueberries (250 g/day of freeze-dried blueberry powder) or placebo. At the end of supplementation, samples were again obtained to determine the inflammatory profiles. Subjects then performed a mechanically-induced muscle stress protocol (9 sets of 10 knee extension exercises) designed to induce muscle inflammation.

Subjects returned to the lab 24 hours post-muscle stress when the final samples were obtained. **Results**: Cytokine and soluble cytokine receptor levels measured from the muscle biopsy samples were not significantly different between groups or within groups before or after BB supplementation. Changes in cytokine and cytokine receptor levels post-muscle stress occurred similarly in the BB and placebo group, indicating BB had no effect on the muscle's inflammatory response. Total plasma antioxidant capacity was 22% higher in the BB group than in the placebo group 24-hours post-muscle stress (Pearson's Correlation $p = 0.08$, Cohen's $d = 0.85$), however, plasma oxidative stress was not different between groups or over time within groups. **Conclusion**: While BB consumption does not appear to affect inflammatory signaling pathways within the muscle nor affect inflammation after a regenerative stimulus in healthy, older adults, a higher plasma antioxidant capacity could contribute to a better long-term regenerative response.

18.9

OVEREXPRESSION OF THE A7B1 INTEGRIN ACCELERATES SKELETAL MUSCLE HYPERTROPHY FOLLOWING CHRONIC OVERLOAD

Ziad Mahmassani[1], Koyal Garg[1], Michael Munroe[1], Slav Dvoretskiy[1], Troy A. Hornberger[2], and Marni D. Boppart[1,3]
[1]Dept. of Kinesiology and Community Hlth., and Beckman Inst. for Advanced Sci. and Technology, Univ. of Illinois at Urbana-Champaign, 405 N. Matthews, Urbana, IL, 61801, [2]Comparative Biosciences, Univ. of Wisconsin, Madison, 2015 Linden Dr., Madison, WI, 53706, [3]Ki-nesiology, Inst. for Genomic Biology, Univ. of Illinois at Urbana-Champaign, Urbana, IL, 61801.

The α7β1 integrin is a focal adhesion protein found at the costameres of skeletal muscle and it provides a critical link between the actin cytoskeleton and laminin in the basement membrane. We have demonstrated that overexpression of the α7BX2 integrin subunit in muscle (MCK:α7BX2) preserves integrity of the sarcolemma and enhances myofiber growth following multiple bouts of eccentric exercise. **Purpose:** The purpose of this study was to determine the extent to which the α7BX2 integrin contributes to hypertrophy following chronic overload. **Methods:** Myotenectomy (MTE) of the gastrocnemius muscles was performed on 6 mo male wild type (WT) and MCK:α7BX2 mice. Hypertrophic signaling and muscle growth was determined at 1 (1D) and 14 days (14D) post-MTE. **Results:** Hypertrophy of the plantaris muscles as determined by muscle weight and mean fiber cross-sectional area, was augmented in MCK:α7BX2 mice 1D post-MTE vs. WT controls ($P<0.05$). The rise in stress response protein HSP70 and damage as determined by IgG staining 1D post-MTE, were both reduced 2-fold in MCK:α7BX2 as compared to WT ($P<0.05$). Phosphorylation of AKT, mTOR, and p70S6k were significantly reduced in MCK:α7BX2 vs. WT at 1D post-MTE. Differences in growth, stress/damage, and hypertrophic signaling were no longer present at 14D post-MTE, but MCK:α7BX2 mice displayed a 2-fold reduction in centrally located nuclei. **Conclusion:** The results from this study suggest that the α7β1 integrin accelerates growth in the early stages of chronic overload and a reduction in damage may contribute to this observation. NIH NIAMS 1 R21 AR065578A.

18.10

ABSENCE OF PHOSPHATIDYLETHANOLAMINE METHYLATION INCREASES SKELETAL MUSCLE ENERGY EXPENDITURE AND PREVENTS OBESITY

Anthony Verkerke[1], Patrick Ferrara[1], Chien-Te Lin[2], Timothy Heden[1], Terence Ryan[2], Edward Wentzler[1], Armondo Balotti[1], P. Darrell Neufer[1,2], and Katsuhiko Funai[1,2]
[1]Dept. of Kinesiology, East Carolina Obesity and Diabetes Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, [2]Dept. of Physiology, East Carolina Obesity and Diabetes Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834.

Membrane phosphatidylethanolamine (PE) can be tri-methylated to form phosphatidylcholine (PC) by the enzyme PE methyltransferase (PEMT). Mice with a whole-body deletion of PEMT (PEMTKO) on high-fat diet (HFD) exhibit elevated whole-body metabolic rate and are protected from diet-induced obesity with no difference in food intake or activity. The mechanism behind increased respiration in PEMTKO mice is unknown. We investigated whether PE methylation deficiency promotes an increase in skeletal muscle energy expenditure. Strikingly, in isolated extensor digitorum longus (EDL) muscle, resting O_2 consumption was greater in PEMTKO mice compared to WT mice. To exclude the possibility that a difference in O_2 consumption was promoted by differences in O_2 delivery to the cell, we measured O_2 consumed in flexor digitorum brevis (FDB) muscle fibers *in vitro*. Under this condition, PEMT knockout also resulted in greater basal O_2 consumption, suggesting that absence of PEMT promotes an increase in skeletal muscle energy expenditure. Mitochondrial energy efficiency, as quantified through ATP production per O_2 reduction in permeabilized fibers or isolated mitochondria, were not different between WT and PEMTKO muscles. Instead, absence of muscle PE methylation promoted an apparent decrease in transport stoichiometry of sarco/endoplasmic reticulum (SR/ER) Ca^{2+}-ATPase (SERCA) (Ca^{2+} uptake / ATP hydrolysis), suggesting that futile energy expenditure of SERCA ATPase might be responsible for increased metabolic rate in these muscles. Phospholipidomic analysis revealed that PEMT knockout results in a deceased PC/PE ratio in muscle SR but not mitochondria. Our preliminary studies show that mice with muscle-specific knockout of PEMT (PEMT-MKO) are protected from diet-induced obesity, exhibit increased energy expenditure, and show improved glucose tolerance. These data suggest absence of skeletal muscle phospholipid methylation is sufficient to increase skeletal muscle energy expenditure to alter susceptibility for obesity. This study was supported by NIH DK095774 and DK109888

18.11

DISSOCIATION BETWEEN SHORT-TERM UNLOADING AND RESISTANCE TRAINING EFFECTS ON SKELETAL MUSCLE NA^+,K^+-ATPASE, MUSCLE FUNCTION AND FATIGUE IN HUMANS

Ben Perry[1,2], Victoria Wyckelsma[1], Robyn Murphy[3], Collene Steward[1], Mitchell Anderson[4], Itamar Levinger[1], Aaron Petersen[1], and Michael McKenna[1]
[1]Inst. of Sport, Exercise and Active Living, Victoria Univ., Cnr. Gordon and Ballarat Rd., Footscray, Melbourne, 3011, Australia, [2]Sch. of Med., Renal Div., Emory Univ., 1639 Pierce Dr., Atlanta, GA, 30322, [3]Dept. of Biochemistry and Genetics, La Trobe Inst. for Molecular Sci., La Trobe Univ., Plenty Rd. & Kingsbury Dr., Melbourne, 3086, Australia, [4]Baker IDI, Baker IDI Heart and Diabetes Inst., 75 Commercial Rd., Melbourne, 3004, Australia.

Physical training increases skeletal muscle Na^+,K^+-ATPase (NKA) and improves exercise performance, but the effects of inactivity per se on NKA in human muscle are unknown. We investigated the effects of 23-days unilateral lower limb suspension (ULLS) and subsequent 4-weeks resistance training (RT) on muscle function and NKA in six healthy adults, measuring quadriceps muscle peak torque; fatigue and venous $[K^+]$ during intense one-legged cycling exercise; and skeletal muscle NKA content ($[^3H]$ouabain binding) and NKA isoform abundances (immunoblotting) in muscle homogenates (α_{1-3}, β_{1-2}) and in single fibers (α_{1-3}, β_1). In the unloaded leg after ULLS, quadriceps peak torque and cycling time to fatigue declined by 22% and 23%, respectively, which were restored with RT. Whole muscle NKA content and homogenate NKA α_{1-3} and β_{1-2} isoform abundances were unchanged with ULLS or RT. However, in single muscle fibers, NKA α_3 in Type I (-66%, p=0.006) and β_1 in Type II fibers (-40%, p=0.016) decreased after ULLS, with other NKA isoforms unchanged. After RT, NKA α_1 (79%, p=0.004) and β_1 (35%, p=0.01) increased in Type II fibers, while α_2 (76%, p=0.028) and α_3 (142%, p=0.004) increased in Type I fibers compared to post-ULLS. Despite considerably impaired muscle function and earlier fatigue onset, muscle NKA content, and homogenate α_1 and α_2 abundances were unchanged, thus being resilient to inactivity induced by ULLS. Nonetheless, fiber-type specific downregulation with inactivity and upregulation with RT of several NKA isoforms indicates complex regulation of muscle NKA expression in humans. Funding: BP was supported by a VU postgraduate research award. VW was supported by an Australian Postgraduate Research Award. IL was supported by Future Leader Fellowship (ID: 100040) from the National Heart Foundation of Australia and AP was part-funded through the Australian Government Collaborative Research Network Scheme.

18.12
INTERNAL OR EXTERNAL CONTROL? A METHODOLOGY REPORT FOR DESIGNING DENERVATION STUDIES

Haiming Liu[1], and LaDora Thompson[1]
[1]Physical Med. and Rehabilitation, Univ. of Minnesota, 2001 6th St. SE, MTRF, Minneapolis, MN, 55455.

Denervation is an established model for elucidating the proteolysis mechanisms in rapid muscle loss. Common methods of denervation include sciatic and tibial nerve transection of one hindlimb while the contralateral-innervated limb serves as the control. Although the use of the contralateral-innervated muscle as the control is the standard practice, it has potential to influence the results and alter the conclusions concerning the hypotheses. Because it is unknown whether the loss of neural input of one hindlimb has an effect on the processes of proteolysis on its contralateral limb, we sought (Aim1) to determine if denervation has an effect on proteolysis on the contralateral-innervated control muscle; and (Aim2) to identify which control, the contralateral-innervated control muscle or the innervated muscle from a nonsurgical mouse, best serves to detect the denervation effect. METHODS: Mice underwent either 14-day tibial nerve transection (DN) or sham surgery. Proteasome activity (caspase- and chymotrypsin-like) and content (α7, β1, PA28, LMP2, MECL1) were determined in the contralateral-innervated gastrocnemius of the DN and Sham and were compared to muscles from intact mice (Aim1). To determine the denervation effect on proteolysis the denervated muscles from DN mice were compared to the contralateral-innervated control muscle (internal) and to muscles from intact mice (external). Results: The sham procedure had no effect on proteolysis. In contrast, the internal control showed significant increases in proteolysis without evidence of atrophy. In the denervated muscle there was 40% atrophy and the markers of proteolysis increased by 38~81% when compared to internal control muscle. When these markers of proteolysis were compared to external control muscle, the increase was 93~334%. For instance, the chymotrypsin-like activity increased by 140% and 38% when compared to external control and internal control, respectively. Likewise, the α7 content increased 334% and 81% when compared to external control and internal control, respectively. These divergent differences are consistent in the other proteolytic parameters. Our results indicate denervation influences the contralateral-innervated muscles and reporting the extent of denervation-induced changes in proteolysis is dependent on which control (internal or external) has been used. Taken together, these results challenge the use of the contralateral-innervated limb as the control in denervation studies. Funding: This study was partially supported by the Doctoral Dissertation Fellowship (University of Minnesota, to H.L), and NIA/NIH R01 AG017768 (to L.V.T).

18.13
CONDITIONAL KNOCKOUT OF THE LYSINE ACETYLTRANSFERASE GCN5 DOES NOT RESULT IN METABOLIC OR FIBRE-TYPE REMODELLING IN MOUSE SKELETAL MUSCLE

Jessica R. Dent[1], Samuel A. LaBarge[2], Elisa H. Buckner[2], Simon Schenk[2], and Andrew Philp[1]
[1]Sch. of Sport, Exercise and Rehabilitation Sci., Univ. of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, [2]Dept. of Orthopaedic Surgery, Univ. of California, San Diego, La Jolla, San Diego, CA, 92093.

Lysine acetylation has emerged as an important post-translational modification, directly affecting signaling pathways that regulate metabolic function. The acetyltransferase, general control of amino acid synthesis 5 (GCN5) has been proposed as a key enzyme regulating mitochondrial biogenesis via its ability to acetylate and inhibit peroxisome proliferator activated receptor coactivator 1α (PGC-1α). However, the specific role of GCN5 in skeletal muscle metabolism and plasticity is currently unknown. To address this, we used CreLoxP methodology to gen-

erate mice with muscle-specific knockout (KO) of GCN5 (mKO). We hypothesized that KO of GCN5 in skeletal muscle would increase PGC-1α activation, and in turn increase mitochondrial biogenesis. GCN5 activity was measured via an acetyltransferase activity assay, while mRNA expression of GCN5, PGC-1α and genes controlling oxidative metabolism was measured via real-time quantitative PCR (RT-qPCR). Immunoblotting was used to determine mitochondrial protein content and silver-staining of myosin-heavy chain subunits was used to determine fibre type distribution. All experiments were approved by, and were conducted in accordance with, the Animal Care Program at the University of California San Diego. GCN5 mRNA expression and activity in skeletal muscle were decreased 86% and 96%, respectively, in mKO vs. floxed/control (CON) littermates. PGC-1α, mitofusin 2, pyruvate dehydrogenase kinase 4 and cytochrome-c mRNA expression in mKO mice was not different from CON mice ($p>0.05$). Similarly, we found no genotype differences in fibre type distribution or the protein abundance of citrate synthase, cytochrome-c or the electron transport chain subunits I through IV ($p>0.05$). Collectively, these findings demonstrate that loss of GCN5 in skeletal muscle does not cause metabolic remodelling in mouse skeletal muscle. This abstract was supported in part through a BBSRC New Investigator Award to AP.

18.14

HIGH-FAT DIET INDUCES LKB1-DEPENDENT ATTENUATION OF SKELETAL MUSCLE P70S6K PHOSPHORYLATION BY INSULIN

Marc Matsumura[1], Ting Chen[1], and David Thomson[1]
[1]Physiology & Developmental Biology, Brigham Young Univ., 4005 LSB, Provo, UT, 84602.

Insulin is an important anabolic hormone. Its signaling through Akt promotes maintenance or increases in muscle mass by activating mTOR, the classic master-regulator of protein synthesis and by decreasing proteolysis. High-fat diet-induced obesity impairs insulin-sensitivity and decreases insulin-stimulated mTOR signaling to its target p70S6k. AMP-activated protein kinase (AMPK) blocks mTOR activity, protein synthesis and muscle growth, and AMPK is activated by high-fat diet feeding, suggesting that it may play a role in high-fat diet-induced resistance of mTOR to insulin stimulation. Therefore, we hypothesized that a loss of AMPK activity through the loss of skeletal muscle LKB1 (the primary AMPK activator in skeletal muscle), would prevent the attenuation of insulin-induced mTOR signaling with high-fat diet-induced obesity. To test this, skeletal muscle specific LKB1 knockout (KO) and wild-type littermate (WT) mice were fed a standard chow diet (SD) or a high-fat diet (HFD) for 14 weeks. Extensor digitorum longus (EDL) muscles were then removed and incubated in the presence or absence of insulin for 30 minutes. Phosphorylation of AMPK, Akt substrates, p70S6k and the p70S6k target rpS6 were measured by western blotting. We found that AMPK phosphorylation was increased while phosphorylation of Akt substrates, p70S6k and rpS6 were decreased by HFD in WT but not KO muscles. Insulin stimulation of Akt substrate, p70S6k and rpS6 phosphorylation was likewise blunted by HF diet in WT but not KO muscles. We conclude, then, that high-fat diet attenuation of basal and insulin-stimulated anabolic signaling via Akt and mTOR is dependent on LKB1.

18.15

EFFECTS OF STATIN TREATMENT ON MUSCLE HYPERTROPHY AND FUNCTION INDUCED BY FUNCTIONAL OVERLOAD IN MICE

Kimberly Huey[1], and Alexander Herold[1]
[1]Pharmacy and Hlth. Sci., Drake Univ., 2720 Forest Ave., Fitch Hall 105, Des Moines, IA, 50311.

Muscle hypertrophy induced by functional overload (FO, removal of major synergists) provides an *in vivo* model to study muscle growth. The most common side effect of statin treatment is skeletal muscle myopathy and we previously reported that statin treatment during running wheel exercise in mice was associated with reduced muscle force production compared to placebo. We hypothesized that statin treatment would also impair contractile and myogenic muscle adaptations to a potent growth stimulus. To test this hypothesis, adult mice underwent FO of the plantaris (removal of gastrocnemius and soleus) or sham surgery. *In vivo* plantaris isometric force and fatigue resistance (% of maximal force after 10 contractions) were measured 14d after FO or sham surgery with a dual mode foot plate system in mice receiving daily atorvastatin (30 mg/kg body mass) or placebo (n= 8-10/group). Basic fibroblast growth factor (bFGF) and insulin-like growth factor 1 (IGF-1) were measured in the plantaris by ELISA and normalized to total protein levels after 14 days of FO or sham surgery. Plantaris mass increased in both groups with increases of 92 and 57% in placebo and statin groups, respectively ($p<0.05$). Plantaris maximal isometric force increased 14% with FO in placebo mice (0.42±0.02 to 0.48± 0.02 g/mg body mass), but decreased 34% in statin mice (0.44±0.03 to 0.32± 0.03 g/mg body mass) when compared to sham ($p<0.05$). Statin treatment did not affect maximal plantaris force compared to placebo in sham groups. Fatigue resistance was not different among all conditions. [IGF] and [bFGF] levels increased with FO in both groups compared to sham ($p<0.05$). However, greater increases were observed in the placebo than the statin treated mice ($p<0.05$). In placebo and statin groups respectively, [IGF-1] increased from 184 ± 30 and 118 ± 22 pg/mg (sham) to 904 ± 64 and 566 ± 70 pg/mg after 14 days of FO. In placebo and statin groups respectively, [bFGF] increased from 161 ± 10 and 131 ± 10 pg/mg (sham) to 404 ± 42 and 292 ± 27 pg/mg after 14 days of FO. These data suggest that statin treatment negatively affects contractile and myogenic adaptations to a hypertrophic stimulus and this is associated with attenuated responses of bFGF and IGF to FO with statin compared to placebo.

18.16

OVEREXPRESSING SIRT1 IN SKELETAL MUSCLE OF ADULT MICE DOES NOT AFFECT MARKERS OF MITOCHONDRIAL BIOGENESIS

Kristoffer Svensson[1], Samuel A. LaBarge[1], and Simon Schenk[1]
[1]Orthopaedic Surgery, Univ. of California, San Diego, 9500 Gilman Dr., #0863, La Jolla, CA, 92093.

The NAD^+-dependent protein deacetylase, sirtuin 1 (SIRT1) has been proposed to be an important modulator of skeletal muscle metabolism and mitochondrial function, as well as insulin action. While models with whole-body overexpression of SIRT1

exhibit positive effects on these parameters, we have previously found that germline muscle-specific overexpression of SIRT1 (mOX) enhances neither insulin sensitivity nor mitochondrial biogenesis. An important point is whether the lack of effect on these parameters in SIRT1-mOX mice is due to the fact that SIRT1 overexpression occurs during early embryonic development. To address this, we generated mice with inducible (i), muscle-specific overexpression (OX) of SIRT1 (i-mOX). For this, floxed mice with loxP sites flanking a transcriptional stop element (FLX) upstream of the *Sirt1* gene were crossed with mice harboring tamoxifen (TMX)-inducible Cre recombinase under the human skeletal actin promoter. Studies were conducted in control/FLX and i-mOX mice, as well as mice with heterozygous (i-mHZ) overexpression of SIRT1. At 12 weeks of age, all mice were orally gavaged with TMX for 5 consecutive days and oral glucose tolerance (OGT) and muscle collection occurred at the age of 14-16 weeks. There were no genotype differences in body weight, fat mass, lean mass, muscle mass or OGT. Moreover, despite ~50- and ~90-fold overexpression of SIRT1 in muscle of i-mHZ and i-mOX, respecttively, there were no differences in mitochondrial electron transport chain protein abundance, or the abundance of proteins related to glucose or fatty acid metabolism. In conclusion, similar to findings in germline SIRT1 mOX mice, the temporal overexpression of SIRT1 in skeletal muscle of adult mice does not alter markers of mitochondrial biogenesis, muscle metabolism or insulin sensitivity.

18.17

AMPK-DEPENDENT ATTENUATION OF SKELETAL MUSCLE PROTEIN SYNTHESIS BY COOLING

Eric Cheung[1], B. Tate Colton[1], and David M. Thomson[1]
[1]Physiology & Developmental Biology, Brigham Young Univ., 4005 LSB, Provo, UT, 84602.

Cooling (or icing) is commonly applied in the treatment of musculoskeletal injuries and after exercise training with the objective of limiting secondary damage and accelerating repair or adaptation. Cooling is known to activate AMP-activated protein kinase (AMPK) in skeletal muscle tissue, which may mediate some desirable adaptations, but could also impair growth and repair since AMPK blocks protein synthesis through inhibition of the mechanistic target of rapamycin (mTOR). Therefore, we hypothesized that the cooling of skeletal muscle would inhibit protein synthesis in an AMPK dependent manner. To test this, we incubated C2C12 myotubes for ½ hour at 37° or at 30° (COLD; temperature of human skeletal muscle during external icing), with or without pre-incubation with Compound C (CC; an AMPK inhibitor). Puromycin was included in the culture media for measurement of protein synthesis. The myotubes were lysed and AMPK phosphorylation, p70 S6-kinase phosphorylation (p70S6k; an mTOR target involved in the stimulation of protein synthesis) and puromycin content were measured by western blotting. Our preliminary results show that protein synthesis (puromycin incorporation) was substantially decreased ($P \leq 0.05$) by COLD, but this decrease was completely blocked by treatment with compound C. Consistent with the decreased protein synthesis, p70S6k phosphorylation tended (non-significantly) to decrease with COLD. We conclude that COLD inhibits skeletal muscle protein synthesis in an AMPK-dependent fashion.

18.19

EFFECTS OF CHRONIC INACTIVITY ON PHYSIOLOGICAL AND BIOCHEMICAL CHARACTERISTICS OF RAT SKELETAL MUSCLE

Hongyang Xu[1], Graham Lamb[1], and Robyn Murphy[1]
[1]Biochemistry, La Trobe Inst. for Molecular Sci., La Trobe Univ., Melbourne, 3086, Australia.

Chronic inactivity is detrimental to human health. It can lead to changes in skeletal muscle structure and function and metabolic processes [1]. The interaction between physiological and biochemical changes between inactive and active muscles are unclear. The laboratory rat is commonly used for studying muscle physiology, however it must be considered a sedentary animal if housed in unenriched cages [2]. To investigate the effect of sedentary behaviour in rat skeletal muscle, 12 wk male Sprague-Dawley rats were individually housed either in normal cages (SED, n=9) or in cages with free access to a running wheel (RUN, n=10), which resulted in rats voluntarily running 1-4 km per day. Following 12 wk intervention, SED and RUN rats were sacrificed with approval from La Trobe University Ethics Committee. The extensor digitorum longus (EDL) muscle (type II fibres) and soleus (SOL) muscle (predominantly type I fibres) were excised for either biochemical measurements in whole muscle homogenates, or for physiological measurements in mechanically-skinned fibres, including calcium sensitivity of the contractile apparatus and the maximum force production. Calcium sensitivity was increased in type II muscle fibres from RUN compared with SED animals, which was reversed by dithiothreitol treatment (n=27 fibres, $p<0.05$), suggestive of oxidative regulation of the contractile apparatus. Maximum force production was increased in RUN compared with SED animals in both type II (↑ 5%) and type I (↑ 25%) fibres. There was a change in the fibre-type composition in EDL but not SOL muscles from RUN compared with SED animals, with ~15% less MHCIIx fibres. There were no changes in the calcium handling proteins calsequestrin and sarcoplasmic reticulum calcium ATPase. In RUN compared with SED animals, there were decreases in glycogen synthase (~40%) and glycogen debranching enzyme (~35%) and an increase of glycogenin (~25%) in SOL muscle, with no changes in EDL muscles or with glycogen phosphorylase or glycogen branching enzyme in either muscle. Despite no fibre type change, the glycolytic enzyme, GAPDH was ~40% lower in SOL muscle, with no change in EDL muscle. The regulatory Na^+/K^+-ATPase α1 protein increased in both muscles (~25% EDL, 35% SOL) in RUN compared with SED animals. These findings suggest that experimental data obtained from sedentary animal models should be used with caution, because the sedentary behaviour can alter many of the muscle parameters both physiologically and biochemically. This study was supported by the National Health and Medical Research Council of Australia. References: 1. Saltin, B., et al., *Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners.* Ann NY Acad Sc, 1977. **301**:3-29. 2. Sherwin, C.M., *Voluntary wheel*

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18.20

INDIVIDUAL RESPONSE TO HIGH-INTENSITY INTERVAL TRAINING (HIIT) – PRELIMINARY DATA FROM THE GENE SMART STUDY

Xu Yan[1,2], Nir Eynon[1,2], Ioannis Papadimitriou[1], Jujiao Kuang[1], Fiona Munson[1], Oren Tirosh[1], Lannie O'Keefe[1], Andrew Garnham[1], and David Bishop[1]

[1]Inst. of Sport, Exercise and Active Living, Victoria Univ., 100 Ballarat Rd., Melbourne, 3011, Australia, [2]Murdoch Childrens Res. Inst., The Royal Children's Hosp., 50 Flemington Rd., Melbourne, 3052, Australia.

Introduction and Aims: The Gene SMART (Genes and the Skeletal Muscle Adaptive Response to Training) Study aims to identify genetic variants that predict the response to both a single bout of High-Intensity Interval Exercise (HIIE) and four weeks of High-Intensity Interval Training (HIIT). While the lead training and testing center is located at Victoria University, Melbourne; four other centers have been launched at Bond University, Queensland University of Technology, Australia; the University of Sao Paulo, Brazil; and the University of Brighton, UK. **Methods:** The overall aim is to recruit 250 moderately-trained, healthy Caucasian males (age range 18-45, BMI range 20-30), currently 45 participants have completed the study. Following 20km time-trial (20K TT), and graded exercise test (GXT) baseline tests, participants underwent 4 weeks of HIIT. The same tests were performed post-training to assess changes in peak power (W_{peak}), lactate threshold (LT), and peak oxygen uptake (VO_{2peak}). Skeletal muscle biopsy and blood were taken before, immediately after and 3 hours post a singe bout of HIIE, with the fourth resting biopsy and blood sample taken after four weeks of supervised HIIT (3 training sessions per week). Mitochondrial respiration and Citrate Synthase (CS) enzyme activity were measured before and after 4 weeks of HIIT. **Results:** W_{peak} improved by 7.15 ± 5.41 % (Mean ± SD, $p < 0.001$, n=45, Figure 1) on average, similarly, LT increased by 7.02 ± 6.88 % after 4 weeks of HIIT ($p < 0.001$). Besides, participants improved their 20K-TT by 3.35 ± 4.89 % ($p < 0.001$). On the contrary, there was no significant improvement in VO_{2peak} is (2.07% ± 6.62%, $p = 0.10$). As expected, the response in W_{peak}, LT, 20K-TT and VO_{2peak} are quite variable. In skeletal muscle samples, we found an average increase of 12.62 ± 17.59 % ($p = 0.004$, Figure 2) in Citrate Synthase (CS) activity (an indicator of mitochondrial content), however, we did not observe significant changes in maximal ADP stimulated mitochondrial respiration (an indicator of mitochondrial function), after four weeks of HIIT (7.82 ± 21.20 %, $p = 0.47$). **Conclusion:** These preliminary results indicate that 4 weeks of HIIT improved Wpeak, LT and 20K-TT, as well as CS activity in human skeletal muscle. We also found that there was quite variable response to the same type of HIIT, and more participants are being recruited, in order to study the genetic basis of individual response.

18.21

LIFE-LONG REDUCTION IN MYOMIR EXPRESSION DOES NOT ADVERSELY AFFECT SKELETAL MUSCLE MORPHOLOGY

Ivan Vechetti Junior[1], Yuan Wen[1], Kevin Murach[2], Laura Peterson[1], Gloria Ming[1], Maeli Dal-Pai-Silva[3], and John McCarthy[1]

[1]Physiology, Univ. of Kentucky, 800 S. Rose St. Med. Sci. Bldg. MS627, Lexington, KY, 40536, [2]Rehabilitation Sci., Univ. of Kentucky, 900 S. Limestone St., Charles T. Wethington Bldg., Lexington, KY, 40536, [3]Morphology, Sao Paulo State Univ., Luis Cassineli St., Botucatu, Brazil.

MicroRNAs (miRNAs) are a family of small non-coding RNAs that repress gene expression through a post-transcriptional mechanism. Biogenesis of miRNAs requires key enzymes such as Dicer, which is necessary for processing the precursor miRNA into the mature form. To determine the importance of miRNAs in skeletal muscle aging, we generated an inducible skeletal muscle-specific Dicer knockout mouse to deplete miRNA levels in adult (~ 3 months old) skeletal muscle. At an average of 24 months, mice were sacrificed and plantaris (Pl) and gastrocnemius muscles collected and prepared for either biochemistry or immunohistochemistry. qPCR confirmed that Dicer mRNA expression was significantly reduced by 80% in the tamoxifen-treated (Tam) group compared to the vehicle-treated control (Veh) group; however, expression of muscle-specific miR-1 and miR-133a was unexpectedly only decreased by ~50% after 21 months of Dicer inactivation. Interestingly, this decrease in myomiR expression did not affect any parameters analyzed in the Pl muscle morphology, such as muscle weight (Veh: 96.26±13.2 vs Tam: 90.28±6.2 mg), muscle cross-section area in both whole muscle (Veh: 885±87 vs Tam: 876±100 μm^2) and fiber-type specific (Type I: 553±140 vs 575±156; Type IIA: 715±42 vs 635±180; Type IIB: 1287±195 vs 1243±212; Type IIX: 984±23 vs 948±124; Veh vs Tam, respectively), fiber-type shift (Veh: 3% Type I, 38% Type IIA, 43% Type IIB, 17% Type IIX; Tam: 1% Type I, 38% Type IIA, 41% Type IIB, 20% Type IIX) , myonuclear number ($DAPI^+$ nuclei within the dystrophin boundary) (Veh: 0.88±0.15 vs Tam: 0.96±0.17 myonuclei/myofiber ratio) and satellite cell abundance (Veh: 0.048±0.003 vs Tam: 0.040±0.008 $Pax7^+$+$DAPI^+$/myofiber ratio). These results suggest the life-long reduction in miRNA levels does not adversely affect skeletal muscle morphology and the intriguing possibility that microRNA expression is uniquely regulated in skeletal muscle. This study is been supported by the São Paulo Research Foundation, Brazil (FAPESP, Proc. 2014/24327-1 and 2015/19193-9) and NIH grant AR061939 to JJM.

18.22

INFLUENCE OF 70 DAYS OF BEDREST AND THE NEXT GENERATION EXERCISE COUNTERMEASURES PROGRAM (SPRINT) ON THIGH AND CALF MUSCLE METABOLIC ENZYMES AND CAPILLARY CONTENT

Kaleen Lavin[1], Bozena Jemiolo[1], Ryan Perkins[1], Steve Ratchford[1], Holmes Finch[1], E. Lichar Dillon[2], Melinda Sheffield-Moore[2], Randall Urban[2], Jeffrey Ryder[3], Lori Ploutz-Snyder[3], Scott Trappe[1], and Todd Trappe[1]

[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave., Muncie, IN, 47306, [2]Dept. of Int. Med., Univ. of Texas Med. Branch, 301 University Blvd., Galveston, TX, 77555,

[3]Univ. Space Res. Assn., NASA Johnson Space Ctr., 3600 Bay Area Blvd., Houston, TX, 77058.

The overarching goal of this investigation was to examine the efficacy of the next generation exercise countermeasures program designed for the International Space Station (SPRINT) on lower limb skeletal muscle health during 70 days of simulated weightlessness (6° head-down-tilt bedrest). Twenty-six individuals underwent bedrest only (BR, n=9), bedrest and an exercise training countermeasure (lower limb resistance training combined with moderate and high intensity aerobic treadmill and cycle training; BRE, n=9), or bedrest and the same exercise training countermeasure along with periodic supplementary low dose testosterone injections (BRE+T, n=8). Muscle biopsies were obtained from the vastus lateralis and soleus prior to and at the end of bedrest for the measurement of metabolic enzyme activities per mg muscle tissue (glycogen phosphorylase, citrate synthase, β-hydroxyacyl-CoA dehydrogenase) and capillarity (capillary density, capillary to fiber ratio, capillaries in contact with each fiber). In BR, vastus lateralis and soleus enzyme activities and capillarity were unchanged (P>0.05), suggesting these aspects of muscle health are proportionally lost with the whole muscle atrophy of the quadriceps (-10%) and triceps surae (-22%) after 70 days of bedrest. In BRE and BRE+T, vastus lateralis and soleus enzyme activities and capillarity were maintained at pre-bedrest levels (P>0.05), in conjunction with maintenance of quadriceps muscle mass (BRE: +3%, BRE+T: +5%) or partial preservation of triceps surae muscle mass (BRE: -7%, BRE+T: -6%). These findings suggest the SPRINT exercise countermeasures program was effective at maintaining the relative metabolic capacity and vascularity of the muscle, while the testosterone provided no additional benefit. To our knowledge, these findings represent the longest human unloading data to date for skeletal muscle enzymes of energy metabolism and capillary network, and suggest in the thigh and calf muscles these components of muscle performance and health generally scale with the atrophy induced by 70 days of unloading and inactivity. Sponsored by NASA grant NNX11AJ62G and NNX10AP86G.

18.23

B-CATENIN REGULATION OF SKELETAL MUSCLE HYPERTROPHY

Yuan Wen[1], Tyler Kirby[2], Alexander Alimov[1], Ivan Vechetti[1], and John McCarthy[1,3]

[1]Physiology, Univ. of Kentucky, 800 Rose St., Med. Ctr., Lexington, KY, 40536, [2]Weill Inst. for Cell and Molecular Biology, Cornell Univ., 439 Weill Hall, Ithaca, NY, 14853, [3]Ctr. for Muscle Biology, Univ. of Kentucky, 800 Rose St., Lexington, KY, 40536.

Cytoplasmic free β-catenin is tightly regulated as a downstream effector in the canonical Wnt signaling cascade, which is capable of implementing a cellular growth program during development and regeneration. A second and equally important function of β-catenin involves linking the cell cytoskeleton with the transmembrane protein, cadherin, which binds to its counterpart in a neighboring cell, thereby forming stable intercellular connections known as adherens junctions. Previous studies suggest that Wnt signaling is intimately involved in the regulation myogenesis and muscle repair, and that β-catenin may be a key contributor to hypertrophic growth in adult skeletal muscle. We generated an adult muscle-specific mouse model of Tamoxifen-induced β-catenin inactivation only in mature myofibers and not in satellite cells, and following 7 days of synergist ablation, it appears that loss of β-catenin leads to blunted myofiber hypertrophy (mean myofiber cross-sectional area increase of 13.10% vs. -1.02% in Vehicle and Tamoxifen treated plantaris, respectively). Additional outcomes of β-catenin inactivation within the myofibers is a decreased ability for myonuclear accretion (48.3% vs. 4.6% increase for Vehicle vs. Tamoxifen treated plantaris) and a concomitant increase in satellite cell proliferation (33.6% vs. 76.1% increase in Pax7+ nuclei for Vehicle vs. Tamoxifen). β-catenin and its interaction with cadherins on the myofiber side may be a necessary component of myofibers' receptivity to fusing myoblasts. Furthermore, loss of myofiber β-catenin may act as a mechanotransduction signal that promotes satellite cell entry into the "G_{alert}" phase.

18.24

ROLE OF MONOCARBOXYLATE TRANSPORTER 4 (MCT4) IN MUSCLE METABOLISM AND PHYSIOLOGY

Sara Bisetto[1], Emanuele Loro[2], Tejvir Khurana[2], and Nancy Philp[1]

[1]Dept. of Pathology, Anatomy and Cell Biology, Thomas Jefferson Univ., Jefferson Alumni Hall, 1020 Locust, Philadelphia, PA, 19107, [2]Dept. of Physiology and Pennsylvania Muscle Inst., Univ. of Pennsylvania, 750 Clinical Res. Bldg., 415 Curie Blvd., Philadelphia, PA, 19104.

Nearly 30 years ago George Brooks proposed the existence of a lactate shuttle that distributes lactate derived from highly glycolytic tissues to organs depending on oxidative phosphorylation. According to his model, what was previously considered a mere byproduct of glycolysis, had acquired a role in sustaining energy metabolism during exercise [1]. The transporters responsible for shuttling lactate were discovered only a decade later. The monocarboxylate transporter (MCT)s are proton-coupled transporters expressed in the plasma membrane of different tissues. The preferential localization of MCT4 in the sarcolemma of fast, glycolytic fibers and of MCT1 in slow, oxidative fibers makes them important components of the lactate shuttle in skeletal muscle. Based on their distribution and the affinity and capacity to transport lactate, MCT1 primarily regulates the transport of lactate into the cells, while MCT4 predominantly exports lactate outside the cells. Given the importance of the lactate for energy metabolism and muscle physiology, we hypothesized that interfering with/disrupting the shuttle will impair muscle function and cause exercise intolerance. To test this hypothesis, we used a global SLC16A3 (MCT4) knock out mouse model. A treadmill test performed on young (3-5 months old) and old (18 months old) $MCT4^{-/-}$ vs control male mice showed that $MCT4^{-/-}$ animals have impaired exercise capacity. Interestingly, female $MCT4^{-/-}$ mice performed better on the endurance test compare to WT littermates. Histological analysis of extensor digitorum longus (EDL) muscle of male animals showed no difference in fiber compositions. Immunofluorescence analysis of $MCT4^{-/-}$ EDL muscle sections showed increased MCT1 expression on

the plasma membrane of intermediate fiber types, suggesting a compensatory effect or a metabolic reprogramming of these muscle fibers. To study the effects of lack of MCT4 on muscle mechanical properties we performed *ex vivo* physiology on isolated EDL. MCT4$^{-/-}$ muscles generated less force than controls. Further experiments are necessary to evaluate the effects of lack of MCT4 on cardiovascular and respiratory function during exercise since heart and diaphragm use lactate as energy substrate during high intensity exercise. Our studies on the MCT4 KO mouse demonstrate for the first time the importance of the lactate shuttle in support of skeletal muscle function and energy metabolism during exercise. Funding source: Grant EY012042 to NJP**.** Reference: [1]Brooks GA. The lactate shuttle during exercise and recovery. Med Sci Sports Exerc 18: 360–8, 1986.

18.25

SKELETAL MUSCLE PHENOTYPE AND EXERCISE IN AGE AND DISEASE: NEUROMUSCULAR JUNCTION INSTABILITY AND TYPE I MYOFIBER GROUPING

Kelley Hammond[1], Neil Kelly[2], and Marcas Bamman[2]
[1]Physical Therapy, Univ. of Alabama at Birmingham, 1720 2nd Ave. S., SHPB 360X, Birmingham, AL, 35294-1212, [2]Cell, Developmental, and Integrative Biology, Univ. of Alabama at Birmingham, 1720 2nd Ave. S., MCLM 934, Birmingham, AL, 35294.

Aging skeletal muscle undergoes varying levels of denervation, whether central (i.e. alpha motor neuron death) or peripheral (i.e. neuromuscular junction (NMJ) deterioration). However, denervation may not always elicit myofiber death, as some denervated myofibers are reinnervated by a branching axon of another local motor neuron and incorporated into that new motor unit (MU). This reorganization of MUs can facilitate the integration of type II myofibers into a type I MU, causing those fibers to express slow myosin heavy chain (MHC; type I), yielding the appearance of type I myofiber grouping. **Purpose:** To assess NMJ degeneration within the context of type I myofiber grouping in Young and Older adults and Parkinson disease (PD) at baseline and following a resistance training (RT) intervention (3d/wk). **Methods:** Muscle tissue specimens were collected via percutaneous needle biopsy from the vastus lateralis in Young (25yr), Older (65yr), and PD (65yr). Myofibers were assessed by MHC expression for type, size, and grouping. Grouping was determined using a statistical model which includes type I distribution and nearest-neighbor methods. Western blotting and qPCR were used to assess markers of NMJ stability. We applied K-means cluster analysis to the Older data to derive three distinct clusters of individuals which displayed low, moderate, and high levels of type I myofiber grouping. **Results:** Percent of grouped type I myofibers is higher in Older and PD compared to Young ($p<0.05$). The average number of myofibers per group is higher in PD and Older (PD>Older>Young; $p<0.05$). The percent of maximal MU activation during a sit-to-stand task follows the same trend. The High cluster of the K-means is driving the large group size and extreme MU activation in Older adults ($p<0.05$). qPCR suggests the denervation signaling cascade is upregulated (Older and PD>Young; $p<0.05$). Protein markers of NMJ degeneration are higher in Older and PD. In Older only, RT reduces AChRD, HDAC4, and RUNX1 expression ($p< 0.05$). RT stimulates increased expression of AChRβ in PD only ($p<0.05$). **Conclusion:** Age- and PD-related changes to muscle include an increase in type I grouping and upregulation of the denervation signaling cascade. Grouping severity in Older and PD corresponds with NMJ instability. RT reduces select denervation-specific transcripts in Older only, while RT leads to an induction of AChRβ expression in PD only. Supported by NIH Grant T32HD071866 and the UAB Center for Exercise Medicine.

18.26

INFLUENCE OF 70 DAYS OF BEDREST AND THE NEXT GENERATION EXERCISE COUNTERMEASURES PROGRAM (SPRINT) ON SOLEUS SINGLE MUSCLE FIBER SIZE AND FUNCTION

Todd Trappe[1], Kiril Minchev[1], Greg Grosicki[1], Ryan Perkins[1], Holmes Finch[1], E. Lichar Dillon[2], Melinda Sheffield-Moore[2], Randall Urban[2], Jeffrey Ryder[3], Lori Ploutz-Snyder[3], and Scott Trappe[1]
[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave., Muncie, IN, 47306, [2]Dept. of Int. Med., Univ. of Texas Med. Branch, 301 University Blvd., Galveston, TX, 77555, [3]Univ. Space Res. Assn., NASA Johnson Space Ctr., 3600 Bay Area Blvd., Houston, TX, 77058.

The overarching goal of this investigation was to examine the efficacy of the next generation exercise countermeasures program designed for the International Space Station (SPRINT) on lower limb skeletal muscle health during 70 days of simulated weightlessness (6° head-down-tilt bedrest). Twenty-six individuals underwent bedrest only (BR, n=9), bedrest and an exercise training countermeasure (lower limb resistance training combined with moderate and high intensity aerobic treadmill and cycle training; BRE, n=9), or bedrest and the same exercise training countermeasure along with periodic supplementary low dose testosterone injections (BRE+T, n=8). Muscle biopsies were obtained from the soleus prior to and at the end of bedrest for the measurement of myosin heavy chain (MHC) I single muscle fiber size (cross-sectional area), strength (P_o), speed (V_o), power, and normalized power (i.e., muscle quality). In BR, MHC I fiber size (-23%), strength (-37%), power (-30%), and normalized power (-11%) decreased ($P<0.05$), while speed increased (+11%, $P<0.05$). In BRE, MHC I fiber size was maintained ($P>0.05$), while speed (+17%), power (+29%), and normalized power (+32%) increased ($P<0.05$). In BRE+T, MHC I fiber size (-23%), strength (-20%), speed (-3%), and power (-20%) decreased ($P<0.05$), while normalized power was maintained ($P>0.05$). The fiber type distribution of the soleus was ~70% MHC I prior to bedrest across the three groups. BR resulted in a reduction in MHC I (-7%) and a concomitant increase in MHC IIx (+10%). Exercise did not prevent the shift from MHC I in BRE (-7%), but contained the shift to the MHC IIa fiber type (+7%). BRE+T showed a large reduction in MHC I (-18%), resulting in a shift toward MHC IIa (+15%) and IIx (+3%) such that more than 50% of the soleus was comprised of Type II MHC at the end of bedrest. These findings suggest the SPRINT exercise countermeasures program was mostly suc-

cessful at targeting the slow twitch muscle fibers of the soleus. Testosterone attenuated the efficacy of the exercise program for the slow twitch fibers, and elicited a substantial shift towards a fast twitch phenotype. SPRINT appeared to be an improvement over previously published findings that examined International Space Station exercise programs with regard to the slow twitch component of the calf muscles, which historically have been difficult to protect during real and simulated long duration space flights. Sponsored by NASA grant NNX11AJ62G and NNX10AP86G.

18.27

INFLUENCE OF 70 DAYS OF BEDREST AND THE NEXT GENERATION EXERCISE COUNTERMEASURES PROGRAM (SPRINT) ON VASTUS LATERALIS SINGLE MUSCLE FIBER SIZE AND FUNCTION

Scott Trappe[1], Kiril Minchev[1], Greg Grosicki[1], Ryan Perkins[1], Holmes Finch[1], E. Lichar Dillon[2], Melinda Sheffield-Moore[2], Randall Urban[2], Jeffrey Ryder[3], Lori Ploutz-Snyder[3], and Todd Trappe[1]

[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave., Muncie, IN, 47306, [2]Dept. of Int. Med., Univ. of Texas Med. Branch, 301 University Blvd., Galveston, TX, 77555, [3]Univ. Space Res. Assn., NASA Johnson Space Ctr., 3600 Bay Area Blvd., Houston, TX, 77058.

The overarching goal of this investigation was to examine the efficacy of the next generation exercise countermeasures program designed for the International Space Station (SPRINT) on lower limb skeletal muscle health during 70 days of simulated weightlessness (6° head-down-tilt bedrest). Twenty-six individuals underwent bedrest only (BR, n=9), bedrest and an exercise training countermeasure (lower limb resistance training combined with moderate and high intensity aerobic treadmill and cycle training; BRE, n=9), or bedrest and the same exercise training countermeasure along with periodic supplementary low dose testosterone injections (BRE+T, n=8). Muscle biopsies were obtained from the vastus lateralis prior to and at the end of bedrest for the measurement of myosin heavy chain (MHC) I and IIa single muscle fiber size (cross-sectional area), strength (P_o), speed (V_o), power, and normalized power (i.e., muscle quality). In BR, MHC I fiber size (-13%), strength (-33%), power (-30%), and normalized power (-21%) decreased ($P<0.05$), with little change in MHC IIa muscle fibers. In BRE, MHC I and IIa fiber size and contractile performance were maintained ($P>0.05$) or increased [MHC IIa speed (+15%), power (+17%), normalized power (+14%); $P<0.05$]. In BRE+T, MHC I and IIa size and contractile performance were maintained ($P>0.05$), with the exception of normalized power which was decreased ($P<0.05$) in MHC I fibers (-15%). These data show the SPRINT exercise program maintained or improved vastus lateralis myocellular size and function. In fact, the increased speed and power of the fast muscle fibers was most likely due to the high intensity intervals in the SPRINT exercise program. Testosterone did not provide any clear myocellular benefit compared to exercise alone and appeared to limit the impact of the exercise on slow and fast muscle fiber quality. The SPRINT exercise program appears to be a viable exercise program for the thigh muscles during long duration bedrest and would likely translate to long duration space flight. Sponsored by NASA grant NNX11AJ62G and NNX10AP86G.

18.28

EXPRESSION OF MUSCLE SPECIFIC RIBOSOMAL PROTEIN L3-LIKE IS UP-REGULATED DURING POST-NATAL DEVELOPMENT

Laura Peterson[1], Alexander Alimov[1], and John McCarthy[1]

[1]Physiology, Univ. of Kentucky, 800 Rose St., Lexington, KY, 40503.

We reported that over-expression of the muscle-specific ribosome protein L3-like (Rpl3l) inhibited myotube growth suggesting that Rpl3l might regulate skeletal muscle hypertrophy. To further investigate the role of Rpl3l in skeletal muscle we generated an antibody against mouse Rpl3l and an inducible Rpl3l knockout mouse. Using the Rpl3l antibody we found, consistent with previous microarray data, that Rpl3l protein is not detectable in one day old (P1) skeletal muscle by Western blot analysis; however, Rpl3l expression is then progressively increased during post-natal development whereas Rpl3 protein is concomitantly down-regulated such that by 8 weeks of age, Rpl3l is highly expressed in skeletal muscle and Rpl3 is barely detectable. Ribosome isolation conclusively demonstrated for the first time that endogenous Rpl3l protein is associated with ribosomes, providing further evidence to support the idea that ribosomes in adult skeletal muscle are specialized. To determine the importance of Rpl3l in skeletal muscle we generated a novel mouse strain using the Flexible Accelerated STOP Tetracycline Operator-Knockin (FAST) system to manipulate Rpl3l gene expression. As expected based on Rpl3l expression, inhibition of Rpl3l expression was not embryonic lethal as mice were born according to Mendelian genetics. Initial observations suggest the loss of Rpl3l expression does not adversely affect post-natal development. Ongoing studies are characterizing skeletal muscle phenotype in adult mice to determine if loss of Rpl3l expression affects muscle fiber size and fiber-type composition. This study is supported by grant NIH AR064896-02.

19.0 ACTIVITY AND EXERCISE DURING PREGNANCY AND EARLY DEVELOPMENT: IMPLICATIONS FOR LONG-TERM HEALTH

19.1

PATERNAL EXERCISE REDUCES ENERGY EXPENDITURE IN OFFSPRING AND ALTERS DNA METHYLATION AND SPERM MICRORNA CONTENT

Alexander Murashov[1], Elena Pak[1], and P. Darrell Neufer[1]

[1]Physiology, East Carolina Univ., 600 Moye Blvd., Brody Bldg., 6N-98, Greenville, NC, 27858.

Metabolic disorders often run in families indicating importance of both genetic factors as well as family diet and lifestyle. The association between maternal obesity and metabolic disorders in offspring has long been known, however, recent observations indicate that fathers may also contribute to offspring metabolic phenotype through presently unknown mechanism. Growing body of research indicates that paternal high fat diet may result

in transgenerational inheritance of the insulin-resistant phenotype. Although diet-induced epigenetic reprogramming *via* paternal lineage has recently received much attention in the literature, the effect of paternal physical activity on offspring metabolism has not been adequately addressed. In the current study, we investigated the effects of long-term free wheel-running in C57BL/6J male mice on their offspring's metabolic phenotype. Our observations show that fathers subjected to wheel-running for 12 weeks produced more metabolically efficient offspring. As a result, the offspring became more susceptible to the adverse effects of a high-fat diet challenge, manifested in increased body weight and adiposity, impaired glucose tolerance, and elevated insulin levels. Long-term paternal exercise also altered expression of several metabolic genes, including *Ogt*, *Oga*, *Pdk4*, *H19*, *Glut4*, and *Ptpn1*, in offspring skeletal muscle. To begin elucidating the potential molecular mechanism of offspring epigenetic programing, paternal sperm was analyzed for changes in methylation of gene promoter regions and in miRNA content. We observed a significant increase in methylation in promotor regions of OGT, Ptpn1, and H19 in F0 exersized mice, in comparison to the methylation levels in sedentary fathers. Long-term exercise also changed miRNA content in F0 spermatozoa. A significant increase was observed for miR-483-3p, -431, and -21. Together our findings suggest that paternal exercise programs offspring for a thrifty phenotype possibly via changes in DNA methylation and/or miRNA-induced modifications. Evolutionarily, this may be an adaptive mechanism of changing offspring phenotypic features in response to environmental challenges experienced by fathers. This research was supported by a seed grant from the East Carolina Diabetes and Obesity Institute, East Carolina University (to A.M.), and was supported in part by a U.S. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases Grant R01 DK096907 (to D.N.).

19.2

EXERCISE DURING PREGNANCY AND LONG-TERM IMPACT ON OFFSPRING HEALTH

Kevin Pearson[1]
[1]Pharmacology and Nutritional Sci., Univ. of Kentucky, 900 S. Limestone, Wethington Rm. 591, Lexington, KY, 40536-0200.

Aging, in part, is due to a decrease in stress resistance and the accumulation of reactive oxygen species over time in an organism. A goal of gerontological research is to decrease stress and age-related disease progression. To date, caloric restriction has been the most reproducible and promising intervention to improve these outcomes. An intense and expanding area of research is focused on discovering other short-term or easily achievable interventions that can have long-lasting beneficial effects, such as caloric restriction mimetics. Instead, our work explores maternal exercise during pregnancy as a potential short-term intervention that can provide a lifetime of benefits for the next generation. In a mouse study, we observed that voluntary exercise during pregnancy and nursing protected against chemical-induced carcinogenesis in adult male and female offspring. Markers of oxidative stress and inflammation were decreased in offspring born to exercised dams compared to those born to sedentary dams. In a separate study, we found that both male and female mouse offspring born to exercised dams had significantly enhanced insulin sensitivity during adulthood compared to offspring born to sedentary moms. Enhancing stress resistance and improving insulin sensitivity could help delay the onset of numerous age-associated diseases. While our studies have been completed in rodents, we are currently working on projects that extend our work to humans. Utilizing neonatal foreskin tissue, which is readily available following circumcision, we have shown that dermal primary fibroblasts can be isolated and grown in culture for living functional studies to examine developmental programming in humans. Our findings highlight pregnancy as a sensitive period when positive lifestyle interventions could have significant and long-lasting beneficial effects on offspring metabolism and disease risk. We believe that mothers will adhere to exercise during pregnancy if we can demonstrate lifelong benefit for their unborn children. Further, understanding what mechanisms maternal exercise alters in offspring may highlight pharmacological therapies for women who cannot exercise during pregnancy. Funding from NIH grants DK090460, CA165086, GM103527, and ES007380.

19.3

IMPACT OF EARLY-LIFE EXERCISE ON ADULT PHYSICAL ACTIVITY AND RELATED PHENOTYPES

Theodore Garland, Jr.[1]
[1]Evolution, Ecology, and Organismal Biology, Univ. of California, Riverside, Dept. of Biology, Riverside, CA, 92521.

Physical activity is a complex trait, initiated by the central nervous system but actuated through peripheral systems. Moreover, feedback from peripheral tissues (e.g., muscle) can affect motivation for activity. In humans and lab rodents, higher levels of physical activity are generally associated with positive health outcomes, although excessive exercise can have adverse consequences. Numerous genetic and environmental influences on adult physical activity have been identified, but effects of experiences during early-life are not well understood. "Early-life" effects can occur at any point prior to sexual maturity, while the brain and body continue to develop, including alterations of sperm or eggs that occur prior to conception, during gestation or egg development, around birth, and while experiencing maternal or paternal provisioning and care (e.g., via lactation). Numerous questions follow from this broad definition. For example, does maternal exercise increase the level of offspring physical activity and/or improve offspring health? Do school physical education programs increase the likelihood of adult activity? Parents' physical activity during pregnancy and early in a child's life is positively associated with the child's physical activity at 11-12 years (Mattocks et al 2008), but this could reflect either environmental effects or genetic inheritance. The few existing experiments with lab rodents show that early-life exercise can affect adult physical activity and related phenotypes. In mice, for example, 3 weeks of wheel access beginning at weaning increased adult voluntary wheel running (but not cage activity) when measured 8 weeks later, although the effect was transitory, and altered adult circulating leptin levels in a genotype-dependent manner (Acosta et al 2015). Also in mice, maternal exercise before and during pregnancy caused adult offspring to be more

physically active (Eclarinal et al 2016). These sorts of developmental-programming effects have important implications for public policy and for understanding the movement ecology and exercise physiology of wild animals. References: Mattocks C, A Ness, K Deere, K Tilling, S Leary, SN Blair, C Riddoch. 2008. BMJ 336:26; Acosta W, TH Meek, H Schutz, EM Dlugosz, KT Vu, T Garland Jr. 2015. Physiol Behav 149:279; Eclarinal JD, S Zhu, MS Baker, ML Fiorotto, RA Waterland. 2016. FASEB J. 30:2541. (NIH/NICHD R21HD075021).

20.0 IMPACT OF EXERCISE ON ADIPOSE TISSUE METABOLISM-BEYOND BROWNING

20.2
EXERCISE EFFECTS ON ADIPOCYTE CELL SIZE AND EXPANDABILITY

Jeffrey Horowitz[1]
[1]Univ. of Michigan, 401 Washtenaw Ave., Ann Arbor, MI, 48109-2214.

Excessive systemic fatty acid mobilization and the resultant ectopic lipid accumulation are central to the development of insulin resistance, which in turn underlies many obesity-related diseases. Importantly, the vast majority of the fatty acids delivered into the systemic circulation are derived from subcutaneous adipose tissue (predominantly abdominal subcutaneous) rather than visceral fat. Therefore, attenuating systemic fatty acid mobilization by enhancing the fatty acid storage capacity of subcutaneous adipose tissue (without increasing adiposity) has important health implications. Regular exercise is often found to improve insulin sensitivity, but whether exercise directly evokes structural and/or metabolic adaptations in subcutaneous adipose tissue to modify fatty acid release remains unresolved. Understanding the direct effects of exercise on adipose tissue (independently of even modest weight loss) is particularly important because most findings suggest exercise programs without dietary intervention do not typically result in weight loss over the long-term. If exercise expands the fatty acid storage capacity of subcutaneous adipose tissue, it may do so via augmenting adipocyte hyperplasia (adipogenesis) and/or hypertrophy. Adipogenesis is a complex process controlled in part by the transcription factors peroxisome proliferator-activated receptor-gamma (PPARγ) and CCAAT/enhancer-binding proteins (C/EBPs). Interestingly, many adipogenic activators (e.g., fatty acids, IGF-1, cortisol, angiotensin, prostacyclin) are commonly elevated during and after a session of exercise. Adipocyte hypertrophy is also very complex, requiring integrated adaptions of the adipose extracellular matrix to allow for the physical expansion of the adipocytes, as well as enhanced angiogenesis to accommodate nutrient exchange for the expanded cell. If regular exercise does indeed enhance subcutaneous adipose tissue storage capacity, this may not be clinically relevant until periods of weight gain. Subcutaneous adipose tissue from a regular exerciser may be primed for more effective energy storage during episodes of energy surplus, which may reduce ectopic lipid deposition, lower pro-inflammatory pathway activation, and protect against insulin resistance in response to weight gain. (NIH R01 DK077966, NIH P30 DK-089503, ADA 1-16-ICTS-048, ADA 1-13-TS-27).

20.4
EXERCISE TRAINING, ADIPOCYTE PRECURSORS AND THE REGULATION OF LIPID METABOLISM

Matthew Watt[1], Arthe Raajendiran[1], Thomas Tsiloulis[1], Marcelo Flores Opazo[2], and Paul Burton[3]
[1]Metabolic Dis. and Obesity Program, Monash Univ., 26 Innovation Walk, Clayton, 3800, Australia, [2]Physiology, Univ. of Melbourne, Melbourne, 3052, Australia, [3]Ctr. for Obesity Res. and Edu., Monash Univ., Alfred Hosp., Prahran, 3181, Australia.

Obesity induced by adipose tissue expansion is associated with metabolic diseases, including type 2 diabetes. However, not all adipose tissue is the same. Expansion of visceral (VAT) and abdominal subcutaneous (ASAT) adipose tissues is associated with metabolic disease and, in contrast, expansion of gluteal and femoral (GFAT) adipose tissue most likely protects against metabolic disease. Whether the intrinsic, cell-autonomous properties of adipocytes located within these regions confer these metabolic differences is unknown. We identified three unique adipocyte precursor cell (APC) populations in the adipose tissue by Fluorescent Activated Cell Sorting using the cell surface markers CD31, CD45, CD29, and CD34. RNASeq analysis demonstrated a distinct transcriptome of these cells and functional analysis identified different proliferative capacities but similar adipogenic potential. The APCs are more highly populated in GFAT compared with VAT and ASAT. Functional analysis using radiolabelled glucose and fatty acid tracers identified a population of adipocytes that have robust lipid turnover and responsiveness to beta-adrenergic stimulation and another that is characterized by slow fatty acid turnover. Together, these studies identify the likelihood that specific APCs generate adipocytes with distinct metabolic functions; however, it is unlikely that differences in the APC populations explain the apparent metabolic differences between adipocytes located in different anatomical regions. In follow up studies we asked whether the intrinsic properties of the APCs can be stably modified by endurance exercise training. These ongoing studies will be presented and the implications discussed.

21.0 PLENARY LECTURE

21.1
ADAPTIVE RESPONSES OF NEURONAL MITOCHONDRIA TO EXERCISE

Mark Mattson[1]
[1]Lab. of Neurosciences, 251 Bayview Blvd., Ste. 100, Rm. 5C218, Baltimore, MD, 21224.

Mammals, including humans, evolved in environments where food was not continuously available, and it was therefore of critical importance for their survival that their brain and neuromuscular systems be functioning optimally so that they could 'figure out' how to find food and be able to expend the necessary physical effort required to obtain the food (e.g, tracking, catching and killing prey). The general mechanism by which exercise and fasting are beneficial to neurons is by engaging coordinated inter- and intra-cellular signaling pathways that promote synaptic plasticity, neurogenesis and cellular stress resistance (Stranahan and Mattson, 2012; *Nat Rev Neurosci.* 13:209-216).

We have obtained data suggesting that running wheel exercise, fasting and excitatory synaptic activity stimulate **mitochondrial biogenesis** by mechanisms involving BDNF signaling and the master transcriptional regulator of mitochondrial biogenesis PGC-1□. We found that PGC-1□ is of critical importance in the both formation of synapses during development and the maintenance of synapses in the adult hippocampus (Cheng et al., *Nature Commun.* 2012; 3:1250. In other studies, we found that the **mitochondrial protein deacetylase SIRT3** mediates adaptive responses of neurons to bioenergetic and excitatory stress, and exercise (Cheng et al. *Cell Metab.* 2016; 23:128-142). Neurons lacking SIRT3 are vulnerable to glutamate-induced calcium overload and excitotoxicity and mitochondrial stress, and AAV-mediated overexpression of SIRT3 is neuroprotective. In models relevant to Huntington's disease and epilepsy, SIRT3-deficient mice exhibit increased vulnerability of striatal and hippocampal neurons, respectively. SIRT3 deficiency results in hyperacetylation of several mitochondrial proteins, including SOD2 and cyclophilin D. Running wheel exercise and fasting increase the expression of SIRT3 in hippocampal and cortical neurons, which is mediated by excitatory glutamatergic neurotransmission and is essential for mitochondrial protein acetylation homeostasis and the neuroprotective effects of running. Thus, SIRT3 may play pivotal roles in adaptive responses of neurons to excitatory and bioenergetic challenges and resistance to degeneration. Finally, in addition to brain intrinsic pathways by which exercise bolsters neuronal mitochondrial bioenergetics and stress resistance, we have found that the ketone □-hydroxybutyrate, which is produced during fasting and vigorous exercise can stimulate BDNF production, which likely contributes the effects of these evolutionarily fundamental bioenergetic challenges on neuronal plasticity and stress resistance. Supported by the Intramural Research Program of the National Institute on Aging.

22.0 SIGNALING

22.1
FIBER-TYPE DEPENDENT DIFFERENCES IN ANABOLIC RESPONSE OF RAT SKELETAL MUSCLE TO RESISTANCE EXERCISE

Ryo Takagi[1], Riki Ogasawara[2], Jyunya Takegaki[1], Arata Tsutaki[3], Koichi Nakazato[3], and Naokata Ishii[1]
[1]Dept. of Life Sci., Univ. of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo, 153-8902, Japan, [2]Dept. of Life and Materials Eng., Nagoya Inst. of Technology, Gokiso-cho, Showa-ku, Nagoya, Aichi, 466-8555, Japan, [3]Grad. Sch. of Hlth. and Sport Sci., Nippon Sport Sci. Univ., 7-1-1 Fukasawa, Setagaya-ku, Tokyo, 158-8508, Japan.

Purpose: Anabolic responses of skeletal muscle to fasting and synergist ablation have been shown to differ between fiber types (1). However, fiber-type dependence of the responses to resistance exercise (RE) remains unclear. This study aimed to see whether the protein synthesis after RE differs between fiber types. **Methods**: 14-wk old male Wistar rats were used. The right gastrocnemius muscle was subjected to RE consisting of moderate eccentric contractions as previously reported with slight modifications (2); tetanic contractions were electrically evoked at supramaximal voltage with simultaneously applied isokinetic dorsiflexion of the ankle joint. Either prior to or 6-h after RE, the muscles were excised and subjected to immunohistochemical analyses. Surface sensing of translation technique was used to measure protein synthesis. For this purpose, the animals were kept fasted for 12-h prior to the excise. **Results**: RE caused an increase of protein synthesis in all fiber types, where myosin heavy chain (MHC) IIx fibers were more responsive to RE than MHC I and IIb fibers. In addition, phosphorylation of ribosomal protein S6 (rpS6) ($Ser^{240/244}$) increased after RE in MHC IIx and IIb fibers, indicating elevated translational efficiency (1). Here, MHC IIx fibers were seen to be more responsive than MHC IIb fibers, too. However, MHC I and IIa fibers did not show significant increase in phosphorylated rpS6. **Conclusion**: RE caused increase of protein synthesis in all fiber types, with the largest magnitude of increase in MHC IIx fibers. This fiber-type dependence would not simply be caused by the difference in translational efficiency at a specific point in time.
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22.2
SKELETAL MUSCLE-SPECIFIC DELETION OF TAK1 ACTIVATES AMPK AND AUTOPHAGY IN MICE

Shuichi Sato[1,2], Sajedah Hindi[2], Guangyan Xiong[2], and Ashok Kumar[2]
[1]Kinesiology, Univ. of Louisiana at Lafayette, Bourgeois Hall, Rm. 123-B, 225 Cajundome Blvd., Lafayette, LA, 70506, [2]Anatomical Sci. and Neurobiology, Univ. of Louisville, Sch. of Med., 511 S. Floyd, Rm., 111, Louisville, KY, 40202.

TGFβ-activated kinase 1 (TAK1) is a member of the MEK kinase (MAP3K) family and a downstream molecule of pro-inflammatory cytokine signaling such as TNF-α and TNF-like weak inducer of apoptosis (TWEAK). Our previous study has demonstrated that TAK1 is necessary for the survival and proliferation of satellite cells during regenerative myogenesis in vitro and in vivo. However, the role of TAK1 in the regulation of skeletal muscle phenotype is unknown. The purpose of this study was to determine if a lack of TAK1 in skeletal muscle alters skeletal muscle mass and metabolism in adult mice. Skeletal muscle-specific TAK1 knockout ($TAK1^{mko}$, n=5) mice were generated by crossing HSA-cre mice with floxed TAK1 ($TAK1^{f/f}$) mice. Tamoxifen was injected intraperitoneally to inactivate TAK1 followed by tamoxifen-containing standard diet. $TAK1^{f/f}$ mice (n=6) were used as control. Exercise tests and glucose tolerance test (GTT) were performed prior to sacrifice and all mice were sacrificed at approximately 3 months of age. Gastrocnemius (GAS) and tibialis anterior (TA) muscles were excised for further analysis. Body and TA muscle weights were smaller in $TAK1^{mko}$ mice (14% and 10%, respectively) com-

pared to TAK1$^{f/f}$ mice. TAK1^{mko} mice showed lower grip strength (39%) in harmony with smaller mean fiber-cross sectional area in TA muscle (42%). Although genetic ablation of TAK1 in skeletal muscle increased phosphorylation levels of AMPK in GAS muscle, no difference was observed in exercise capacity or GTT between two groups. TAK1^{mko} mice exhibited increased mRNA levels of TNF-α and TNFR1 as well as up-regulation of autophagy-associated gene and protein expressions in GAS muscle. Taken together, these data indicate that deletion of TAK1 promotes autophagy via AMPK activation, which potentially leads to skeletal muscle atrophy in the mice. Supported by NIH Grant R01AR059810, R01AG029623, and R01AR068313 to AK.

22.3

RESISTANCE TRAINING IMPROVES INSULIN-STIMULATED AKT ACTIVATION CONCOMITANT WITH INCREASED APPL1 EXPRESSION IN SKELETAL MUSCLE OF TYPE 2 DIABETIC RATS

Kohei Kido[1], Satoru Ato[1], Yusuke Nishimura[1], Tatsuki Miyake[1], Koji Sato[2], and Satoshi Fujita[1]

[1]Fac. of Sport and Hlth. Sci., Ritsumeikan Univ., 1-1-1 Nojihigashi, Kusatsu, Japan, [2]Grad. Sch. of Human Development and Environment, Kobe Univ., 3-11 Tsurukabuto, Nadaku, Kobe, Japan.

Introduction: It is well known that chronic aerobic (AT) and/or resistance training (RT) improve skeletal muscle (SM) insulin resistance in type 2 diabetes (T2D). However, the molecular mechanisms of improvement in insulin sensitivity by exercise, especially RT, is still unclear. Recently, adapter protein containing PH domain, PTB domain, and leucine zipper motif 1 (APPL1) has recently been reported as a positive regulator for Akt activation and subsequent glucose uptake. Additionally, a previous study showed that APPL1 expression was reduced in SM of obese animals, but was improved by AT. Accordingly, we hypothesized that chronic RT recovers attenuated APPL1 expression and improves insulin-stimulated Akt activation in SM. Purpose: To investigate whether chronic RT improves APPL1 expression and insulin-stimulated Akt activation, and to identify the relationship between APPL1 expression and insulin-stimulated Akt activation in SM of T2D rats. Methods: LETO and OLETF rats were used as control and T2D models, respectively. The right gastrocnemius muscles in 20 weeks aged LETO (LE-RT) and OLETF rats (OL-RT) were isometrically exercised with RT via percutaneous electrical stimulation (total of 18 sessions in 6 wks), while the left gastrocnemius muscle served as the control (LE-CT and OL-CT). One week after the completion of final RT bout, 12 h-fasted LETO and OLETF rats were injected with insulin (0.5 U/kg) and were sacrificed 30 min after the injection. Their gastrocnemius muscle were removed, and analyzed using western blotting analysis to assess the phosphorylation status of Akt (Ser473; p-Akt) and GSK3β(Ser9; p-GSK3β) as well as the expression level of APPL1. Results: The fasting blood glucose level in OLETF was significantly higher than LETO after the intervention ($p<0.01$). RT significantly increased gastrocnemius muscle wet weight in both groups ($p<0.01$). Insulin-stimulated p-Akt was significantly reduced in OL-CT as compared with LE-CT, but significant improvement was seen in OL-RT ($p<0.05$). p-GSK3β in response to insulin was also increased significantly in OL-RT as compared with OL-CT ($p<0.05$). Additionally, baseline expression of APPL1 was significantly increased in OL-RT as compared with OL-CT ($p<0.05$). Furthermore, APPL1 expression significantly correlated with insulin-stimulated p-Akt and p-GSK3β level in control and trained muscle ($p<0.01$). Conclusions: RT improves insulin-stimulated Akt activation concomitant with increased APPL1 expression in the skeletal muscle of T2D rats. Moreover, insulin-stimulated Akt activation was significantly correlated with APPL1 expression level.

22.4

INHIBITION OF LPCAT3 ENHANCES INSULIN SIGNALING AND DECREASES PPARγ TRANSCRIPTIONAL ACTIVITY IN SKELETAL MUSCLE

Patrick Ferrara[1], and Katsuhiko Funai[1,2]

[1]Dept. of Kinesiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27858, [2]Dept. of Physiology, East Carolina Diabetes and Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27858.

Aberrant lipid metabolism has been linked to skeletal muscle insulin resistance. The exact identity of the lipid species that promote skeletal muscle insulin resistance among the human population remains unclear. In this study we utilized primary muscle cells isolated from lean-insulin sensitive (LN) or obese insulin-resistant (OB) individuals to characterize differences in the muscle lipidome free of contaminating cell types. OB muscles contained lower levels of various species of lysophospholipids (lyso-PLs) compared to LN, a finding that has never been previously described. RNAseq experiments in the same set of samples identified three genes involved in lyso-PL metabolism (PPAP2A, LPIN3, and LPCAT3) to have greater expression in OB vs. LN. Strikingly, lentivirus-mediated deletion of LPCAT3 in C2C12 myotubes resulted in increased insulin signaling (phosphorylation of IR, Akt, and AS160) in the absence of, and at various concentrations of insulin. Transcriptional factor peroxisome proliferator-activated receptor γ (PPARγ) is known to affect skeletal muscle insulin sensitivity. Deletion of LPCAT3 resulted in a significant decrease in the transcriptional activity of PPARγ and expression of its target gene aP2. LPCAT3 deletion had no effect on cell morphology, myotube differentiation, fiber type, or abundance of enzymes of the electron transport chain. Future studies will focus on the cellular mechanisms by which LPCAT3 modulates PPARγ activation and how this might potentially mediate the insulin-sensitizing effect of LPCAT3 deletion in skeletal muscle. This study was supported by NIH grants DK095774 and DK109888.

22.5

PROLONGED FASTING SUPPRESSES MTORC1 SIGNALING IN RESPONSE TO RESISTANCE EXERCISE IN RAT SKELETAL MUSCLE

Kohei Sase[1], Satoru Ato[1], Kohei Kido[1], Tatsuki Miyakee[1], and Satoshi Fujita[1]

[1]Sport and Hlth. Sci., Ritsumeikan Univ., Noji higashi 1-1-1, Kusatsu, Japan.

Introduction: Skeletal muscle mass is important for muscle strength and exercise performance, especially in athletes. It is well known that resistance exercise (RE) increases protein synthesis through mTORC1 signaling pathway and causes skeletal muscle hypertrophy. A lot of athletes in weight-class sports reduce their body weight to qualify their competitions by rapid weight loss (i.e. severe food restriction including fasting or skipping meals). These severe food restrictions activate skeletal muscle AMPK. Previous studies have reported that AMPK activation attenuates mTORC1 signaling and subsequent protein synthesis. Accordingly, severe food restrictions-induced AMPK activation may hinder RE-induced mTORC1 signal activation. However, the effect of RE on skeletal muscle mTORC1 signal during severe food restrictions has not been reported. Therefore, this study investigated the effect of severe food restriction-induced AMPK activation on RE-induced mTORC1 signaling activation inskeletal muscle. **Methods**: Male Sprague-Dawley rats were divided into four groups: non-exercise control with overnight fasting group (C), 72 h fasting group (F), RE after overnight fasting group (E) and RE after 72 h fasting group (FE). The animals in exercise groups were sacrificed and muscle samples were taken at immediately after and 3 h after resistance exercise. RE was conducted by percutaneous electrical stimulation in right gastrocnemius muscle. Western blotting analysis was used to measure phosphorylation status of signaling proteins associated with mTORC1 pathway. **Results**: Phosphorylation of AMPK (Thr172) was significantly increased in 72 h fasting group as compared with control group. Phosphorylation of mTOR (Ser2448) was significantly increased immediately after in RE after overnight fasting group, but there was no significant difference in phosphorylation of mTOR (Ser2448) in RE after 72 h fasting group. Phosphorylation of p70S6K and rpS6 was significantly increased 3 h after RE in both groups, but the phosphorylations were significantly suppressed in RE after 72 h fasting group as compared with RE after overnight fasting group. **Conclusion**: mTORC1 signal is activated by RE in both fed and fasted state, but prolonged fasting attenuates the RE-induced activation of mTORC1 as compared with fed state.

22.6
THE ROLE OF INTEGRINS IN THE REGULATION OF MECHANICAL STRESS-INDUCED MYOTUBE HYPERTROPHY *IN VITRO*

Masahiro Iwata[1,2], Wakako Tsuchida[1], Yoshita Ohno[2], Shingo Matsuo[1,2], Mitsuhiro Fujiwara[2,3], Yuji Asai[1], and Shigeyuki Suzuki[2]

[1]Dept. of Rehabilitation, Nihon Fukushi Univ., 26-2 Higashihaemi-cho, Handa, 475-0012, Japan, [2]Program in Physical and Occupational Therapy, Nagoya Univ. Grad. Sch. of Med., 1-1-20 Daikominami, Higashi-ku, Nagoya, 461-8673, Japan, [3]Dept. of Rehabilitation, Kamiiida Rehabilitation Hosp., 3-57 Kamiiidakitamachi, Kita-ku, Nagoya, 462-0802, Japan.

Mechanical stimuli increase skeletal muscle growth in a mammalian target of rapamycin (mTOR)- and p70 S6 kinase (p70S6K)-dependent manner. It has been proposed that costumeric proteins at Z bands sense tension and transfer this information to these initiators of protein translation, but few such proteins have been identified. The purpose of this study was to examine the role of integrins in the activation of hypertrophic signaling and growth in response to passive mechanical stretch in C2C12 cells. Fully differentiated C2C12 myotubes were subjected to 15% cyclic uniaxial stretch for 72 hours at a frequency of 1/6 Hz. Consistent with previous studies, mechanical stretch increased C2C12 myotube diameter. This effect was abolished by the mTOR inhibitor rapamycin or an arginine-glycine-aspartate (RGD)-containing disintegrin, echistatin. We next evaluated the temporal pattern of signaling through phosphatidylinositol 3-kinase (PI3K)/Akt and mTOR in response to mechanical stretch. Our results indicated that activation of signaling through PI3K/Akt, as assessed by Akt phosphorylation status (T308 and S473), is a transient event (<60 min), while activation of mTOR, as indicated by a significant increase in p70S6K phosphorylation at T389 and T421/S424, is sustained for a long duration (>24 h). Furthermore, inhibition of PI3K by wortmannin was sufficient to block the stretch-induced activation of Akt but not that of mTOR. Pretreatment with echistatin blocked the mechanical stretch-induced activation of mTOR, with no effect on Akt signaling. We also determined that the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK)-dependent pathway was activated by mechanical stretch. Echistatin blocked the stretch-induced activation of ERK1/2 (increased phosphorylation of T202/204), whereas rapamycin did not. These observations indicate that, in addition to regulating myotube hypertrophy, integrins plays a critical role in the response of skeletal myotubes to mechanical stimuli by activating downstream components of mTOR and ERK activity.

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22.7
RESISTANCE EXERCISE AND PROTEIN/CARBOHYDRATE INGESTION ALTERS MTORC1 CELLULAR LOCALIZATION AND PROTEIN COMPLEX INTERACTION IN HUMAN SKELETAL MUSCLE

Chris McGlory[1], Nathan Hodson[2], Everson Nunes[1], Sara Oikawa[1], Evelyn Tsakiridis[1], and Stuart Phillips[1]

[1]Kinesiology, McMaster Univ., 1280 Main St. W., Hamilton, ON, L8S4K1, Canada, [2]Sch. of Sport, Exercise and Rehabilitation Sci., Univ. of Birmingham, Edgbaston, Birmingham, B152TT, UK.

Exercise- and feeding-induced increases in skeletal muscle protein synthesis are dependent on increased activity of the mechanistic target of rapamycin complex 1 (mTORC1). Mechanisms of mTORC1 activation in human skeletal muscle are still not fully understood. Cell- and rodent-based studies have reported that mTORC1 translocates to the lysosome in response to anabolic signals such as amino acids, growth factors, and contractions. However, the spatial localization of mTORC1 in human skeletal muscle in response to exercise and nutrition is largely unknown. To address this question, 8 healthy males (22±3yr; 80±9kg; 1 repetition maximum leg extension 87±5kg

[all data mean±SEM]) completed 4 sets of unilateral knee extension at 70%1RM interspersed with a 2min rest interval, followed by the immediate consumption of a beverage (Gatorade Recover®) that provided 20, 44, and 1g of protein, carbohydrate, and fat respectively to achieve marked hyperinsulinemia and aminoacidemia. Skeletal muscle samples were collected from the *vastus lateralis* pre-exercise, and at 1h and 3h post-exercise from both the exercised (EXFED) and non-exercised (FED) legs. Visualization of mTOR and associated proteins was via immunofluorescence labelling, whilst surrogate measurements of mTORC1 activity were performed using immunoblotting. Pre-exercise, mTOR was strongly associated with the lysosome-associated membrane protein (LAMP2 positive staining). In response to feeding and exercise, co-localized mTOR/LAMP2 was redistributed from within to the membrane of the myofiber, with a (27±15%), and (40±14%) increase in mTOR/WGA association observed at 1h in FEDEX and FED respectively. The magnitude of this localisation continued to increase in EXFED at 3h (48%±7% from pre exercise) whereas localisation began to decrease in FED (22±11% from pre exercise). This increase in mTOR-lysosomal association with the myofiber membrane coincided with an increase in 'mTOR activity' at 1h in EXFED only (100±10-fold change from pre exercise in ribosomal protein S6 Ser240/244 phosphorylation). Collectively, these data suggest that the spatial localization of mTOR/lysosomal co-localized proteins are associated with the anabolic signalling responses to resistance exercise and protein/carbohydrate ingestion. Supported by the National Sciences and Engineering Council of Canada (NSERC).

22.8

POSSIBLE ROLE OF MITOCHONDRIALLY-DERIVED PEPTIDES IN MEDIATING RETROGRADE SIGNALING IN MAMMALIAN MUSCLE

Ashley Oliveira[1], and David Hood[1]
[1]Mus. Hlth. Res. Ctr., Sch. of Kinesiology and Hlth. Sci., York Univ., 4700 Keele St., Toronto, M3J 1P3, Canada.

Mitochondria exist in a dynamic reticulum within the cell and rely heavily on the coordination of the mitochondrial and nuclear genomes for their maintenance and expansion. Since over 99% of mitochondrial proteins are nuclear-encoded, mitochondria require a highly regulated method of protein import, as well as the capacity to fold proteins upon entry into a mature conformation. The maintenance of a properly folded mitochondrial proteome is achieved through a compartment-specific mechanism termed the unfolded protein response (UPR^{mt}). The UPR^{mt} has been well characterized in *C. elegans,* but little is known of its regulation in mammalian systems, particularly in skeletal muscle. In *C. elegans*, misfolded proteins are degraded and the subsequent peptides are released into the cytosol, where they inhibit the protein import machinery. The consequence of this is that a protein termed ATFS-1 is not imported, but rather translocated into the nucleus in a retrograde fashion where it acts as a transcription factor to upregulate the expression of mitochondrial chaperones and proteases. To assess the possibility of proteolytically-derived peptides having a role in retrograde signaling in a mammalian model, mitochondria were isolated from skeletal muscle of C57BL6 mice. Following isolation, mitochondria were incubated at 30° to allow for proteolysis and the subsequent release of peptides into the medium. To evaluate the effect of these peptides on mitochondrial protein import, radiolabelled ornithine transcarbamylase (OCT) was transcribed and translated in vitro, and then incubated with mitochondria in the presence or absence of peptides. Our data suggest that peptides inhibit protein import in both a time- and dose-dependent manner. Inhibition of import was progressive with time to a maximum of 30 minutes. The addition of 6ug of released peptides resulted in a 48% decrease in import of the matrix protein OCT. This suggests that mitochondrially-released peptides can exert an inhibitory effect on the protein import pathway, as a possible negative feedback mechanism to inhibit excessive protein import. The inhibition of import into the organelle may also serve a retrograde function, to modify nuclear gene expression and improve organelle folding capacity, or alter the expression of protein import machinery components. This work is supported by the Natural Science and Engineering Research Council (NSERC) of Canada.

22.9

HIGH INTENSITY INTERVAL CYCLING PERFORMED PRIOR TO RESISTANCE EXERCISE STIMULATES AUTOPHAGY SIGNALING TO A LARGER EXTENT THAN RESISTANCE EXERCISE ALONE

William Apró[1], Marcus Moberg[1], Björn Ekblom[1], Hans-Christer Holmberg[2], and Eva Blomstrand[1,3]
[1]Åstrand Lab., Swedish Sch. of Sport and Hlth. Sci., Lidingövägen 1, Stockholm, 11433, Sweden, [2]Dept. of Hlth. Sci., Mid Sweden Univ., Swedish Winter Sports Res. Ctr., Kunskapens väg 8, Östersund, 831 25, Sweden, [3]Dept. of Physiology and Pharmacology, Karolinska Inst., Nanna Svartz Väg 2, Stockholm, Sweden.

Introduction: High intensity interval cycling performed prior to resistance exercise potently increases AMPK activity and mRNA expression of the muscle specific E3 ligases MuRF1 and MAFbx, suggesting a link between AMPK activation and muscle breakdown (1). Autophagy, another catabolic process, is also influenced by AMPK. AMPK phosphorylates ULK1 at Ser317 resulting in the activation of autophagy and the subsequent breakdown of proteins. Thus, AMPK-mediated activation of this process may represent a pathway by which training adaptations are modulated in response to various training modes. The aim of this study was therefore to examine if autophagy signaling is activated to a higher degree by concurrent exercise compared to resistance exercise alone. **Methods:** Eight male subjects performed two trials in a randomized order. In the ER trial, they performed five 4-min intervals at a work rate of 85% of each subject's maximal oxygen uptake. Fifteen minutes after the last interval, subjects performed 3 warm-up sets after which they performed 10 sets of heavy-resistance exercise; 4 sets of 8–10 repetitions at ~80% 1RM, 4 sets of 10–12 repetitions at ~70% 1RM, and 2 sets to fatigue at ~60% 1RM. In the R trial, the exercise was identical except that the cycling was replaced by rest. Muscle biopsies were sampled at rest before exercise, immediately after cycling in the ER trial and after rest at the corresponding time point in the R trial, immediately after

resistance exercise and at 90 and 180 minutes during recovery in both trials. Tissue samples were analyzed for the phosphorylation status of ULK1 at Ser317 using western blot. **Results:** After cycling in the ER trial, phosphorylation of ULK1 at Ser317 was increased by ~ 130% compared to before exercise ($p<0.05$). Phosphorylation of S317 was maintained at a similar level (+110%; $p<0.05$) immediately after resistance exercise. In the R trail, phosphorylation of Ser317 was increased by ~ 50% ($p<0.05$) compared to before exercise, but this increase was significantly smaller than that seen at the same time point in the ER trial. **Conclusion:** Endurance exercise-induced activation of AMPK increases phosphorylation of ULK1 at Ser317, likely resulting in increased autophagy. These findings provide a novel mechanism by which concurrent exercise may alter training adaptations compared to single mode resistance exercise. **Funding:** Swedish National Centre for Research in Sports (CIF P2012-0114), Karolinska Institutet (2011 FoBi0780) and Mid Sweden University. **References:** Apró et al. Am J Physiol Endocrinol Metab. 2015 Mar 15;308(6):E470-81.

22.10

INTRACELLULAR SODIUM IS NOT SUFFICIENT TO ACTIVATE ENDOGENOUS CALPAIN-3 IN SKELETAL MUSCLE, BUT IONIC CONDITIONS THAT DO NOT RESEMBLE THE PHYSIOLOGICAL ENVIRONMENT RESULT IN ABERRANT CALPAIN-3 BEHAVIOR

Robyn Murphy[1], Stefan Wette[1], and Graham Lamb[1]
[1]La Trobe Inst. for Molecular Sci., La Trobe Univ., Plenty Rd., Melbourne, 3086, Australia.

Calpain-3 is a skeletal muscle specific, Ca^{2+}-dependent protease. If absent, an individual develops limb-girdle muscular dystrophy 2A. The only known physiological circumstance that results in the autolysis (activation) of calpain-3 is eccentric exercise (1,2), with concentric exercise having no effect (3). It has also been reported that calpain-3 is a Na^+ dependent protease (4), although $[Na^+]$ used were not physiologically relevant, which is ~10-36 mM in resting or highly contracted muscle, respectively. We explored the suggested Na^+-dependency on endogenously expressed calpain-3 in skeletal muscle fibres, using physiologically relevant $[Na^+]$ and $[K^+]$ (~130 mM) and heavily buffered $[Ca^{2+}]$. There was little detectable calpain-3 autolysis in rat muscle fibres exposed to a physiologically-based intracellular solution (i.e. ionic strength, osmolality, pH, $[K^+]$, $[Na^+]$ and heavily buffered with 50 mM EGTA for low $[Ca^{2+}]$) for 0-90 min (3,5). When all K^+ was replaced with Na^+ (final $[Na^+]$ 162 mM, which would never occur inside a living cell), calpain-3 autolysed in a time dependent manner, despite the low $[Ca^{2+}]$. In homogenates from human muscle, we showed a tight relationship between $[Ca^{2+}]$ and calpain-3 autolysis over 10 nM to 500 μM Ca^{2+} using typical intracellular $[Na^+]$ (36 mM) and $[K^+]$ (126 mM). Basally, at 10 nM Ca^{2+}, 36 mM Na^+ and 126 mM K^+, there was ~27% calpain-3 autolysis, however, in the same muscle samples homogenised in non-physiological solution (162 mM Na^+ and no K^+, 10 nM Ca^{2+}), calpain-3 autolysis reached ~60% over ~2 h (N=4 subjects). In addition, the high $[Na^+]$ solution altered calpain-3 distribution from the myofibrillar localisation (5), becoming almost evenly distributed between cytosolic, membrane and myofibrillar fractions. In conclusion, calpain-3 is not a Na^+-dependent protease under physiological intracellular conditions. When major ion constituents of muscle are altered to non-physiological levels, however, calpain-3 is significantly autolysed. Solution composition should be duly considered when examining protein behaviour. References: 1. Murphy et al (2007) Calpain-3 is autolyzed and hence activated in human skeletal muscle 24 h following a single bout of eccentric exercise. *J Appl Physiol* **103**, 926-31. 2. Murphy et al (2011) Activation of skeletal muscle calpain-3 by eccentric exercise in humans does not result in its translocation to the nucleus or cytosol. *J Appl Physiol* **110**, 1448-58. 3. Murphy et al (2006) mu-Calpain and calpain-3 are not autolyzed with exhaustive exercise in humans. *Am J Physiol* **290**, C116-22. 4. Ono et al (2010) Skeletal muscle-specific calpain is an intracellular Na+-dependent protease. *J Biol Chem* **285**, 22986-98. 5. Murphy RM & Lamb GD (2009) Endogenous calpain-3 activation is primarily governed by small increases in resting cytoplasmic [Ca2+] and is not dependent on stretch. *J Biol Chem* **284**, 7811-19.

23.0 BRAIN AND NEURAL RESPONSES

23.1

RUNNING FOR REST: EXERCISE ATTENUATES IMPAIRED COGNITION, SICKNESS BEHAVIOR AND NEUROINFLAMMATION IN THE HIPPOCAMPUS OF AGED ANIMALS

Aderbal Aguiar Jr[1,2], Karine Dallagnol[2], Aline Remor[2], Rodrigo Silva[2], Rui Prediger[3], and Alexandra Latini[2]
[1]Dept. de Fisioterapia, Univ. Fed. de Santa Catarina, UFSC, Rod Gov Jorge Lacerda, nº 3201, 88906-072, Brazil, [2]Lab. de Bioenergética e Estresse Oxidativo, LABOX, Univ. Fed. de Santa Catarina, UFSC, Univ. Fed. de Santa Catarina, Ctr. de Ciências Biológicas, Bloco C, Campus Univ., Trindade, Florianópolis-SC, 88040-900, Brazil, [3]Lab. Exp. de Doenças Neurodegenerativas, LEXDON, Univ. Fed. de Santa Catarina, UFSC, Ctr. de Ciências Biológicas, Bloco D, Campus Univ., Trindade, Florianópolis-SC, 88040-900, Brazil.

Exercise improves mental health and synaptic function in the aged brain. However, the molecular mechanisms involved in exercise-induced healthy brain aging are not well understood. Evidence supports the role of neurogenesis and neuroplasticity in exercise-induced neuroplasticity. The RE1-silencing transcriptiton factor (REST) and an anti-inflammatory role of exercise are also candidate mechanisms. We evaluate the effects of exercise (running wheels for mice and treadmill for rats) on sickness behavior, cognition, neurogenesis and hippocampal gene expression of brain-derived neurotrophic factor (BDNF and downstream signaling), REST, and interleukins IL-1β and IL-10 of adult and aged mice and rats. The aged animals exhibited impaired cognition, depressive-like and sickness behavior: decreased mobility in the RW and open field and severe immobility in the tail suspension test. The gene expression of REST, IL-1β, and IL-10 was increased in the hippocampus of aged mice. Exercise was a cognitive enhancer, anxiolytic and antidepressant and improved motor behavior in aged animals. Exercise also boosted neurogenesis, BDNF (and downstream signaling) and REST expression and decreased IL-1b and IL-10

expression in the hippocampus of aged animals. These results support the beneficial role of REST in the aged brain, which can be further enhanced by cognitive enhancer and antidepressant effects of regular exercise.

23.2

MOTIVATION FOR WHEEL RUNNING IS ENHANCED BY PERIPHERAL PPAR-ALPHA STIMULATION IN MICE

Tetsuya Shiuchi[1,2], and Yuki Kito[1]
[1]Dept. of Integrative Physiology, Tokushima Univ. Grad. Sch., 3-18-15, Kuramoto, Tokushima, 770-8503, Japan, [2]PRESTO, Japan Sci. and Technology Agency, 7, Gobancho, Chiyoda, Tokyo, 102-0076, Japan.

Exercise habituation has a benefit for the health of body and mind although it is difficult to begin and/or continue the exercise for many people, who especially ought to exercise for their health. We found that transient intake of high fat diet increased spontaneous wheel running activity in rodents. Previous papers indicated that some kind of fatty acids activate peroxisome proliferator-activated receptor (PPAR)-alpha in the gut, thereby inhibiting food intake partly through the vagal afferent-dopaminergic neuronal pathway. In this study, we tried to clarify the mechanism which high fat diet-induced increase of wheel running activity in mice focusing on PPAR-alpha in the gut. Wheel running activity following high fat diet feeding for 2 hours was higher in wild type mice than that of PPAR-alpha knock out mice. Oral administration of PPAR-alpha agonist (Wy-14643 or fenofibrate) increased wheel running activity in male C57BL/6J mice. This effect was reduced by intracerebroventricular injection of dopamine receptor antagonist, olanzapine. Moreover, oral PPAR-alpha agonist-induced enhancement of wheel running activity was not inhibited by the intracerebroventricular injection of PPAR-alpha antagonist, GW6471. These results suggest that peripheral PPAR-alpha, probably in gut, is an important molecule for the regulation of exercise motivation for wheel running with activation of dopaminergic pathway in mice.

23.3

THE EFFECTS OF CALCITONIN GENE-RELATED PEPTIDE ON THE EXPRESSION OF NERVE GROWTH FACTOR AND GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR IN CARDIAC CELLS

Gabriel Almeida Alves[1], John-Mary Vianney[1], and John M. Spitsbergen[1]
[1]Dept. of Biological Sci., Western Michigan Univ., 3425 Wood Hall, Mail Stop 5410, Kalamazoo, MI, 49008.

Calcitonin Gene-Related Peptide (CGRP) is a 37 amino acid peptide produced by peripheral and central neurons. It is found in a variety of organs and systems, regulating important functions in the target tissues. The αCGRP isoform is present in sensory neurons and it has been suggested to play a role in preventing hypertension, pulmonary hypertension, and ultimately acting as a potent vasodilator, improving blood flow distribution and wound healing. Studies have shown that exercise increases the levels of CGRP in skeletal and cardiac muscle cells. For these reasons, CGRP has been an important subject of study due to its effects on those organs and systems. Glial cell line-derived neurotrophic factor (GDNF) and Nerve growth factor (NGF) are neurotrophic factors (NF) synthesized in skeletal, smooth and cardiac muscle cells and play roles in the maintenance, survival, and continued synaptic plasticity in the parasympathetic, sympathetic and sensory nervous systems. Studies in our laboratory suggest that GDNF may play an important role in preventing hypertension, where rats that underwent exercise training showed increased GDNF expression in vascular tissues, increased sensory innervation in the vasculature and lower blood pressure. Other studies have shown that exercise increases NGF and GDNF levels in the cardiovascular system, leading to an increase in parasympathetic and sensory innervation. The relationship between CGRP and NF expression is not well understood. Therefore, the aim of our study is to determine the effects of CGRP on the expression of NFs in HL1 cells, an atrial-derived cell line that spontaneously contracts in vitro. HL1 cells were treated with three different concentrations of CGRP (10nM, 100nM and 400nM). Culture medium samples and cells were collected after 2 and 24 hours following treatment. Cell growth density and contractile frequency were measured by light microscopy. NF levels were measured by enzyme-linked immunesorbent assay and Western Blot. Our results showed a dose dependence increase in NF expression following treatment with CGRP. In addition, treatment with CGRP resulted in a decrease in contractile frequency of HL1 cells. These results suggest that neurons releasing CGRP may be able to regulate their own supply of NFs. Increased expression of NFs could lead to changes in cardiac innervation pattern, preventing hypertension.

23.4

A KETOGENIC DIET IS BENEFICIAL TO PAIN SENSITIVITY AS COMPARED TO A HIGH FAT DIET IN MICE

Michael Cooper[1], Janelle Ryals[1], and Doug Wright[1]
[1]Anatomy & Cell Biology, Univ. of Kansas Med. Ctr., KLSIC, Rm. 2036, 2106 Olathe Blvd., Kansas City, KS, 66160.

Nondiabetic mice fed a high-fat diet display clinical symptoms of prediabetic patients, including obesity, hyperglycemia, and increased pain sensitivity (mechanical allodynia). The molecular changes altered by a high-fat diet that induce these neuropathic symptoms have yet to be identified. Previous research has shown that exercising mice on a high-fat diet (54% kcal from fat) develop mechanical allodynia over the first 6 weeks, which is then rescued to baseline levels during weeks 6-12 in mice that are allowed to exercise. The present study compares how an extremely high-fat 'ketogenic' diet (~90% kcal from fat) may alter prediabetic clinical symptoms to better understand the role of fats and fat processing in the development of pre and overt diabetes. In addition, the study addresses mechanisms by which exercise may provide its benefit on reducing mechanical allodynia in high-fat fed mice. Unlike mice on a high-fat diet, ketogenic fed mice do not develop mechanical allodynia, suggesting that the consumption of fat is not the defining cause of the mechanical allodynia developed in this model of prediabetes. Other groups researching ketogenic diets have shown alterations in thermal sensitivity, though we did not see any changes in ther-

mal sensitivity regardless of diet or exercise. Though behavior sensitivity were unaltered by a ketogenic diet, sensory nerve conduction velocities displayed a significantly faster sensory nerve conduction velocities for ketogenic mice as compared to high-fat sedentary mice. Motor nerve conduction velocities were significantly faster in ketogenic and high-fat sedentary mice, but were not changed in exercised high-fat mice. Ketogenic fed mice display increased body weight and hyperglycemia, mirroring levels seen in high-fat fed mice given access to exercise; though fat mass by percent of total mass in both ketogenic and exercised mice are less than that of high-fat sedentary mice. Interestingly though, ketogenic diet-fed mice do not display the insulin increases seen in both high-fat sedentary and exercised mice. Together, these results suggest that a ketogenic diet is able to correct many of the clinical symptoms of high-fat fed prediabetic mice, mirroring many changes observed in high-fat fed exercised mice.

23.5

EFFORT, THE CENTRAL PRESSOR RESPONSE AND MUSCLE FATIGUE DURING HUMAN STANDING

Richard Fitzpatrick[1], and Billy Luu[1]
[1]NeuRA, Univ. of New South Wales, Barker St., Sydney, Australia.

We had 10 subjects aged 19-55 stand and consider the force applied to the ground. A brace was quickly positioned to hold them in the same posture with the muscles relaxed. They then made a plantarflexion contraction to reproduce the force perceived during standing. They underestimated the exerted active force when standing by 71.8% ($P<0.001$). When the experiment was performed with subjects balancing an inverted pendulum matched to their own bodies, they overestimated by 5.3%. This indicates that cortical perceptual centres cannot access the signal of force exerted during standing because the cortical system does not issue the motor command. This implicates a subcortical system in balance drive to the muscles. Reciprocal changes in corticomuscular coherence and galvanic-evoked vestibular reflexes corroborate this. When a muscle is contracted voluntarily, a centrally generated pressor signal sent to medullary cardiovascular centres raises blood pressure (BP). We asked whether this response is also generated by the subcortical balance drive. Subjects were supported upright in the standing posture with the muscles relaxed for 5 minutes. BP was stable. The brace was then removed so that subjects stood by contracting the leg muscles (18.2% of maximal force). BP did not change. Thus, there was no significant metaboreflex response from the muscle. When repeated by producing a matched contraction voluntarily to balance the inverted pendulum, BP increased by 6.2 mmHg or 7.2% ($P < 0.001$) after 3 minutes. In 8 subjects, we stimulated over the tibialis anterior motor point with supramaximal tetanic trains (5 @ 40ms) repeated at 1Hz; a workload similar to the calf muscles during standing). When force output was stable, muscle perfusion pressure was changed by raising or lowering the leg. This produced a rapid decline of 4.8% in force output for the 6.2mmHg loss of pressor response, equivalent to that reported for a hand muscle. In the hand muscle, loss of this augmented contractility through the pressor response meant that muscle fatigued twice as fast. Thus, without this pressor response, the leg muscles rely crucially on the hydrostatic head of pressure provided by orthostatic posture. We conclude that the neural pathways through which a muscle is activated, which can vary with motor task, determine the acute cardiovascular adaptations that maintain muscle perfusion homeostasis. Supported by the National Health and Medical Research Council of Australia.

23.6

EXERCISE PRECONDITIONING REDUCES TRPA1-MEDIATED JOINT PAIN IN MICE: PERIPHERAL VERSUS CENTRAL FACTORS

Timothy Griffin[1], Erika Barboza[1], Joanna Hudson[1], Paige Parrack[1], Kevin Gaffney[1], Carlton Fernandez[1], Tessa Kovats[1], and Michael Kinter[1]
[1]Aging and Metabolism Res. Program, Oklahoma Med. Res. Fdn., 825 NE 13th St., MS 21, Oklahoma City, OK, 73104.

Background: Exercise therapy is strongly recommended for long-term management of osteoarthritis joint pain. However, the mechanistic basis for this clinical observation is not well understood. One recently described mediator of knee OA pain is the transient receptor potential ankyrin-repeat 1 (TRPA1) ion channel. TRPA1 is expressed primarily in small unmyelinated non-peptidergic nociceptive neurons, which we predicted are present in the joint capsule and throughout the infrapatellar fat pad (IFP) of the knee joint. **Objective:** To determine the effect of exercise on TRPA1-mediated knee pain behavior and mediators of TRPA1 activation in peripheral versus central sites (i.e., IFP versus dorsal root ganglion (DRG), respectively). **Design and Methods:** 14 wk old WT and $TRPA1^{-/-}$ mice were studied following an approved IACUC protocol. Mice exercised voluntarily on wheels for 2 wks or were housed in standard cages ($n\geq5$ per group). TRPA1 expression patterns were analyzed by immuno-staining in knee tissue sections. Knee pain was induced by injecting allyl isothiocyanate (TRPA1 agonist) into the IFP. Pain behaviors were monitored 2-48 hrs following injections, including home cage activity, gait biomechanics, and mechanical allodynia via von Frey filament testing. Additional cohorts were used for IFP and DRG gene and protein expression assays before and after exercise training and TRPA1 activation. **Results:** TRPA1 was expressed in the IFP extra-cellular matrix, synovial lining, and particularly along the IFP deep to the patellar tendon. TRPA1 activation in sedentary WT mice induced spontaneous and evoked pain-related behaviors, as indicated by reduced locomotor activity and limb forces and increased mechanical allodynia ($p<0.05$). Exercise preconditioning abolished TRPA1-induced mechanical allodynia, and no exercise-induced changes were observed in $TRPA1^{-/-}$ mice, indicating TRPA1-specific protection. Exercise increased pro- and anti-inflammatory gene expression and protein content of the antioxidant catalase in the IFP. Exercise reduced expression of the chemokine CCL2 and anti-inflammatory cytokine IL-10 in the DRG following 2 wks of exercise. **Conclusion:** Exercise pre-conditioning inhibits TRPA1-induced mechanical allodynia in mice. This protection was associated with increased expression of pro- and anti-inflammatory mediators in peripheral nociceptive joint tissues and

decreased expression in central pain pathways. Funding: Arthritis Foundation, NIH R03AR066828, OMRF.

23.7

CANNABINOID RECEPTORS IN THE VMH IMPAIR EXERCISED-INDUCED IMPROVEMENTS IN GLUCOSE TOLERANCE

Carlos Castorena[1], Teppei Fujikawa[1], Newaz Ahmed[1], Caleb Lord[1], Charlotte Lee[1], Claudia Vianna[1], Syann Lee[1], and Joel Elmquist[1]

[1]Div. of Hypothalamic Res., Int. Med., Univ. of Texas Southwestern Med. Ctr., 5323 Harry Hines Blvd., Dallas, TX, 75290-9007.

The cannabinoid 1 receptor (CB1R) in the central nervous system (CNS) regulates energy balance, though the precise CNS sites mediating these effects are unclear. The ventromedial hypothalamic nucleus (VMH) has a high level of CB1R expression. Exercise is a potent activator of the cannabinoid system by increasing the levels of circulating endogenous lipid-derived cannabinoids. In addition, evidence from our lab and others suggest that the VMH is critical for the coordinated metabolic response to exercise. Our objective was to determine the effect of exercise on glucose tolerance in mice either lacking CB1R (Null-CB1R) or in mice that express CB1Rs only in neurons of the VMH (SF1-CB1R-RE). We developed a "re-activatable" CB1R mouse model in which the null CB1R allele can be re-expressed exclusively in the VMH in the presence steroidogenic factor-1 (SF1)-Cre recombinase. Glucose tolerance tests were performed on sedentary mice or after a single bout of treadmill exercise. Consistent with previous reports of CB1R knockouts, sedentary Null-CB1Rs have reduced body weight and improved glucose tolerance compared to littermate controls. While Null-CB1R and littermate controls have comparable improvements in glucose tolerance following acute exercise, exercise failed to enhance glucose tolerance in SF1-CB1R-RE mice. These findings support a model predicting that CB1Rs in the VMH may blunt exercise-induced improvements in glucose metabolism. Research Support: NIH R01-DK100659 to J. K. E.; NIH F32-DK104659 to C. M. C.; AHA 14SDG17950008 to T. F.; This work was done in part with support from Sanofi-Aventis.

24.0 BEHAVIOR

24.1

LOSS OF NUCLEUS ACCUMBENS CDK5 FUNCTION DECREASES VOLUNTARY WHEEL RUNNING AND MAY MEDIATE AGE-RELATED DECLINES IN PHYSICAL ACTIVITY

Gregory Ruegsegger[1], Ryan Toedebusch[1], Tom Childs[1], and Frank Booth[1]

[1]Biomedical Sci., Univ. of Missouri, E102 E. Rollins St., Columbia, MO, 65211.

Increases in age are often associated with reduced levels of physical activity which, in turn, leads to the development of numerous chronic diseases. We aimed to assess molecular differences in the nucleus accumbens (NAc), a specific brain nucleus postulated to influence rewarding behavior, associated with reductions in voluntary wheel running between 8 and 14 wks of age in female, Wistar rats. RNA-sequencing was used to interrogate transcriptomic changes between 8 wk and 14 wk-old wheel running rats, and select transcripts were later analyzed by qRT-PCR in age-matched sedentary rats. Follow-up experiments to assess NAc dendritic density at 8 and 14 wks and running distance following intra-NAc infusion of the Cdk5 inhibitor roscovitine (40 and 80nmol/0.5ul) were also performed. Voluntary wheel running was greatest at 8 wks and had significantly decreased by 12 wks. From 619 differentially expressed genes, bioinformatics suggested that cAMP-mediated signaling, DARPP-32 feedback, and synaptic plasticity were greater in 8 compared to 14 wk-old running rats. In depth analysis of these networks showed significant (~20-30%; $p < 0.05$) decreases in Cadm4 and p39 mRNAs, as well as their proteins from 8 to 14 wks of age in running and sedentary rats. Further, Cadm4, Cdk5, and p39 mRNAs were significantly correlated with voluntary running distance ($p < 0.05$). Analysis of dendritic spine density in the NAc showed that wheel access increased spine density ($p < 0.001$), while spine density was inherently lower at 14 wk compared to 8 wk ($p < 0.05$). Intriguingly, intra-NAc injection of the Cdk5 inhibitor roscovitine, dose-dependently decreased wheel running following 5 days of continuous injection ($p < 0.05$). Collectively, these experiments highlight Cdk5 activity in the NAc as a potential regulator of voluntary wheel running, and suggest age-dependent reductions in mRNAs central to Cdk5 activity and synaptic plasticity, and dendritic density in the NAc may be partially responsible for age-related declines in voluntary running behavior.

24.2

MU-OPIOID RECEPTOR INHIBITION DECREASES RUNNING IN HIGH VOLUNTARY RUNNING RATS IN A DOPAMINE-DEPENDENT MANNER

Gregory Ruegsegger[1], and Frank Booth[1]

[1]Biomedical Sci., Univ. of Missouri, E102 E. Rollins St., Columbia, MO, 65211.

The mesolimbic dopamine and opioid systems are postulated to influence the central control of physical activity motivation. We utilized selectively bred rats for high (HVR) or low (LVR) voluntary running behavior to examine 1) inherent differences in mu-opioid receptor (Oprm1) expression and function in the nucleus accumbens (NAc), a brain region postulated to influence rewarding behavior; 2) if dopamine-related mRNAs, wheel-running, and food intake are differently influenced by intraperitoneal (i.p.) injection of the mu-opioid receptor antagonist naltrexone in HVR and LVR rats; and 3) if dopamine is required for naltrexone-induced changes in running and feeding behavior in HVR rats. Oprm1 mRNA and protein expression were greater in the NAc of HVR rats, and application of the Oprm1 agonist [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) to dissociated NAc neurons produced greater depolarizing responses in neurons from HVR versus LVR rats. Naltrexone injection dose-dependently decreased wheel running and food intake in HVR, but not LVR rats. Naltrexone (20mg/kg) decreased tyrosine hydroxylase mRNA in the ventral tegmental area and Fos, Drd1, and Drd5 mRNA in NAc shell of HVR, but not LVR, rats. Additionally, lesion of dopaminergic neurons in the NAc with 6-hydroxydopamine (6-OHDA) ablated the decrease in

running, but not food intake, in HVR rats following i.p. naltrexone administration. Collectively, these data suggest the higher levels of running observed in HVR rats, compared to LVR rats, are mediated, in part, by increased mesolimbic opioidergic signaling that requires downstream dopaminergic activity to influence voluntary running, but not food intake.

24.3

LONG-TERM PERFORMANCE, ENERGETIC, AND MORPHOLOGICAL CONSEQUENCES OF FATHERHOOD IN THE BIPARENTAL CALIFORNIA MOUSE (*PEROMYSCUS CALIFORNICUS*)

Jacob Andrew[1], Ted Garland Jr. [1], Wendy Saltzman[1], and Mark Chappell[1]
[1]Biology, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521.

Pregnancy and lactation in mammalian mothers increase energy demands and are associated with numerous morphological and metabolic alterations. Whether parallel changes occur in fathers has received little attention. In biparental species, in which both parents provide care for their offspring, fathers are known to undergo systematic changes in several morphologically, metabolically, and behaviorally important hormones, in association with their mate's pregnancy and the birth of their offspring. However, the consequences of these hormonal changes for fathers' exercise performance are not known. Our research was designed to characterize effects of fatherhood on performance, energetics, and morphology in the California mouse, *Peromyscus californicus*, a genetically monogamous and biparental rodent in which fathers show similar parental behavior to mothers, with the exception of lactation, and play important roles in the survival and development of their offspring. In a previous study, we found few short-term effects of fatherhood on male performance, energetics, and morphology for first-time fathers (Andrew J.A. et al. 2016. Physiol. Biochem. Zool. 89, 130-140). In the present study, we tested for possible long-term effects on fathers after raising multiple litters (up to seven). Each male was paired with either an intact female (breeding males), an ovariectomized female treated with estrogen and progesterone to stimulate mating (mated non-breeding males) or an ovariectomized female not treated with estrogen and progesterone (non-breeding males). From before the birth of their first litter through shortly before the birth of their eighth litter, we compared fathers with control males for several ecologically relevant measures of locomotor performance (sprint speed, maximal aerobic metabolic rate [VO_2max], grip-strength, and predatory aggression), energetics (resting metabolic rate [RMR]), hematocrit, and morphology (fat, lean, and body mass). Males were then euthanized and organs weighed. Results are expected to provide novel insights into effects of reproduction on exercise performance, as well as on relevant physiological and morphological characteristics, in males. Ultimately, this work may provide insights into potential costs, or perhaps benefits, of paternal care in mammals, beyond those associated with reproductive output per se.

24.4

HABITUAL AEROBIC EXERCISE INCREASES SERUM TESTOSTERONE LEVELS IN OVER-WEIGHT AND OBESE MEN.

Hiroshi Kumagai[1], Toru Yoshikawa[2], Kanae Myoenzono[2], Tomoko Kaneko[2], Asako Zempo-Miyaki[3], Takehiko Tsujimoto[1], Kiyoji Tanaka[1], and Seiji Maeda[1]
[1]Fac. of Hlth. and Sport Sci., Univ. of Tsukuba, 1-1-1 Tennodai, Tsukuba, Japan, [2]Grad. Sch.of Comprehensive Human Sci., Univ. of Tsukuba, 1-1-1 Tennodai, Japan, [3]Fac. of Sports and Hlth. Sci., Ryutsu Keizai Univ., 120 Hirahata, Ryugasaki, Japan.

Testosterone is a male sex hormone and low circulating testosterone levels lead to various health disorders in men. Obesity, one of the biggest problems in the world, results in reduction in circulating testosterone levels in men. We have previously demonstrated that lifestyle modifications (combination of aerobic exercise and well balanced dietary modification) increase circulating testosterone levels in overweight/obese men. However, the effect of habitual aerobic exercise on circulating testosterone levels has not been clarified yet. The purpose of this study was to investigate the effect of 12-week aerobic exercise intervention on circulating testosterone levels in normal and overweight/obese men. Sixteen normal weight men (BMI < 25 kg/m^2) and twenty-eight overweight/obese men (BMI $\geqq 25$ kg/m^2) completed 12-week aerobic exercise intervention (walking and jogging, 40-60 minutes/day, 1-3 days/week). Before and after the intervention, we measured serum levels of total testosterone (TT), free testosterone (FT) and bioavailable testosterone (BT), and light, moderate and vigorous physical activity in all participants. FT and BT were calculated on the basis of serum levels of TT, sex hormone binding globulin and albumin according to the formula shown on the International Society for the Study of the Aging Male website. At baseline, serum TT, FT and BT levels were significantly lower in overweight/obese men than those in normal weight men (all $P < 0.01$). After the 12-week aerobic exercise intervention, serum TT, FT and BT levels significantly increased in overweight/obese men ($P < 0.01$), but not in normal weight men (P for interaction = 0.031). In addition, the changes in vigorous physical activity independently associated with increase in serum TT levels ($\beta = 0.47$, $P = 0.011$) in overweight/obese men. In conclusion, we demonstrated that 12-week aerobic exercise intervention increased serum TT, FT and BT levels in overweight/obese men. Moreover, we suggest that the increase in vigorous physical activity need to increase circulating testosterone levels in overweight/obese men.

24.5

EFFECTS OF EARLY-LIFE EXPOSURE TO WESTERN DIET AND VOLUNTARY EXERCISE ON ADULT ACTIVITY LEVELS, EXERCISE PHYSIOLOGY, AND ASSOCIATED TRAITS IN MICE

Marcell Cadney[1], Jarren Kay[1], Layla Hiramatsu[1], Zoe Thompson[1], Jennifer Singleton[1], Ralph Albuquerque[1], Margaret Schmill[1], and Theodore Garland, Jr.[1]
[1]Biology, Univ. of California, Riverside, 900 University Ave., Riverside, CA, 92521.

Physical activity is important for both physical and mental health. Variation in voluntary exercise (VE) and spontaneous physical activity (SPA), in both humans and laboratory rodents, are known to be under partial genetic regulation. VE and SPA are also affected by numerous environmental factors, potentially including early-life experiences that may have long-lasting effects. The current experiment was designed to explore genetic, environmental, and early-life effects in a novel mouse model: 4 replicate high runner [HR] lines and 4 non-selected control [C] lines). The HR lines have been selectively bred for >75 generations for total revolutions run on day 5&6 of a 6-day period of wheel access as young adults. In the present experiment, we altered VE by granting wheel access or not and administered either standard or Western diet (WD: Teklad Rodent Diet (W) 8604) during the juvenile period from weaning to 6 weeks of age (sexual maturity). We measured voluntary wheel-running behavior, home-cage activity, growth rate, food consumption, WD and sucrose preference, maximal aerobic capacity (VO_2max), open-field activity, body composition, organ masses, and blood-lipid profiles. (Studies of the gut microbiome and circulating concentrations of corticosterone, leptin, and adiponectin are in progress.) Here, we provide a progress report for this study. As adults, HR mice ran more than C regardless of treatment; however, we found significant interactions between early-life wheel access and linetype, as well as diet and linetype. Specifically, juvenile wheel access increased adult wheel-running for C (+14%), but deceased it for HR mice (-12%). Juvenile WD increased adult running for HR (+19%) but not for C (-6%), consistent with previous reports (e.g., Meek et al. 2010. International Journal of Obesity 34:960–969). Juvenile wheel access decreased adult relative heart mass, increased relative triceps surae muscle mass, and increased adult subdermal fat mass. Overall, these results demonstrate that both juvenile exercise environment and diet can have long-lasting effects on adult activity behaviors and related phenotypes. Future studies may examine possible transgenerational effects of these exposures. This research is supported by NIH R21 HD084856 to TG.

24.6

EFFECTS OF REGULARLY SCHEDULED EXERCISE ON EXERCISE PERFORMANCE OF MICE DURING THE INACTIVE PERIOD

Naoya Takei[1], Hirohide Minagawa[1], Yutaka Matsunaga[1], Yuki Tamura[1], and Hideo Hatta[1]

[1]Dept. of Sports Sci., Univ. of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo, 1538902, Japan.

Purpose: Human has a circadian rhythm of exercise performance which is low in the morning and high in the early night. In many sports events, the final competitions have often been held in the early night. Nowadays, however, the final competitions sometimes are held in the morning. Therefore, in order to propose a way to improve the morning exercise performances, we conducted the experiment to resolve this problem. **Method**: Thirty six male mice were randomly divided into two groups (training at ZT4 or ZT8). Moreover, those groups were further divided into another two conditions in which mice took exercise performance test (PT) at ZT4 or ZT8. Therefore, there were four groups in which mice trained at ZT4 or ZT8 and took PT at the same or different time they usually trained. Generally, mice are inactive from ZT0 to ZT12. The training period was 2 weeks (treadmill running, 20-30 m/min, 30 min, 5 times/week). Before (pre) and after (post) the training period, we measured locomotor activities (by infrared sensor) and exercise performances (running time to exhaustion). 24-hours after the post PT, mice were sacrificed and the muscles were harvested. We measured the muscle weight, citrate synthase (CS) protein content and maximal CS activity. **Results**: Significant delay of the phase of the locomotor activity was observed in mice trained at ZT4 comparing to pre and to mice trained at ZT8. Exercise performance was significantly improved in the post PT comparing to pre PT in all groups. However, significantly lower exercise performance was observed in mice trained at ZT4 and took PT at ZT8 than all other groups. On the other hand, mice trained at ZT8 and took PT at ZT4 showed almost same exercise performance comparing to other two groups. It might suggest that mice trained at ZT8 and took PT at ZT4 was already prepared for PT which was done 4 hours before the time of usual training. There were no differences in the muscle weight, CS protein content and maximal CS activity among all groups. **Conclusion**: Training at the different time of a day affects circadian rhythms and changes the exercise performance at the different time of a day. In this study conditions, usual training at the same time of PT prevented decrease in exercise performance.

24.7

CHANGES IN SATISFACTION WITH PHYSICAL FUNCTION AND APPEARANCE AFTER STRRIDE AT/RT AND STRRIDE PD

Lorrie Elliot-Penry[1], Cris Slentz[1], Leslie Willis[1], Lori Bateman[1], Esther Granville[2], Lucy Piner[1], Connie Bales[2], and William Kraus[1]

[1]Duke Molecular Physiology Inst., Duke Univ. Med. Ctr., 300 N. Duke St., Durham, NC, 27707, [2]Div. of Geriatrics, Duke Univ. Med. Ctr., 300 N. Duke St., Durham, NC, 27707.

In STRRIDE (Studies of Targeted Risk Reduction Interventions through Defined Exercise) we have investigated the effects of different modes, intensities, amounts, and diet and exercise on many variables of interest. In STRRIDE AT/RT we studied Aerobic versus Resistance training. In STRRIDE PD, we studied different amount and intensities of aerobic exercise compared to the gold standard Diabetes Prevention Program (Diet/Ex). In this report we report on the effects of these interventions on satisfaction with physical function (PF) and appearance (Appear). **Methods**: In STRRIDE-AT/RT we randomized subjects into low-amount/vigorous-intensity aerobic exercise (LAVI), resistance training (RT), both (AT/RT) and high-amount/vigorous-intensity (HAVI). In addition, all subjects had a 4-month control/run-in period (Cont). In STRRIDE PD we randomized subjects in to low-amount/moderate-intensity (LAMI), HAMI, HAVI and Diet/Ex. The Satisfaction with PF & Appearance questionnaire was administered to each subject before and after interventions. A 7-point integer scale was used with scores ranging from -3 (very dissatisfied) to +3 (very satisfied). Paired t-tests tested for changes within a group, ANOVA's tested for differences between groups. [as all subjects were in the control group in STRRIDE AT/RT, controls

were not included in the ANOVA]. **Results:** For STRRIDE AT/RT, change scores were, in order, Cont, LAVI, RT, AT/RT, HAVI for PF: 0.1, 1.8, 2.2, 2.6, 2.8 and for Appear: 0.0, 1.1, 0.8, 1.5, 2.4. For STRRIDE PD scores for LAMI, HAMI, HAVI, Diet/ex for PF: 1.8, 2.1, 2.5, 1.8 and for Appear: 1.3, 0.9, 1.5, 2.2. All interventions, except control, reported significant improvements in satisfaction with PF and Appearance (t-tests; $p<0.01$). In STRRIDE AT/RT the AT/RT group had a significantly greater improvement in PF then LAVI. The HAVI group had a significantly larger improvement in Appearance score compared to LAVI and RT-only. In STRRIDE-PD, the HAVI group improved more than Diet/Ex and LAMI in PF. For Appearance, the Diet/Ex group had the biggest improvement and was significantly greater than HAMI & LAMI. **Summary:** Perhaps the most interesting and important finding was that any exercise intervention resulted in significant improvements in the participants satisfaction with both physical function and appearance. It was not surprising that diet/ex resulted in the greatest improvement in Appearance, whereas HAVI experienced the greatest improvement in satisfaction with PF.

25.0 ADAPTIVE RESPONSES

25.1
ACUTE EXERCISE STRESS ELICITS DIFFERENTIAL GENE EXPRESSION PROFILES IN SEDENTARY VS. DETRAINED SOLEUS MUSCLES

J. P. Hyatt[1], Emily Brown[2], Elisa Bienenstock[3], and Gary McCall[2]
[1]Coll. of Letters and Sci., Arizona State Univ., 411 N. Central Ave., #300, Phoenix, AZ, 85004, [2]Exercise Sci., Univ. of Puget Sound, 1500 N. Warner St., Tacoma, WA, 98416, [3]Coll. Public Service & Community Solutions, Arizona State Univ., 411 N. Central Ave., #400, Phoenix, AZ, 85004.

Maintaining a consistent and long-term regimen of physical activity can be difficult. Repeated cycling through activity-inactivity periods implies that the corresponding physiological adaptations would fluctuate according to the volume of the activity/inactivity period. Here, we investigated whether a previous period of physical activity influenced the global gene expression response to acute exercise following a period of reduced physical activity. Using microarray analyses, we assessed genome-wide expression in soleus muscles of sedentary (8 wk normal cage activity) and detrained (4 wk voluntary wheel running + 4 wk sedentary) Sprague-Dawley rats after a 1 hr acute exercise bout of forced running compared to trained (8 wk voluntary wheel running) conditions. Transcriptome profiles between groups were compared using a range of inclusion criteria based on expression fold differences and statistical significance. Using this inclusion criteria strategy, we found a consistently greater number (1.5- to 31-fold) of genes differentially expressed in the soleus muscles of detrained than sedentary groups as compared to trained profiles, and this observation was consistent at varying levels of expression threshold and statistical inclusion criteria. Ingenuity Pathway Analysis (e.g., network analyses) predicted inhibition of "morbidity and mortality" functional pathways in the detrained but not sedentary group after acute exercise stress, suggesting a reactivation of health-associated expression profiles that may have been established during previous training periods. There were no sustained structural or phenotypic changes found after 4 weeks of detraining as assessed by muscle capillary number and fiber type composition. We propose that an enhanced gene expression sensitivity is acquired from previous aerobic exercise may persist during subsequent periods of reduced activity and, once an exercise stimulus resumes, facilitate potentially health-related benefits and/or faster readaptation of skeletal muscle function.

25.2
ROLE OF B-ADRENERGIC SIGNALLING IN PGC-1A MEDIATED MITOCHONDRIAL ADAPTATIONS IN SKELETAL MUSCLE

Nina Brandt[1], Lene Nielsen[1], Jens Bangsbo[2], and Henriette Pilegaard[1]
[1]Biology, Univ. of Copenhagen, Universitetsparken 13, Copenhagen, 2100, Denmark, [2]Nutrition, Exercise and Sports, Univ. of Copenhagen, Universitetsparken 13, Copenhagen, 2100, Denmark.

PGC-1α is suggested as a key regulator of exercise training-induced adaptations in skeletal muscle oxidative capacity. The factors regulating PGC-1α are not fully elucidated, but adrenaline has been suggested to play a role. The aim of the present study was to test the hypothesis that adrenergic signaling increases mitochondrial capacity in skeletal muscle through PGC-1α. Muscle specific PGC-1α knockout (MKO) and littermate lox/lox controls (lox/lox) received 1) Regular water (CON) or water supplemented with the β2-adrenergic agonist Clenbuterol (CLEN) or 2) Regular water (CON), Regular water with access to running wheel (EX) or water supplemented with the β-adrenergic antagonist Propanolol and access to running wheel (PROP+EX) for 5 weeks. Running endurance was not affected by CLEN in lox/lox mice, but increased in both EX and EX+PROP in lox/lox with lower endurance in MKO. Fat percentage was lower in CLEN than CON in both genotypes and lower in EX and EX-PROP than CON within lox/lox. Quadriceps muscle (Q) PGC-1α mRNA content was lower in CLEN than CON without effect of exercise training or PROP. Hexokinase (HK)II protein content was unaffected by CLEN, but increased similarly in EX and EX+PROP in both genotypes. While citrate synthase (CS) and 3-hydroxyacyl dehydrogenase activities (HAD) were unaffected by CLEN, CS - but not HAD - increased with exercise training without effect of PROP. CS activity in MKO was lower and did not change with exercise training. OXPHOS complex I and IV decreased with CLEN and all OXPHOS complexes increased in EX and EX+PROP only in lox/lox mice. OXPHOS protein content was lower in MKO than lox/lox. In conclusion, exercise training increased skeletal muscle mitochondrial oxidative capacity in a PGC-1α dependent manner, but independent of β-adrenergic signaling, while prolonged β2-adrenergic signaling decreased mitochondrial oxidative capacity. This study was supported by a grant from The Danish Council for Independent Research.

25.3
MILD-INTENSITY EXERCISE TRAINING ALTERS SKELETAL MUSCLE PHOSPHOLIPID COMPOSITION IN OBESE ADULTS

Jenna B. Gillen[1], Rachael K. Nelson[1], Douglas W. Van Pelt[1], Lisa M. Guth[1], and Jeffrey F. Horowitz[1]
[1]Kinesiology, Univ. of Michigan, 500 S. State St., Ann Arbor, MI, 48109.

Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are the primary phospholipid constituents of cellular membranes. The relative abundance of PC and PE (PC:PE ratio), as well as alterations in their chain lengths and saturation states have been implicated in maintaining cell membrane integrity, which can influence insulin signaling. Although exercise is often found to improve skeletal muscle insulin action, the effect of exercise training on skeletal muscle phospholipid composition is not well resolved. The purpose of the present study was to determine the effects of a 12-wk, mild-intensity endurance exercise program on skeletal muscle phospholipid composition and insulin sensitivity. Eight obese adults (30±7y, 35±4kg/m^2, 46±8% body fat) underwent 12 weeks of endurance exercise training (50% VO_2peak, 40min/d, 5-6d/wk) without weight loss. Before training and 24h after the last exercise session, a skeletal muscle biopsy sample was obtained from the vastus lateralis and a hyperinsulinemic-euglycemic clamp was performed. An untargeted skeletal muscle lipidomic profile was completed using liquid chromatography mass-spectrometry (MS). Relative quantification of lipid species was provided as peak areas and lipids were identified by matching MS/MS fragments to the LipidBlast database. MetaboAnalyst 3.0 was used to explore changes in the lipidomic profile. Exercise improved insulin sensitivity (glucose rate of disappearance/steady state insulin: 2.5±0.6 vs. 3.4±1.1 mg/min/(mU/ml), $p<0.05$). Skeletal muscle lipidomic analyses revealed increased abundance of total PE, lyso-PE, PC and cardiolipin after training ($p<0.05$). The skeletal muscle PC:PE ratio decreased in response to training (7.8±0.8 vs. 6.8±0.5, $p<0.01$) due to the relatively large increase in PE compared with PC. Investigation into the changes of individual PE species revealed increased abundance of five long-chain (>36 carbons) polyunsaturated PEs after training ($p<0.05$ after false discovery rate correction). In conclusion, improved insulin sensitivity after mild-intensity endurance training was accompanied by a reduction in skeletal muscle PC:PE ratio, due largely to increased abundance of long-chain, polyunsaturated PEs. This explorative lipidomic investigation aids in developing targeted hypotheses regarding the relationship between skeletal muscle phospholipid composition and exercise-induced improvements in insulin sensitivity. Funding sources: NIH R01 DK077966, NIH P30 DK-089503, NIH 2UL1TR000433, NIH #T32DK007245, NIH #T32DK10135702.

25.4

BASELINE IRISIN CONCENTRATIONS NOT ALTERED BY HIGH-INTENSITY RESISTANCE TRAINING

Matthew Short[1], Eunhee Chung[1], Jacalyn McComb[1], Shelby Kloiber[1], Eneko Larumbe-Zabala[2], Latha Ramalingam[3], and Maria Fernandez del Valle[1]
[1]Kinesiology & Sport Management, Texas Tech. Univ., PO Box 43011, Lubbock, TX, 79409, [2]Clinical Res. Inst., Texas Tech. Univ. Hlth. Sci. Ctr., 3601 4th St., Stop 8183, Lubbock, TX, 79430, [3]Nutritional Sci., Texas Tech. Univ., PO Box 41270, Lubbock, TX, 79409.

Irisin is a recently identified myokine believed to increase the browning of white adipose tissue. Secretion of irisin is thought to increase with exercise. Purpose: The objective of this study was to determine if 3 weeks of high-intensity resistance training has an effect on baseline serum irisin levels in young, healthy adults. Methods: 12 young, healthy adults were selected to participate in a three-week exercise study (age 21.2 ± 2.9 years, body mass index [BMI] 22.6 ± 1.7 kg/m^2, lean body mass [LBM] 45.0 ± 11.3 kg and relative body fat [%BF] 28.2 ± 10.9%). The subjects were blocked by sex, BMI, and LBM. Subjects were randomly assigned to either an exercise group (n=6) or a resting control group (n=6). Blood was collected at the beginning of exercise sessions 1, 3, 6 and 9. The training circuit consisted of 10 repetitions per exercise of 7 exercises: horizontal leg press, bent-over rows, back squats, weighted abdominal sit-ups, dead-lifts, bench press and weighted jump squats. Approximately 30 seconds of rest in between each exercise occurred, based on the estimated time needed to move from one station to the next. Each participant completed the circuit 3 times, with 2 to 3 minutes of rest between each circuit. Both lactate and rate of perceived exertion (RPE) were used to monitor intensity. Results: Irisin (μg/mL) levels (mean ± SD) for the control and intervention group were 5.4 ± 0.7 and 6.3 ± 0.6 at baseline, 5.6 ± 0.6 and 5.7 ± 0.9 before Session 3, 5.6 ± 1.0 and 6.1 ± 1.1 before Session 6 and 6.0 ± 0.6 and 6.3 ± 1.4 before Session 9. No significant effects were observed (time x group $F[3,30]=0.50$, $p=0.687$; time $F[3,30]=0.71$, $p=0.560$; group $F[1,10]=2.26$, $p=0.160$). CONCLUSIONS: Despite having a homogeneous group and a controlled environment, the irisin serum concentrations did not appear significantly different between the groups over an extended period of time. Blood analyzed for this study was collected pre-exercise. Additional research looking at different time points may yield different results in irisin concentrations. In addition, increased serum irisin levels prior to Session 9 of the control group (non-significant) raises questions about the validity and sensitivity of available commercial assays. More applied research is needed to understand the responses of irisin to exercise in humans.

25.5

IMPACT OF PGC-1A IN LIFELONG EXERCISE TRAINING-INDUCED REGULATION OF UPR IN MOUSE LIVER

Caroline Kristensen[1], Stine Ringholm[1], Jesper Olesen[1], and Henriette Pilegaard[1]
[1]Dept of Biology, Univ. of Copenhagen, August Krogh Bldg., Universitetsparken 13, Copenhagen, 2100, Denmark.

Aging has been suggested to reduce the ability to activate the unfolded protein response (UPR) in several tissues. On the other hand, it has also been suggested that increased ER stress with age causes accumulation of hepatic triglycerides (TG). Furthermore, exercise training has been demonstrated to prevent hepatic lipid accumulation. PGC-1α, a transcriptional coactivator, has been suggested to contribute to exercise-induced UPR in skeletal muscle and metabolic adaptations in the liver. However, the potential impact of PGC-1α in exercise training-induced regula-

tion of UPR in the liver with aging is yet unknown. Therefore, the aim of the present study was to test the hypotheses that lack of PGC-1α exaggerates age-associated changes in hepatic UPR and that PGC-1α is required for effects of lifelong exercise training on UPR regulation in the liver. Liver was obtained from whole body PGC-1α knockout (KO) and littermate wildtype (WT) mice that were 3 months old (Young) or 15 months old without (Aged) or with access to a running wheel from 3 months of age (Aged+ExT). In WT, aging increased hepatic TG content, which was prevented by exercise training. Lack of PGC-1α increased hepatic TG content without effect of exercise training. Overall hepatic protein carbonylation was lower in PGC-1α KO than WT mice, but not affected by aging or exercise training. Hepatic BiP protein content in WT was higher in aged than young mice, while there was no difference between the exercise trained aged and young mice. BiP protein content in PGC-1α KO was higher than in WT in all groups and increased with aging without effect of exercise training. IRE1 protein content increased in the liver with aging and this was prevented with exercise training in both genotypes. Hepatic PERK protein content decreased with exercise training in WT and was reduced with aging in PGC-1α KO mice. There were no changes in hepatic IRE1, PERK and eIF2α phosphorylation or eIF2α protein content. In conclusion, PGC-1α seems to be involved in the lifelong exercise training-induced prevention of age-associated changes in hepatic TG content and UPR components indicating PGC-1α-dependent regulation of UPR with exercise training during aging. In addition, the lack of difference in hepatic protein carbonylation between groups suggests that changes in UPR with aging and exercise training are not related to hepatic oxidative stress. The study is funded by the Danish Medical Research Council, Danish Diabetes Academy, Novo Nordisk Foundation, Augustinus Foundation.

25.6

THE IMPACT OF HYDRATION STATUS DURING HEAT ACCLIMATION ON PHYSIOLOGICAL STRAIN AND EXERCISE PERFORMANCE

Michael Schleh[1], Brent Ruby[1], and Charles Dumke[1]
[1]Hlth. and Human Performance, Univ. of Montana, 32 Campus Dr., 203 McGill Hall, Missoula, MT, 59812.

Heat acclimation improves thermal tolerance by attenuating physiological and perceptual strain associated with heat stress, and adaptations may be upheld when attenuating fluid delivery. **Purpose:** To determine i) the effect of fluid delivery by inducing dehydration (DEH=0.5 ml·kg^{-1}·15min^{-1}) compared to euhydration (EUH=2.0 ml·kg^{-1}·15min^{-1}) concurrent with three heat acclimation bouts on heat stress factors, and ii) determine the effect of aerobic performance in the heat following DEH and EUH acclimation periods. **Methods:** Thirteen aerobically fit males (23±1 yrs, 82.1±2.0 kg, 53.2±1.5 ml·kg^{-1}·min^{-1} VO_{2max}) completed a 90-minute heat stress test (HST) in hot conditions (40°C, 30% RH) walking at 50% VO_{2max} PRE and POST three EUH and DEH acclimation trials. Following each HST, aerobic performance was assessed by a graded ramp protocol by increasing treadmill grade 1% until 15%, then increasing speed 1.6 km·h^{-1} every minute to volitional exhaustion. Acclimation trials consisted of three heat exposures in the same environmental conditions, intensity, and duration as previously stated on alternating days. Subjects wore standard wildland firefighter (WLFF) Nomex: yellow shirt, green pants, and a cotton T-shirt. Peak core temperature (T_C), skin temperature (T_{SK}), heart rate (HR), rating of perceived exertion (RPE), physiological strain index (PSI), aerobic performance, and sweat rate were collected following HST. Blood samples were obtained at rest PRE and POST acclimation, and compared changes in plasma volume. All data was analyzed by a two-way analysis of variance (ANOVA) 2 (Trt) x 2 (Time). **RESULTS:** Acclimation significantly decreased peak values for Tc ($P<0.001$), T_{SK} ($P=0.005$), HR ($P<0.001$), RPE ($P<0.001$), PSI ($P<0.001$), and increased aerobic performance in time to exhaustion ($P<0.001$) in both DEH & EUH groups (main effect for time). There was no main effect for time for peak SBF or recovery ($P=0.31$, $P=0.36$ respectively). Sweat rate increased greater in DEH compared to EUH (TrtXTime interaction: $P=0.015$), and blood plasma volume increased in effect for time for the DEH group (7.1%±1.8, $P=0.009$), but not EUH (4.1%±2.5, $P=0.30$). **Conclusion:** Short-term heat acclimation attenuates heat stress and improves aerobic performance in the heat. Limiting fluid delivery during acclimation does not affect thermal strain or performance, but increases sweat capacity and plasma volume. *This study was supported by the US Forest Service.*

25.7

EFFECTS OF MARATHON TRAINING ON HEART RATE VARIABILITY DURING SUBMAXIMAL EXERCISE – A COMPARISON OF ANALYSIS DOMAINS

Christopher Lundstrom[1], George Biltz[1], Sophia Pulice[1], Katelyn Uithoven[1], Morgan Betker[1], and Eric Snyder[1]
[1]Sch. of Kinesiology, Univ. of Minnesota, 1900 University Ave., SE., Minneapolis, MN, 55455.

Introduction: Measures of heart rate variability (HRV) describe the degree and manner in which R-R intervals fluctuate. At rest, time and frequency domain analyses of HRV are used to assess health and adaptability. During exercise, HRV diminishes as intensity increases, and fractal and entropy domain analyses may be more useful in detecting changes in health or fitness. The purpose of this study was to compare HRV analysis domains during submaximal running before and after a marathon training exercise intervention. **Methods:** Forty-two recreational runners (21.1 ± 1.5 years, 28f) training for a 42.2-km marathon completed a 2-mile (3.218-km) time trial (2MI) to establish baseline fitness, then performed a submaximal run (SUBMAX) at 75% of 2MI velocity for 6 min. After completing 18 weeks of marathon training, the 2MI and SUBMAX were repeated. The final 3 min of SUBMAX were analyzed for HRV measures. Changes in HRV measures, as well as VO_2max, percent body fat, body mass, and 2MI were assessed with paired samples *t* tests. Percent change was calculated for all the variables, and Pearson's *r* was used to assess correlations between the changes. **Results:** Time and frequency domain measures of HRV did not change, with the exception of RMSSD (4.1 ± 1.3, 4.9 ± 2.0; $p = 0.050$). Some fractal and entropy domain measures of HRV changed: Poincare plot SD1 (PPSD1) (2.9 ± 0.9, 3.5 ± 1.5; $p = 0.039$), Sample Entropy (SampEn) (0.96 ± 0.50, 1.08 ± 0.46; p

= 0.039), and Detrended Fluctuation Analysis α1 (0.95 ± 0.25, 0.82 ± 0.28; p = 0.006). Both 2MI (15.6 ± 2.0 min, 14.2 ± 1.7 min; p ≤ 0.001) and VO_2max (50.6 ± 7.6, 52.7 ± 7.3; p = 0.049) improved with training. Mean HR during SUBMAX did not change (161.1 ± 9.4, 158.9 ± 9.1; p = 0.143) despite the higher velocity during post-testing. Of the variables that significantly changed with training, change in SampEn was correlated with change in 2MI (r = -.323, p = 0.042) and approached significance in correlation with change in VO_2max (r = 0.303; p = 0.057). Change in RMSSD was correlated with change in PPSD1 (r = .988; p ≤ 0.001). **Conclusions:** Decreased 2MI and increased VO_2max indicate improved aerobic capacity. SampEn appears to be related to the physiological adaptations of prolonged aerobic training experienced by a population of college-aged runners training for a marathon. RMSSD and PPSD1 both change with training and are strongly correlated with each other, but do not appear to be related to change in aerobic capacity.

25.8

INDIVIDUAL RESPONSES OF OLDER WOMEN IN TRADITIONAL HEALTH RISK FACTORS TO MODERATE-INTENSITY EXERCISE

Xuewen Wang[1], Kimberly Bowyer[1], Charity Breneman[1], Ryan Porter[1], and Sabra Custer[2]
[1]Dept. of Exercise Sci., Univ. of South Carolina, 921 Assembly St., Columbia, SC, 29208, [2]Coll. of Nursing, Univ. of South Carolina, 1601 Greene St., Columbia, SC, 29208.

Health organizations recommend regular participation in exercise for individuals to achieve health benefits. There is great variability in individuals' responses to exercise training. Most of the previous research focused on mean level changes in health risk factors. Less is known whether some individuals may experience improvements in some but deleterious effects in other risk factors. This information is important to encourage individuals to engage in physical activity in order to achieve long-term health. The purpose of this study was to examine the effects of an exercise program on multiple traditional health risk factors in older women, with a focus on individual responses. **Methods:** A total of 63 women (aged 60-75 years) participated in a 4-month exercise program which included supervised moderate intensity walking on 3-4 days a week. Before and after completion of the exercise program, waist circumference and blood pressure were measured, and fasting blood samples were drawn to determine lipids and glucose concentrations. An improvement in a risk factor was defined as a reduction in waist circumference > 2.54 cm (1 inch), systolic blood pressure > 5 mmHg, diastolic blood pressure > 5 mmHg, glucose > 5 m/dL, triglycerides > 15 mg/dL, or an increase in HDL cholesterol > 3 mg/dL. A worsening effect was defined as a change in the opposite direction in these factors with the same magnitude. A change with a smaller magnitude was considered unchanged. The study was approved by the University of South Carolina Institutional Review Board. **Results:** Eight (8) women (12.3% of total) had improvements in 5 or more risk factors, 12 (19%) had improvements in 3, 25 (39.7%) had improvements in 2, 16 (25.4%) had improvements in one factor, and 2 women (3.2%) did not experience improvement in any risk factor. On the other hand, 13 women (20.6%) had 3 or 4 factors worsened, 14 women (22.2%) had 2 factors worsened, and 19 women (30.2%) had one factor worsened. The 46 women who had any worsened risk factor, except 2 women, also had simultaneous improvements in other factors. **Conclusion:** A moderate-intensity exercise training induced favorable response in some risk factors in almost all women. About three quarters of women had worsened risk factors; however, they also had improvements in other risk factors. Personalized exercise programs may be needed to target specific risk factors.

25.9

EFFECTS OF RESISTANCE EXERCISE TRAINING WITH/WITHOUT PROTEIN SUPPLEMENTATION IN BARTH SYNDROME

William Cade[1], Adam Bittel[1], Kathryn Bohnert[1], Linda Peterson[2], Manuela Corti[3], Barry Byrne[3], and Dominic Reeds[2]
[1]Physical Therapy, Washington Univ. Sch. of Med., Campus Box 8502, 4444 Forest Park Ave., St. Louis, MO, 63108, [2]Int. Med., Washington Univ. Sch. of Med., 660 S. Euclid Ave., St. Louis, MO, 63110, [3]Pediatrics, Univ. of Florida, 1600 SW Archer Rd., Gainesville, FL, 32607.

Background. Barth syndrome (BTHS) is a rare X-linked disorder resulting in mitochondrial dysfunction. Cardioskeletal myopathy in BTHS contributes to exercise intolerance, fatigue, skeletal muscle weakness/atrophy, and reduced quality of life. The effects of RET in BTHS are unknown. Whole-body protein catabolism is increased in BTHS, thus individuals with BTHS may derive further benefit from the addition of a protein supplement to RET. The purpose of this pilot study was to determine if RET is safe/feasible in BTHS, and to characterize changes in muscle strength and performance, body composition, exercise capacity, and quality of life following 12 weeks of RET. We also examined whether protein supplementation could enhance the effect of RET. Methods: Adolescents and young adults with BTHS (n=6, 21 ± 6 yrs) and age and activity matched controls (CON, n=3, 22 ± 2 yrs) underwent baseline testing to assess muscle strength and performance (1 repetition maximum testing (1RM), isokinetic dynamometry), exercise capacity (VO_{2peak}), body composition (lean and fat mass, and bone mineral density using DXA), and health-related quality of life. Subsequently, 5 participants with BTHS performed 12 weeks of supervised RET (60 min, 3/wk). Two participants also consumed a daily oral whey protein supplement (42 g/day) during RET. All testing was repeated post-RET. Results: At baseline, compared to CON, BTHS had reduced 1RM strength of the upper and lower extremities, lower extremity muscle torque, work, and power. RET was well-tolerated and adhered to (100% of visits completed). RET increased muscle strength ($p<0.05$ for all 1RM), and arm ($p=0.03$) and lumbar spine ($p=0.04$) bone mineral density. RET promoted modest reductions in whole-body and regional fat mass (1.6-3.2%), increases in whole-body and regional lean mass (0.24-5.8%), as well as improvements in max work rate (mean 5.8%), and quality of life (mean 4.2%). The protein supplemented participants had greater improvements in quality of life ($p=0.02$), and trends toward greater improvements in lean tissue mass, 1RM strength (mean 15%), VO_{2peak} (mean 7.4%), and maximal work rate on the graded exercise test (mean 4.2%), than RET without protein. Conclusions:

RET is well-tolerated in BTHS and promotes increases in strength, bone density, lean mass, and exercise tolerance, which are augmented by the addition of a whey protein supplement. Adding protein supplementation might enhance benefits from RET in BTHS.

25.10

RESPONSE AND ADAPTATION OF SKELETAL MUSCLE TO ENDURANCE TRAINING BASED ON CIRCADIAN RHYTHMS OF CLOCK GENE EXPRESSION

Hisashi Takakura[1], Hisashi Kato[1], Shinya Masuda[2], Daishisn Ueno[3], Mutsuko Hieda[1], and Tetsuya Izawa[1]

[1]Fac. of Hlth. & Sports Sci., Doshisha Univ., 1-3 Tatara-Miyakodani, Kyotanabe City, 610-0394, Japan, [2]Clinical Res. Inst., Natl. Hosp. Organization Kyoto Med. Ctr., 1-1 Fukakusamukaihatacho, Fushimi-ku, Kyoto City, 612-8555, Japan, [3]Grad. Sch. of Biological Sci., Nara Inst. of Sci. and Technology, 8916-5 Takayama-cho, Ikoma City, 630-0192, Japan.

Objective: Circadian rhythmic fluctuations of body temperature, hormone secretion, and gene expression were reported to be regulated by the molecular clock. Major clock genes (Bmal1 and Per2) exhibit circadian rhythm, and the expression pattern of Per2 mRNA is synchronous with that of PGC-1α mRNA in skeletal muscles, which is a master regulator of mitochondrial biogenesis. Additionally, PGC-1α mRNA expression is increased as an acute response to endurance exercise. Therefore, timing of exercise may induce the difference in PGC-1α mRNA expression levels after a few hours of acute exercise, leading to different training-induced adaptations in skeletal muscles. The purpose of this study was to determine whether the timing of exercise enhances exercise training-induced increases in the levels of mitochondrial proteins in skeletal muscles. Method: Male Wistar rats were randomly assigned to the following training and control groups: the Tr@6AM group, exercise training at 6:30 AM; Tr@8PM group, exercise training at 8:00 PM; Con@6AM group, time-matched to the Tr@6AM group; and Con@8PM group, time-matched to the Tr@8PM group (each group, n = 9-10). The rats in the Tr groups underwent treadmill-running training at ~30 m/min for ~90 min, 5 days a week for 9 weeks. In addition to the above training experiment, the rats underwent acute exercise (17 m/min, 60 min) at two time points: when Per2 mRNA expression showed the highest and lowest expression (Ex@8PM and Ex@6AM) (each group, n = 6). The gastrocnemius muscle was excised forty-eight hours after the last exercise training or immediately, 3 h, or 6 h later after acute exercise. For evaluating exercise training-induced adaptation and acute response, the expression levels of mitochondrial proteins [COXIV, citrate synthase (CS)] and PGC-1α in the deep portion of the gastrocnemius muscle was measured by western blotting, enzyme activity measurement or real-time PCR. Results: COXIV level and CS activity were significantly higher in the Tr groups than in the Con groups. Moreover, COXIV level and CS activity in the Tr@6AM group were significantly increased compared to those in the Tr@8PM group. PGC-1α mRNA expression was significantly increased immediately after acute exercise only at Ex@6AM. Conclusion: The timing of exercise training influenced training-induced adaptation. The differential adaptation in skeletal muscle might be caused by the differential PGC-1α expression upon acute exercise.

25.11

CD36 IS ESSENTIAL FOR EXERCISE TRAINING-INDUCED IMPROVEMENT IN RUNNING ENDURANCE

Mark Christian Manio[1], Shigenobu Matsumura[1], Daisaku Masuda[2], and Kazuo Inoue[1]

[1]Grad. Sch. of Agriculture, Kyoto Univ., Kitashirakawa Oiwake-cho, Sakyo-ku, Kyoto, Kyoto, 606-8502, Japan, [2]Grad. Sch. of Med., Osaka Univ., 1-1 Yamadaoka, Suita, Osaka, 565-0871, Japan.

CD36 is a transmembrane protein that participates in the uptake of long-chain fatty acids. The absence of CD36 negatively impacts acute exercise performance, fuel selection and utilization during exercise. However, the effect of exercise training on running endurance and whole-body metabolism during exercise, and compensatory metabolic adaptation in the absence of CD36 have not been explored. **Methods:** To determine the effects of training in endurance performance, whole-body metabolism and metabolites at exhaustion, the following was conducted. Eight (8)-week old wild-type (W) and CD36 knock-out (K) mice were trained (T) on a treadmill daily for 30 days. Untrained mice (U) of both genotypes served as controls. During the training period, mice were fed a standard diet containing 30% kcal from fat. About 48 hours after the last training session, mice were forced to run until exhaustion with simultaneous measurement of whole-body metabolism by indirect calorimetry. At exhaustion, energy metabolites in blood, gastrocnemius and liver were measured. To determine how the absence of CD36 influences exercise adaptation after a single exercise bout, 12 week-old mice (fed the same standard diet from 8 weeks) were made to run (R) for 50 min at 15 m/min. No-run (N) groups served as controls. Eight (8) hours later, gastrocnemius was collected. Citrate synthase activity, *Pgc1a* and *Pdk4* mRNA expression were measured. **Results:** In wild-type mice, training (WT) improved endurance compared to untrained controls (WU) ($p<0.001$). This was absent in knock-out trained (KT) mice relative to untrained controls (KU). In support of earlier studies, KU had impaired endurance relative WU ($p<0.0001$). In the first 60 min of the run, oxygen consumption (VO2) was unchanged between WU and WT. KU had higher (n.s.) VO2 relative to WU. Interestingly, KT had lower VO2 than KU ($p<0.01$). Higher average respiratory exchange ratio (RER) was observed in KU and KT compared to WU and WT, respectively ($p<0.001$). There was no difference in average RER between KU and KT while that of WT decreased compared to WU ($p<0.05$). Calculated substrate oxidation showed decreased carbohydrate oxidation (CHO) in trained groups without concomitant increases in fat oxidation (FAT). Observed elevated average RER in K groups relative to W groups can be attributed to elevated CHO and low FAT. Despite running equal distances, differences in concentration of metabolites were observed between KU and KT. After a single bout run, mRNA expression of *Pgc1a*, an exercise responsive and adaptation-related gene, increased in knock-out mice that ran (KR) relative to no-run control (KN) ($p<0.001$). Interestingly, *Pgc1a* relative expression in KR was

significantly lower relative to wild-type mice that ran (WR) ($p<0.05$). These suggest that CD36 is essential for improvement in running endurance by exercise-training.

25.12

SIX WEEKS OF SPRINT TRAINING IMPROVES SPRINT TIME AND AEROBIC FITNESS INDEPENDENT OF TRAINING PERFORMED ON A TRACK OR TREADMILL

Manuel Amador[1], Cesar Meza[1], Jeremy Perales[1], Sandor Dorgo[1], and Sudip Bajpeyi[1]
[1]Kinesiology, Univ. of Texas at El Paso, 500 W. University Ave., El Paso, TX, 79902.

Previous studies on sprint training have shown an improvement in sprint speed, aerobic fitness, body composition and also in ventilatory threshold. However, it remains unclear weather sprint training above ground is more effective in improving these variables compared to training on a high-speed treadmill. The aim of this study was to examine the effects of a 6-week track (TR) vs. high-speed treadmill (TM) sprint training on ventilatory threshold (VT), aerobic fitness, and body composition. Eleven subjects were randomly assigned to the TR (n=4; 3 females, 1 male) or TM training group (n=5; 2 female, 3 male) All subjects performed 2 training sessions per week. Sessions were composed of 4 maximal sprints with 3-4 minutes of rest in between attempts. Four cones were placed along the track to simulate progression of speed to replicate conditions on the treadmill. The TR group started from an upright jog position and progressively increased speed at each cone (60%, 70%, 80%, and 90%) of maximal speed and 100% maximal speed through the designated recording zone (5-6 seconds). A treadmill speed test was used to determine the subjects maximal speed until the loss of control while suspended from a safety harness. VO2 max and ventilatory threshold were measured using Parvomedics True Max 2400 metabolic cart and body composition was measured using Dual Energy X-ray absorptiometry (DXA) at baseline and after the 6 weeks of training. Treadmill sprint speed improved significantly in both groups (TR 16.36±0.54 to 17.79±0.52 miles/hr, p=0.0003; TM 17.13±0.84 to 18.63±0.93 miles/hr, p=0.0018). VO2 max was improved in both groups (TR 46.60±2.03 to 49.54±1.71 ml/kg/min, p=0.03; TM 47.59±4.152 to 51.05±4.445 ml/kg/min, p=0.04). There was no significant change in body mass index (TR 24.1±1.0 to 24.0±1.0 kg/m^2; p=0.51; TM 24.5±0.7 to 24.1±0.8; p=0.30) or in lean mass (TR 44.08±3.12 to 43.80±2.62 kg; p=0.73; TM 48.41±5.29 to 44.55±7.49 kg; p=0.36) in either group. There was a significant decrease in percent body fat in the TR group (30.36±3.75 to 29.20±3.75%; p=0.01) but not in the TM group (27.83±5.50 to 27.20±5.95%; p=0.38). There was no significant change in ventilatory threshold (TR 58.69±3.46 to 53.29±3.613 % VO_2max; p=.322; TM 54.48±2.922 to 55.04±2.148 % VO_2max;p=.88). In conclusion, both track and treadmill sprint training modalities demonstrated to be effective to improve sprint speed, aerobic power after the 6 weeks of training without any improvement in ventilator threshold. However, only the track sprint training group appears to be beneficial towards decreasing body fat.

25.13

EXERCISE TRAINING REDUCES LIVER FAT CONTENT AND IMPROVES PERIPHERAL BUT NOT HEPATIC INSULIN SENSITIVITY IN OVERWEIGHT AND OBESE MEN WITH NON-ALCOHOLIC FATTY LIVER

Bram Brouwers[1], Vera B. Schrauwen-Hinderling[1], Tomas Jelenik[2], Anne Gemmink[1], Bas Havekes[1], Yvonne Bruls[1], Dennis Dahlmans[1], Michael Roden[2], Patrick Schrauwen[1], and Matthijs Hesselink[1]
[1]Dept. of Human Biology and Human Movement Sci., Maastricht Univ. Med. Ctr., Universiteitssingel 50, Maastricht, Netherlands, [2]Inst. for Clinical Diabetology, German Diabetes Ctr., Leibniz Ctr. for Diabetes Res. at Heinrich-Heine Univ. Düsseldorf, Stadtbezirk 3, Auf'm Hennekamp 65, Duesseldorf, Germany.

Non-alcoholic fatty liver (NAFL) is associated with insulin resistance and the development of type 2 diabetes mellitus (T2DM). We investigated the degree of metabolic aberrations in obese people with or without NAFL compared to T2DM patients. We further examined if exercise training could improve these metabolic aberrations in parallel to improving intrahepatic lipid (IHL) content. Eleven males with NAFL, 13 with T2DM and 11 BMI-matched controls (CTRL) performed a 12-week supervised, progressive, combined aerobic and resistance, exercise training program. VO_2max (spiroergometry), one repeated maximum (1RM), IHL (proton magnetic resonance spectroscopy (^{1}H-MRS)) and insulin sensitivity (hyperinsulinemic-euglycemic clamp) were measured before and after exercise training. Before exercise training, VO_2max (27.6±1.4, 26.1±1.4 and 25.6±1.0 ml/min/kg for CTRL, NAFL and T2DM, $p>0.05$, respectively) and 1RM (78.9±4.2, 89.5±5.4, 74.5±2.6 kg for CTRL, NAFL and T2DM, $p>0.05$, respectively) was comparable between groups. IHL was significantly lower in CTRL (1.9±0.4%) than in NAFL (9.7±2.0%, $p<0.001$) and T2DM (8.9±3.3%, p=0.045), while IHL was comparable in the latter two (p=0.251). Hepatic (p=0.977), skeletal muscle (p=0.713) and adipose tissue (p=0.678) insulin sensitivity was similarly reduced in NAFL and T2DM when compared to CTRL (all $p<0.05$). Exercise training significantly improved VO_2max (to 30.4±1.5, 29.9±1.4, and 26.8±0.9 ml/min/kg, all $p<0.05$, in CTRL, NAFL and T2DM, respectively) and 1RM (to 93.3±6.2, 109.0±5.3, and 86.7±2.3 kg, all $p<0.05$, in CTRL, NAFL and T2DM, respectively) in all groups. Exercise training significantly decreased IHL by 22.7% in NAFL (to 7.5±1.3 %, p=0.038), but not in T2DM (to 9.9±4.1 %, p=0.378) and CTRL (to 1.5±0.3 %, p=0.182). Skeletal muscle insulin sensitivity improved by 36% in NAFL (from 10.8±2.5 to 14.7±3.1 µmol/min/kgFFM, p=0.014) and 22% in CTRL (from 33.3±2.9 to 40.6±3.8 µmol/min/kgFFM, p=0.036) upon exercise training. Hepatic and adipose tissue insulin sensitivity was unaffected (all $p>0.05$). Surprisingly, insulin sensitivity did not improve in T2DM (all $p>0.05$). These data indicate that obese individuals with NAFL were characterized by severe insulin resistance, comparable to T2DM patients. Exercise training reduced IHL and improved skeletal muscle insulin sensitivity in NAFL. Exercise training did not affect hepatic or adipose tissue insulin sensi-

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25.14

PHYSICAL TRAINING PREVENTS THE IMPAIRED THERMAL BALANCE IN HYPERTENSIVE ANIMALS DURING EXERCISE

[1]Coimbra, C. C., [1]Campos, H. O., [1]Drummond, L. R., [1]Gonçalves, G. K., [1]Lima, P. M. A., [1]Horta, N. A. C., and [2]Prímola-Gomes, T. N.

[1]Dept. of Physiology and Biophysics, Inst. of Biological Sci., Univ. Fed. de Minas Gerais, Belo Horizonte/MG, [2]Dept. of Physical Edu., Lab. of Exercise Biology, Univ. Fed. de Viçosa, Viçosa/MG.

The aim of this study was to investigate the effects of physical training on thermal balance in SHR during exercise. Male SHR and Wistar (WIS) rats at 5-weeks age old were divided into four groups with eight animals each: untrained WIS (WIS-UT), trained WIS (WIS-T), untrained SHR (SHR-UT) and trained SHR (SHR-T). Experimental procedures were approved by the CEUA-UFMG (#49/2015). Aerobic exercise training was performed on a treadmill for 8 weeks. Incremental exercise running test until fatigue was performed at two different times: pre- and post- exercise training. On the day of the experiments, T_b, T_{tail}, and oxygen consumption (VO_2) were recorded during constant-speed exercise until fatigue (60% maximum speed) and the mechanical efficiency was calculated. After constant-speed exercise, the animals were euthanized, and the brown adipose tissue was collected to quantification of uncoupling protein 1 (UCP1) by western blot. Exercise training increased the physical performance in the WIS-T (68.1 ± 3.3 min) and SHR-T (64.7 ± 1.5 min) compared with WIS-UT (49.8 ± 4.2 min) and SHR-UT (44.8 ± 1.6 min) groups, respectively ($p < 0.05$, *two-way* ANOVA). The heat production during the constant exercise was similar between the four groups ($p > 0.05$, *two-way* ANOVA). Heat dissipation, analyzed by ΔT_{tail}, was higher in SHR-T when compared with WIS-T from 3-16 min ($p < 0.05$, *two-way* ANOVA). SHR-UT had higher ΔT_b compared with WIS-UT ($p < 0.05$, *two-way* ANOVA), while the ΔT_b was similar between SHR-T and WIS-T during all exercise trial ($p > 0.05$, *two-way* ANOVA). UCP1 expression in BAT was higher in SHR-T (1.28 ± 0.23 u.a) when compared with WIS-T (0.26 ± 0.07 u.a.) ($p < 0.05$, *two-way* ANOVA). The SHR-UT (9.3 ± 1.2 %) and SHR-T (16.0 ± 0.3 %) groups had lower mechanical efficiency when compared to WIS-UT (26.9 ± 3.2 %) and WIS-T (27.2 ± 2.6 %), respectively ($p < 0.05$, *two-way* ANOVA). However, the exercise training increased the mechanical efficiency of hypertensive animals (SHR-T: 16.0 ± 0.3 % *vs.* SHR-UT: 9.3 ± 1.2 %, $p < 0.05$, *two-way* ANOVA). In conclusion, exercise training prevented the deficit of thermal balance in hypertensive rats during exercise that was associated with an improved mechanical efficiency in hypertensive rats. **Financial support**: CNPq, CAPES, FAPEMIG.

25.15

REGULAR EXERCISE INDUCES CHANGES IN BASAL DAILY TURNOVER OF DOPAMINE AND SEROTONIN IN THE PRE-OPTIC AREA

Cândido Coimbra[1], Frederico Machado[1], Quezia Rodrigues[1], Nayara Horta[1], Thaís Araújo[1], Nayara Aquino[1], Raphael Szawka[1], and Maristela Poletini[1]

[1]Phisiology and Biophysics, UFMG, Antonio Carlos Av 6627, Belo Horizonte, 31270901, Brazil.

Background. Physical activity entrains the circadian system. These effects might be mediated by central nervous system adaptations induced by regular exercise, such as HPA axis activity and tuning of the thermoregulatory system. Thus, we investigated if 8 weeks of exercise training affected catecholamine turnover in distinct brain areas involved in thermoregulation, motor control and reward processes. Methods. Wistar rats, housed at a 12/12-light/dark cycle, were submitted to 8 weeks of exercise training. At the last week of training, core body temperature (Tc) and locomotor activity (LA) were continuously recorded with an implantable telemetry sensor. The tail skin temperature (Tsk) was also taken before and after the exercise sessions. Two days after the last exercise test, animals were euthanized and the brains were processed for HPLC analysis in the caudate putamen, pre-optic area and paraventricular nucleus. Results. Training sessions induced daily episodes of hyperthermia and cutaneous vasodilation only in trained animals. Besides, trained animals exhibited increased exercise capacity and thermoregulatory efficiency ($p<0.0001$). During the training protocol, 24 h cycles of Tc and LA were affected by regular physical activity ($p<0.0001$). Furthermore, trained animals showed higher LA in the active phase ($p<0.0001$). These changes were followed by decreased basal turnover of dopamine and serotonin in the pre-optic area. In contrast, the turnover of cathecolamines in the caudate and the paraventricular nucleus were not directly affected by the training paradigm. Conclusions. Taking these findings together, we conclude that central adaptation induced by daily exercise might be related to adjustments in the circadian timing system, reinforcing its role as an independent entraining agent. Funding agencies: FAPEMIG, CNPq and PRPQ/UFMG.

26.0 CARDIOVASCULAR

26.1

POSTNATAL UNDERNUTRITION ALTERS FEMALE MOUSE CARDIOMYOCYTE STRUCTURE AND FUNCTION LEADING TO IMPAIRMENT IN EXERCISE CAPACITY

David Ferguson[1,2,3], Tanner Monroe[2], Ryan Fleischmann[3], George Rodney[2], George Taffet[4], and Marta Fiorotto[3]

[1]Kinesiology, Michigan State Univ., 308 W. Circle Dr., Off. 27S, East Lansing MI, MI, 48824, [2]Molecular Physiology and Biophysics, Baylor Coll. of Med., 1 Baylor Plaza, Houston, TX, 77030, [3]Children's Nutrition Res. Ctr., Baylor Coll. of Med., 1 Baylor Plaza, Houston, TX, 77030, [4]Geriatrics, Baylor Coll. of Med., 1 Baylor Plaza, Houston, TX, 77030.

Epidemiological studies have shown that adults who were born with low birth weight are at increased risk of developing cardiovascular disease in adulthood. However, little is known about the contribution of cardiac mechanisms to this increased disease risk. Using a mouse model we evaluated cardiovascular function at the whole animal, organ, and cell level to determine the effect

of a short episode of nutritionally-induced growth retardation on adult functional capacity following nutritional rehabilitation. Pups born to control dams were suckled from birth to postnatal day 21 (PN21) on dams fed either a control (20% protein) or a low protein (8% protein) isocaloric diet to induce a reduction in milk production. After weaning (PN21), all offspring were fed the control diet until adulthood (PN70). At PN70 cardiac function was measured by a maximal treadmill test (VO_{2max}), echocardiography with Doppler blood flow analysis (with and without beta adrenergic stimulation). Cardiomyocytes were isolated by Langendorff reperfusion and cell nucleation and calcium transients (with and without beta adrenergic stimulation) quantified. Results showed that mice that were undernourished and then refeed (UNRF) did not experience complete catch-up growth and had impairment in exercise capacity and cardiac output. The impairment in cardiac function did not arise from a reduction in heart size but rather impairment in structure and function. Specifically, the UNRF mice had more mononucleated cardiomyocytes and a limited ability to alter calcium flux and heart rate when stressed with adrenergic stimulation as compared to controls. This led to an inability for the UNRF mice to increase cardiac output when additional load was placed on the heart. Thus, a brief episode of undernutrition in early postnatal life altered cardiac structure and function leading to a reduction in exercise/functional capacity and thereby increasing the risk for the development of cardiovascular morbidities and chronic metabolic diseases.

26.2

LEG RESISTANCE HIGH-INTENSITY INTERVAL EXERCISE IMPROVES ENDOTHELIAL FUNCTION IN OLDER ADULTS WITH AND WITHOUT TYPE 2 DIABETES

Monique Francois[1], Cody Durrer[1], and Jonathan Little[1]
[1]Sch. of Hlth. and Exercise Sci., Univ. of British Columbia, Okanagan, 3333 University Way, Kelowna, BC, V1V 1V7, Canada.

Introduction: Different modes and exercise intensities result in distinct patterns of endothelial shear stress; not only within the active muscle bed but also across the inactive vasculature. Low volume high-intensity interval training (HIIT) is a time-efficient form of exercise shown to elicit numerous physiological health benefits including improved endothelial function. To date no study has examined the acute effect of leg resistance-based HIIT on brachial artery endothelial function. **Method:** We examined the effect of a single session of resistance- and cardio-based HIIT compared to a time-matched control condition on endothelial function in 12 age-matched T2D participants, 12 untrained and 11 trained adults (age = 56 ± 7 y). Flow-mediated dilation (%FMD) of the brachial artery was assessed at baseline and immediately, 1 and 2 h after an acute bout of Cardio-HIIT, resistance-HIIT (Res-HIIT) and seated control (CTL); these interventions were randomized and separated by > 2 days. Cardio-HIIT involved 7 X 1-min cycling intervals at 85% of peak power with 1-min recovery between. Res-HIIT involved the same pattern of 7 X 1-min intervals using leg resistance exercises. **Results:** Endothelial function (%FMD) was improved after Res-HIIT in all groups (Condition X Time interaction, $p<0.01$), an effect that was most robust in T2D where %FMD was increased immediately (+4.0 ± 2.8%), 1 h (+2.5 ± 2.5%) and 2 h (+1.9 ± 1.9%) after Res-HIIT compared to CTL ($p<0.01$ for all). Cardio-HIIT improved %FMD in T2D at 1-h post-exercise (+1.6 ± 2.2%, $p=0.03$) and in trained participants 2-h post-exercise (+2.4 ± 1.5%, $p<0.01$). Baseline blood flow and vascular conductance were significantly increased immediately after Cardio- and Res-HIIT in all groups (all $p<0.05$). **Conclusion:** In conclusion, our data indicate a potential therapeutic effect of resistance HIIT on endothelial function in older adults with and without type 2 diabetes. The mechanisms underlying these effects warrant further investigation.

26.3

LIFESTYLE AND OCCUPATIONAL INFLUENCES ON CARDIOVASCULAR HEALTH IN POLICE OFFICERS

Morgan Betker[1], Ian West[2], Gabrielle Brewer[2], Zachary Peters[2], and Eric Snyder[2]
[1]Kinesiology, Univ. of Minnesota, 2700 Harriet Ave., S., Apt. 302, Minneapolis, MN, 55408, [2]Kinesiology, Univ. of Minnesota, 1900 University Ave., SE, Minneapolis, MN, 55455.

Introduction: Police officers have greater risk for sudden cardiac death on duty than any other private sector occupation. Previous work has demonstrated that traditional risk factors (blood lipids and inflammatory markers) may be partially responsible for increased CVD between police officers and the general population. Lifestyle factors such as shift work, physical inactivity, BMI, body composition (BF%), sleep and job stress may also impact this risk. To our knowledge, no previous study has evaluated heart rate variability (HRV) and heart rate recovery (HRR, post-maximal exercise), and their relationship to these lifestyle variables. Therefore, the objective of this study was to assess HRV, VO_{2MAX}, HRR, resting heart rate (RHR), shift time, exercise, sleep and job duty. **Methods:** 52 male officers (age 33.4±5.3, ht 66±1.7in, wt 163±46.4lbs, BMI 26.21±7.0, %BF 28.5±6.9) and 12 female officers (age 40.1±8.9, ht 71.3±2.5in, wt 204.8±31.0, BMI 28.3±3.7, BF% 21.54±6.66) completed the study. Lifestyle factors were self-reported. Subjects' RHR and HRV were then assessed (Kubios HRV 2.2, Kuopio, Finland) while the subject rested supinely in a dark room for 30 minutes. A graded exercise test measured VO_{2MAX} and HRR post-exercise. **Results:** Multiple regression analysis of cardiovascular health and lifestyle variables showed that age was significant and negatively correlated with HRV ($r=-0.652$, $p<0.001$). When BMI was accounted for, those within normal range (BMI 18.5-24.9) had moderate correlations between lifestyle variables and HRV ($r=0.91$, $p=0.296$), however those in the overweight category (BMI 25-29.9) demonstrated stronger, and significant ($r=0.87$, $p= 0.012$), relationships between shift time and HRV when standardized for shift time. For those in the largest BMI category (BMI >30), there was a significant relationship between HRV and BF%, overtime hours, exercise time per week and HRR ($p<0.05$), while VO_{2MAX} was trending toward significance ($p=0.052$). **Conclusion:** These results indicate that job and lifestyle indicators of overall health are related to HRV (an index of autonomic nervous system function) only in individuals with a BMI greater than 30. These results confirm previous

work in the general population suggesting the paramount importance of maintaining a healthy weight.

26.4

DETERMINING THE THRESHOLD FOR PROTECTIVE EFFECTS OF AEROBIC EXERCISE ON AORTIC STRUCTURE IN A MOUSE MODEL OF MARFAN SYNDROME ASSOCIATED AORTIC ANEURYSM

Christine P. Gibson[1], Michael Farney[1], Douglas Gaufin[1], Roshanak Rahimian[2], Tom Broderick[3], Johana Vallejo-Elias[3], and Mitra Esfandiarei[1]

[1]Biomedical Sci., Coll. of Hlth. Sci., Midwestern Univ., 19555 N. 59th Ave., Glendale, AZ, 85308, [2]Physiology & Pharmacology, Thomas J. Long Sch. of Pharmacy & Hlth. Sci., Univ. of the Pacific, 3601 Pacific Ave., Stockton, CA, 95211, [3]Physiology, Arizona Coll. of Osteopathic Med., Midwestern Univ., 19555 N. 59th Ave., Glendale, AZ, 85308.

Aortic aneurysm is the leading cause of death in Marfan syndrome (MFS), a connective tissue disorder caused by mutations in fibrillin-1 gene. MFS aneurysm is characterized by weakening of the aortic wall. The above-average height make young adults with MFS desirable candidates for sports; but little is known about the exercise limit at which they will be at risk for aortic rupture. Yet, aerobic exercise has been shown to have protective effects on the heart and aorta. In this study, our objective was to investigate the effects of various levels of exercise intensity on the progression of aortic aneurysm in the mouse model. At 4 weeks of age, we subjected control and MFS mice to different levels of exercise intensity (8m/min, 10m/min, 15m/min, and 20m/min, corresponding to 55%, 65%, 75%, and 85% of $\dot{V}O_2$ max) on a treadmill for 30 minutes per day, 5 days a week for the duration of the study. At 24 weeks of age, aortic tissue were isolated and subjected to structural and functional studies using histology and wire myography in order to evaluate the effects of different exercise routines on elastin fragmentation and organization and aortic wall elasticity. Our data shows that exercise training at the intensity levels between 55-75% significantly reduces elastin fragmentation and disorganization. The reversibility of elasticity was also significantly restored in MFS mice subjected to 55-75% intensity. Our data also shows that smooth muscle cells (SMCs) contraction in response to vasoconstrictor agent phenylephrine is significantly reduced in sedentary MFS aorta as compared to control. At 55%, exercise did not rescue SMC contraction, while at higher intensity levels, SMC contraction in response to phenylephrine was significantly increased as compared to sedentary MFS aorta. This study provides the first evidence that high intensity exercise (e.g. 85%) may not provide the most beneficial effects on aortic function and structure during the progression of aortic aneurysm in MFS mice. Based on our observations, medium intensity exercise (e.g. 65%) seems to provide the utmost protective effects on aortic structure and function in MFS mice. These findings provide new insights into the potential capacity, in which MFS patients could participate in various aerobic exercise routines, especially in young adults affected by cardiovascular complications particularly aortic aneurysm. This work was funded by Midwestern University Research Fund.

26.5

CHRONIC LOW-INTENSITY EXERCISE TRAINING PREVENTS BK_{CA} CHANNEL-DEPENDENT CORONARY VASCULAR DYSFUNCTION IN AORTIC-BANDED MINI-SWINE

T. Dylan Olver[1], Brian Ferguson[1], Jessica Hiemstra[1], Pamela Thorne[1], Jan Ivey[1], Melissa Cobb[1], Michael Hill[2,3], M. Harold Laughlin[1,2,3], and Craig Emter[1]

[1]Biomedical Sci., Univ. of Missouri, Columbia, 1600 E. Rollins, Columbia, MO, 65211, [2]Med. Pharmacology & Physiology, Univ. of Missouri, Columbia, One Hospital Dr., Columbia, MO, 65212, [3]Dalton Cardiovascular Res. Ctr., Univ. of Missouri, Columbia, 134 Research Park Dr., Columbia, MO, 65211.

Conventional treatments have failed to improve the prognosis of heart failure with preserved ejection fraction (HFpEF) patients. We previously reported chronic low-intensity interval exercise training (LI-ET) attenuates coronary vascular dysfunction in aortic-banded (AB) mini-swine characterized by the loss of smooth muscle cell Ca^{+2}-activated potassium channel current. The purpose of this study was to determine if the specific loss of large conductance Ca^{+2}-activated potassium (BK_{Ca}) channels is a key mechanism underlying coronary vascular dysfunction in HF that is treatable with exercise training. The therapeutic dose of exercise was optimized through examination of LI-ET and low-intensity moderate continuous exercise training (LI-CT) in parallel. We hypothesized exercise would prevent AB-induced decreases in BK_{Ca} channel-dependent coronary vasodilatory capacity. Male intact Yucatan mini-swine were divided into 4 groups (n=7/group): sedentary control (CON), sedentary AB-HF (HF), AB-HF LI-CT (HF-CT), and AB-HF LI-ET (HF-IT). *In vivo* coronary blood flow (CBF) and vascular conductance (CVC) after intracoronary infusion of the BK_{Ca} channel α-subunit agonist NS-1619 (200 μg/min) were measured in the left anterior descending coronary artery under anesthesia. *In vitro* assessment of isolated coronary arteriole function was examined using pressure myography following an NS-1619 dose response curve ($1e^{-10}$ - $1e^{-4}$). Skeletal muscle citrate synthase activity was decreased and left ventricular (LV) brain natriuretic peptide mRNA levels increased in HF vs. CON & HF-IT animals. These effects of HF were not prevented in the HF-CT group. NS-1619-dependent coronary vasodilatory reserve (max. Δ in CBF & CVC) was decreased in HF vs. CON animals. Coronary reserve was normal in HF-CT and increased in HF-IT animals relative to CON. Isolated coronary arteriole vasodilatory capacity in response to NS-1619 was decreased in the HF vs. CON, HF-CT, and HF-IT groups. In conclusion, these results demonstrate BK_{Ca} channel-mediated coronary dysfunction is associated with pressure-overload HF in a translational model with potential relevance to human HFpEF. Exercise intensity was important to optimizing functional benefit, as LI-ET was most effective at preventing both central and peripheral hallmark adaptations of HF. These data illustrate the therapeutic efficacy of exercise training for treating HFpEF from a whole body perspective. Support - NIH R01 HL112998, PI: CAE.

26.6

EFFECT OF GLUCAGON-LIKE PEPTIDE-1 AND AEROBIC EXERCISE ON CARDIOVASCULAR FUNCTION IN GOTO-KAKIZAKI RATS

Rebecca Scalzo[1], Leslie Knaub[1], Amy Keller[1], Lori Walker[3], and Jane Reusch[1,3]

[1]Endocrinology, Metabolism, and Diabetes, Univ. of Colorado, Denver, 12801 E. 17th Pl., Aurora, CO, 80045, [2]Cardiology, Univ. of Colorado, Denver, 12801 E. 17th Pl., Aurora, CO, 80045, [3]Endocrinology, Denver VA Med. Ctr., 1055 Clermont St., Denver, CO, 80220.

Functional exercise capacity is inversely related to all-cause and cardiovascular mortality and it is impaired in people with type 2 diabetes mellitus (T2D). Additionally, T2D is associated with vascular dysfunction. Defining the relationship between impaired functional exercise capacity and vascular function in T2D is critical for delivering the benefits of exercise in patients with T2D. Glucagon-like peptide-1 (GLP-1), an insulin secretagogue, has a direct effect on cardiovascular function. We previously reported that the dipeptidyl peptidase-4 inhibitor saxagliptin, an agent that decreases degradation of endogenous GLP-1, augments the improvement in functional capacity observed with exercise training. Here, we explore the direct action of GLP-1 on functional capacity. We hypothesized that exenatide, a GLP-1 receptor agonist, would improve cardiovascular responsiveness and exercise capacity in Goto-Kakizaki rats (GK), a rodent model of T2D. Male Wistar (n=31; aged 14-15 weeks) and GK rats (n=30; aged 20-22 weeks) were randomized to 4 groups: sedentary control, exercise (EX; 3 weeks of progressive treadmill running), exenatide (GLP-1; 4 weeks continuous delivery via subcutaneous osmotic pump), or EX + GLP-1. Run to fatigue distance was significantly greater with EX as compared with controls for both Wistar (2337 ± 501 m vs. 675 ± 405 m; mean ± SE; $P < 0.0001$) and the GK (1827 ± 415 m vs. 323 ± 77 m; $P = 0.009$). There was no effect on functional capacity with GLP-1. In the GK exercised rats only, there was a significant increase in *ex vivo* aortic contraction in response to potassium ($P = 0.026$) and acetylcholine mediated relaxation ($P = 0.033$); these metrics were unchanged in the Wistar rats. Finally, left ventricular mitochondrial respiration (Oroboros O2K) was unaffected by EX/GLP-1 in any animals. These data suggest that aerobic exercise training improves functional capacity in a rodent model of T2D through a potential reduction in arterial stiffness (increased responsiveness to potassium) and augmented vasodilation. Of interest, we have previously observed improved vascular function with twice daily intraparitoneal injections of GLP-1 in Wistar rats; however, those results were not reproduced in the current investigation, suggesting that the phasic delivery and/or variation in receptor activity of GLP-1 is important for improvements in cardiovascular function. AstraZeneca, supported this investigator-initiated study.

26.7

REDUCTION OF ARTERIAL STIFFNESS BY AEROBIC EXERCISE TRAINING IS ASSOCIATED WITH ENDOTHELIAL NITRIC OXIDE SYNTHASE ACTIVATION VIA INCREASING ARTERIAL ADROPIN LEVELS IN TYPE 2 DIABETIC RATS

Shumpei Fujie[1,2], Natsuki Hasegawa[1,2], Naoki Horii[1], Koji Sato[3], and Motoyuki Iemitsu[1]

[1]Sport and Hlth. Sci., Ritsumeikan Univ., 1-1-1, Noji-higashi, Kusatu, Shiga, Japan, [2]DC, Res. Fellow of Japan Soc. for the Promotion of Sci., 5-3-1, Kojimachi, Chiyoda, Tokyo, Japan, [3]Human Development and Environment, Kobe Univ., 3-11, Tsurukabuto, Nada, Kobe, Hyogo, Japan.

It is well known that increased arterial stiffness is related to cardiovascular mortality in patients with type 2 diabetes. Regular aerobic exercise induces reduction of arterial stiffness. Vasodilator nitric oxide (NO) is related to a mechanism of the beneficial effect by regular aerobic exercise. Adropin is a regulator of endothelial NO synthase (eNOS) and NO release, and circulating adropin level decreases in patients with type 2 diabetes. Our recent study demonstrates that the elevated circulating adropin levels by aerobic exercise training is significantly associated with exercise training-induced changes in arterial stiffness and plasma nitrite/nitrate (NOx) levels in healthy middle-aged and older adults. However, it is unclear whether arterial adropin level is elevated by aerobic exercise training in type 2 diabetic rats. Purpose: This study aimed to clarify whether the aerobic exercise training-induced elevation of arterial adropin levels is associated with activation of eNOS and reduction of arterial stiffness in type 2 diabetic rats. Methods: Twenty 20-week-old male obese type 2 diabetic rats (OLETF) were used in this study, and ten male LETO rats used as healthy sedentary control. OLETF rats were randomly divided into two groups; 8-week sedentary control and aerobic exercise training (5 times a week with 25m/min treadmill running for 60 min). We evaluated aortic pulse wave velocity (PWV) as an indicator of arterial stiffness. Results: Aortic PWV was significantly increased in OLETF-control group as compared to LETO group, whereas the aortic PWV was significantly reduced in OLETF-exercise group ($p<0.05$). Although OLETF-control rats had significantly lower arterial eNOS and Akt phosphorylations and plasma NOx level than in LETO rats, OLETF-exercise rats significantly increased compared with OLETF control group ($p<0.05$). Furthermore, arterial adropin level in OLETF-exercise rats significantly increased as compared to OLETF-control rats ($p<0.05$). Additionally, significant correlation was observed between plasma NOx level and aortic PWV ($p<0.05$, $r=-0.448$). Conclusion: These results suggest that aerobic exercise training induces the elevation of arterial adropin levels as well as eNOS-Akt activation in type 2 diabetic rats. Thus, the increased arterial adropin level is associated with the beneficial effects of training on arterial stiffness.

26.8

EVIDENCE OF LEGACY EFFECTS OF THREE 8-MONTH EXERCISE PROGRAMS ON CARDIO-METABOLIC HEALTH: GROUP-SPECIFIC BENEFITS OBSERVED 10 YEARS LATER

Johanna Johnson[1], Cris Slentz[1], and William Kraus[1]

[1]Duke Molecular Physiology Inst., Duke Univ. Med. Ctr., 300 N. Duke St., Durham, NC, 27707.

STRRIDE (Studies Targeting Risk Reduction Interventions through Defined Exercise) was an 8-mo exercise study from

1998-2003. Subjects were randomized to control and one of three exercise groups differing in intensity and amount. To determine if there were legacy effects of the program 10 years after completion, we invited 161 individuals who completed the exercise intervention phase to return for a 10-yr Reunion study. **Methods:** Subjects completed questionnaires; height, body weight, resting blood pressure and minimal waist circumference were obtained; peak VO_2 measured; and fasting blood drawn for glucose, insulin and lipids. Of the 161, 153 were within a 10 y (± 6 m) window of STRRIDE program completion. Of these, 28 were lost to follow-up and 21 declined, 13 refused peak VO_2, and one blood sample was unobtainable. Overall, 104 (83.2% eligible) participated. Change over time was considered as 10-year reunion value minus pre-intervention value. To determine significant changes within a group, two-tailed t-tests on the 10-year change scores were calculated. To detect differences between groups, an analysis of variance (ANOVA) was conducted for each of the variables of interest ($p \leq 0.05$ was considered significant). **Results:** The subjects originally randomized to moderate intensity exercise had significantly lower fasting insulin at 10 years compared to control and the high amount/vigorous intensity group, as well as significantly lower mean arterial blood pressure than the other 3 groups. Both the moderate intensity exercise and control groups experienced ~10% decreases in peak VO_2, whereas both vigorous intensity groups experienced only ~5% decreases. **Summary:** Ten years after STRRIDE, we report group-specific benefits suggesting a possible legacy effect of exercise training in previously sedentary subjects. It will be important to conduct specifically designed studies to follow up on this important possible benefit.

26.9

RECRUITING FOR LARGE EXERCISE STUDIES: EFFICIENCY OF DIFFERENT RECRUITING STRATEGIES

Leslie Kelly[1], Cris Slentz[1], Lori Bateman[1], Johanna Johnson[1], Leslie Willis[1], and William Kraus[1]
[1]Duke Molecular Physiology Inst., Duke Univ. Med. Ctr., 300 N. Duke St., Durham, NC, 27707.

Purpose: To compare the efficiency (in time and money) of different methods for subject recruitment; and to report on the number of phone screens needed per recruited subject for large exercise training studies. **Methods:** In STRRIDE I (Studies Targeting Risk Reduction Interventions through Defined Exercise) we did an in depth analysis of the many recruiting approaches we used including: advertising in local newspapers (non-special event), advertisements in local newspapers (special events), flyers, university newspapers, TV, Radio, word-of-mouth, and other. As a result, we used our experience from STRRIDE I to inform recruitment strategies for subsequent large exercise training studies. In STRRIDE AT/RT (Aerobic Training/Resistance Training) and STRRIDE PD (in subjects with PreDiabetes) we report the subject recruitment flow. **Results:** In STRRIDE I, we found TV and radio ads to be the least time efficient (353 and 180 min screening time per enrollee) and most expensive ($205 and $190 per enrollee). Newspaper ads and flyers were the most time efficient (average time of ~90 min per enrollee) and were less expensive (~$25 per enrollee); only word of mouth was cheaper and more time efficient. As a result of these findings in STRRIDE I, we used newspaper ads and flyers almost exclusively for STRRIDE AT/RT and for STRRIDE PD recruiting. Furthermore, in STRRIDE AT/RT we phone screened 3145, of which 85% (2661) phone screened out; we consented 484 (15%) of which 49% were screened out; this resulted in 249 (7.9%) recruited for the study. In STRRIDE PD we had very similar numbers with a final 9.4% of the number phone screened being recruited for the study. **Summary:** Printed ads (newspaper ads and flyers) were more successful for recruiting subjects than non-printed ads from TV and radio (even when numerous radio ads were used). Ads for exercise studies were especially successful when they were combined with big sporting news or other big events. Furthermore we found, as have others, that the number of subjects who are phone screened is quite large compared to the number eventually recruited. As a result, strategies that reduce time used during phone screening will be important for further improving efficiency.

26.10

LEFT VENTRICLE TRANSCRIPTOMIC ANALYSIS REVEALS CONNECTIVE TISSUE ACCUMULATION ASSOCIATES WITH THE INITIAL AGE-DEPENDENT DECLINE IN VO_{2PEAK} FROM ITS LIFETIME APEX

Frank Booth[1], Gregory Ruegsegger[1], and Ryan Toedebusch[1]
[1]Biomedical Sci., Univ. of Missouri, E102 E. Rollins St., Columbia, MO, 65211.

Peak oxygen consumption (VO_{2peak}) strongly predicts morbidity and mortality better than other established risk factors, yet all mechanisms associated with its age-related decline are unknown. Our lab has shown that VO_{2peak} first begins to decrease at the same age of 19 weeks old in Wistar in both sedentary and wheel-running, female Wistar rats. Here, we employed RNA-sequencing to determine the extent to which transcriptomic alterations in the left ventricle associate with age-related decreases in VO_{2peak}. Transcriptomic comparisons were made within both sedentary (SED) and wheel-running (RUN) rats between 19 and 27 wks (n= 5-8/group). From 19 to 27 wks, 273 and 347 mRNAs in SED were up- and down-regulated at 19 wks, respectively, and 272 and 68 mRNAs in RUN were up- and down-regulated at 19 wks, respectively. Analysis of mRNAs in shared in SED and RUN between 19 and 27 wks found 17 up-regulated (e.g. Adra1d, Rpl17, Xpo7) and 8 down-regulated (e.g. Cdo1, Ctfg, Sfrp1) mRNAs, at 19 wks, respectively. Furthermore, bioinformatics analysis of mRNAs common to RUN and SED produced networks suggestive of increased connective tissue development at 27 vs. 19 wks. Additionally, connective tissue growth factor (Ctfg) mRNA was negatively associated with VO_{2peak} in both RUN and SED ($p< 0.05$). Our findings that networks indicate increased connective tissue development in the left ventricle associates with age-related reductions in VO_{2peak}, independent of physical activity, may represent one potential mechanism responsible for the initial decline in VO_{2peak} from its lifetime apex.

26.11

ASSOCIATIONS BETWEEN ANTIOXIDANT ENZYMES IN CARDIOMYOCYTES AND SKELETAL MUSCLE DURING DOXORUBICIN TREATMENT

Catherine L. Jarrett[1], Andrew C. D'Lugos[1], Tara Mahmood[1], Rayna J. Gonzales[2], Taben M. Hale[2], Chad C. Carroll[3], Jared M. Dickinson[1], and Siddhartha S. Angadi[1]

[1]Exercise Sci. and Nutrition, Arizona State Univ., 425 N. 5th St., Phoenix, AZ, 85004, [2]Basic Med. Sci., Univ. of Arizona, 425 N. 5th St., Phoenix, AZ, 85004, [3]Physiology, Midwestern Univ., 19555 N. 59th Ave., Glendale, AZ, 85308.

Doxorubicin (DOX - a common chemotherapeutic agent used for breast cancer) is associated with severe cardiac and skeletal muscle toxicity due to oxidative stress. We have previously demonstrated preservation of cardiac antioxidant status with exercise preconditioning prior to DOX administration. However, cardiac antioxidant status is difficult to examine *in vivo* clinically. We thus examined if skeletal muscle antioxidant status can function as a surrogate measure of cardiac antioxidant levels. The purpose of this study was to examine the relationship between antioxidant enzymes in skeletal muscle and cardiomyocytes following high-intensity interval exercise preconditioning and training with bi-weekly DOX treatments in a rodent model. We hypothesized that antioxidant enzymes Mn-superoxide dismutase (SOD2) and catalase (CAT) in cardiac tissue would be correlated with levels found in skeletal muscle. Eight-week old female ovariectomized Sprague Dawley rats were randomized to one of four treatments: Exercise+DOX (Ex-DOX); Exercise+Vehicle (Ex-Veh); Sedentary+DOX (Sed-DOX); and Sedentary+Veh (Sed-Veh). DOX (4mg/kg) or Veh (saline) intraperitoneal injections were performed bi-weekly for a total of 3 injections (cumulative dose 12mg/kg). Ex animals underwent high intensity (85-95 %VO_2peak) interval exercise (4×4 min bouts) 5d/wk starting 1 week prior to the first injection and continued throughout study duration. Animals were euthanized 5 days following the last injection, following which the soleus and gastrocnemius muscles and left ventricular cardiac tissue were extracted for western blot analyses. For the purpose of this analysis we grouped together Ex-DOX, Ex-Veh and Sed-DOX values which were all relative to Sed-Veh. There was a strong correlation for SOD2 found between cardiac tissue and both gastrocnemius and soleus skeletal muscle ($r=-0.782$, $p=0.008$; $r=0.903$, $p<0.001$, respectively). Catalase in the cardiac tissue was strongly correlated with gastrocnemius muscle ($r=0.766$, $p=0.010$), with a trend for soleus ($r=0.539$, $p=0.109$). These preliminary analyses indicate that skeletal muscle antioxidant status may have utility as a surrogate measure for cardiac antioxidant status. Funding: intramural funds from Arizona State University and Midwestern University.

26.12

EFFECTS OF EXERCISE AMOUNT AND INTENSITY VERSUS A COMBINED EXERCISE AND LIFESTYLE INTERVENTION ON METABOLIC SYNDROME IN ADULTS WITH PREDIABETES: FROM STRRIDE PD A RANDOMIZED TRIAL

Cris Slentz[1], Leslie Willis[1], Lori Bateman[1], Esther Granville[2], Lucy Piner[1], Connie Bales[2], and William Kraus[2]

[1]Duke Molecular Physiology Inst., Duke Univ. Med. Ctr., 300 N. Duke St., Durham, NC, 27707, [2]Div. of Geriatrics, Duke Univ. Med. Ctr., 300 N. Duke St., Durham, NC, 27707.

Aim: Although the Diabetes Prevention Program (DPP) established lifestyle changes (diet, exercise and 7% weight loss) as the 'gold standard' preventive therapy for diabetes, the relative contribution of exercise alone to the combined diet and exercise effect of DPP is unknown; furthermore, the optimal intensity of exercise for metabolic improvement remains very controversial. In STRRIDE PD (Studies of Targeted Risk Reduction Interventions through Defined Exercise in PreDiabetics) we compared the effects of a DPP-like intervention to that obtained through different amounts and intensities of exercise training on metabolic syndrome. Methods: We compared three six-month aerobic exercise groups differing in amount and/or intensity to an exercise plus diet group similar to the Diabetes Prevention Program. Sedentary, overweight adults (45-75 years) with prediabetes (fasting plasma glucose 95-125 mg/dL) were randomized to: 1) Low-Amount/Moderate-Intensity (10 kcal/kg/week at 50% peak VO2); 2) High-Amount/Moderate-Intensity (16 kcal/kg/week at 50% peak VO2); 3) High-Amount/Vigorous-Intensity (16 kcal/kg/week at 75% peak VO2); or 4) Low-Amount/Moderate-Intensity (10 kcal/kg/week at 50% peak VO2) + Diet (7% weight loss). We calculated a continuous MetSyn z-score on participants with complete data for all five MetSyn criteria before and after the six-month intervention. Results: All four groups significantly improved the MetSyn z-score with no statistical differences between groups by ANOVA. Interestingly, the high-amount/vigorous group experienced significant improvements in four of the five variables: blood pressure, HDL-cholesterol, triglycerides and waist circumference. The high-amount/moderate-intensity group had significant improvements in two of five: waist circumference and fasting glucose. The diet/exercise group improved all five metabolic syndrome variables. Conclusion: All three six-month exercise-only training programs were effective at improving metabolic syndrome; but, the effect of vigorous-exercise training may improve more cardiometabolic risk factors than moderate-intensity exercise. The findings suggest that a significantly greater effect in improved MetSyn risk is obtained when adding a weight loss diet to the Low-Amount/Moderate-Intensity exercise intervention. NIDDK–NIH Grant # R01–DK081559. Clinical Trial Registration # NCT00962962.

28.0 MICROCIRCULATION

28.1

CIRCULATING FACTORS FROM PATIENTS WITH T2DM IMPAIR CAPILLARY-LIKE NETWORK FORMATION

Rian Landers-Ramos[1], Jacob Blumenthal[1], and Steven Prior[1]

[1]Dept. of Med., Univ. of Maryland Sch. of Med. and the Baltimore Vet. Affairs, 10 N. Greene St., Baltimore, MD, 21201.

Type 2 diabetes mellitus (T2DM) is associated with impaired angiogenesis, microvascular rarefaction, and increased risk for cardiovascular disease (CVD). These vascular complications may, in part, be attributable to endothelial dysfunction that is

mediated by circulating factors. This study tested the hypothesis that serum from individuals with T2DM and impaired glucose tolerance (IGT) would reduce *in vitro* capillary-like network formation of human retroviral telomerized endothelial cells (HRVTs) and human primary coronary artery endothelial cells (CAECs), compared with normal glucose tolerant (NGT) controls. Subjects were sedentary, older (55-65 yrs) adults with NGT, IGT or T2DM (n=10/group) and were matched for BMI. HRVTs or CAECs were cultured in triplicate on Matrigel® using endothelial basal medium supplemented with 7.5% serum. After incubation for 15 hours, the entire well was imaged and network length analyzed using ImageJ Angiogenesis Analyzer (NIH). In the HRVT assay, network length when using serum from the T2DM group was 32% and 35% lower than when using serum from the NGT and IGT groups, respectively ($P<0.05$ for both). In the CAEC assay, serum from T2DM subjects resulted in network formation that was 11% and 8% lower than when using serum from NGT and IGT subjects, respectively ($P<0.05$). There were no significant differences in HRVT or CAEC network formation between NGT and IGT conditions ($P>0.05$). Despite higher plasma glucose levels in the T2DM patients compared to the NGT and IGT groups ($P<0.05$ for both), the *in vitro* glucose levels used in this experiment were not substantially different than normal blood glucose concentrations (99.3±0.16, 99.7±0.38 and 103±0.55 mg/dL for NGT, IGT and T2DM, respectively; IGT vs. T2DM and NGT vs. T2DM both $P<0.05$). These preliminary results suggest that circulating factors present in the serum of T2DM individuals impair *in vitro* endothelial cell function in both primary and telomerized endothelial cell lines potentially leading to alterations in angiogenic potential. Our findings may have implications for the microvascular complications associated with T2DM. Funding Sources: K23- AG040775 (NIH and the American Federation for Aging Research) I01-CX000730 (Department of Veterans Affairs) Baltimore Veterans Affairs Geriatric Research, Education and Clinical Center (GRECC).

28.2

MECHANISMS OF CORONARY MICROCIRCULATION DYSFUNCTION IN HEART FAILURE: WHAT CAN WE LEARN FROM THE HEART'S RESPONSE TO ACUTE EXERCISE?

Daphne Merkus[1], Oana Sorop[1], Shawn Bender[2], Ilkka Heinonen[3], M Harold Laughlin[2], and Dirk Duncker[1]
[1]Cardiology, Erasmus MC, PO Box 2040, Rotterdam, 3000CA, Netherlands, [2]Biomedical Sci., Univ. of Missouri, E102 Vet Med. Bldg, Columbia, MO, MO65211, [3]Turku PET Ctr., Univ. of Turku, P.O. Box 52, Turku, 20521, Finland.

Coronary microvascular function and cardiac function are closely related in that proper cardiac function requires adequate oxygen delivery through the coronary microvasculature. Due to the close proximity of cardiomyocytes and coronary microvascular endothelium, cardiomyocytes not only communicate their metabolic needs to the coronary microvasculature, but endothelium-derived factors also directly modulate cardiac function. We propose that the coronary microvasculature plays a key role in the progression of LV dysfunction. Risk factors like hypertension, diabetes and/or hypercholesterolemia directly affect the coronary microvasculature. Evidence is accumulating that the myocardial oxygen balance is disturbed in the failing heart due to increased extravascular compressive forces and coronary microvascular dysfunction. Importantly, coronary microvascular dysfunction is associated with adverse cardiovascular events. Since alterations in microvascular as well as cardiac function are first revealed during increased physical activity, exercise testing provides a valuable method to interrogate coronary microvascular function. Identification of abnormal microvascular responses, i.e. alterations in neurohumoral influences, endothelial dysfunction and oxidative stress, is an essential step to provide targets for therapeutic interventions to improve microvascular function and thereby delay progression of LV dysfunction to overt heart failure.

28.3

SKELETAL MUSCLE DERIVED EXOSOMES REGULATE ENDOTHELIAL CELL FUNCTIONS BY TRANSFERRING MIR-130A

Yaohui Nie[1], and Timothy Gavin[1]
[1]Hlth. and Kinesiology, Purdue Univ., 915 W. State St., West Lafayette, IN, 47906.

Loss of skeletal muscle capillarization, known as capillary rarefaction, is found in type 2 diabetes, chronic heart failure, and healthy aging and is associated with impaired delivery of substrate to muscle. However, little is known about the interaction and communication of skeletal muscle with endothelial cells. Exosomes are a type of secreted extracellular microvesicle containing mRNAs, proteins, and especially miRNAs that exert paracrine and endocrine effects. We investigated whether skeletal muscle-derived exosomes regulate endothelial cell function. We demonstrate that C2C12 muscle cell derived exosomes (SkM-Exo) increase the proliferation by 50% and prompt the migration and tube formation of human umbilical vein endothelial cells (HUVECs). SkM-Exo also enhance the expression of angiogenic factors, angiopoietin-like 4 (Angptl4), interleukin-8 (IL-8) and brain-derived neurotrophic factor (BDNF) in HUVECs. SkM-Exo induced improvements in HUVEC function were due in part to SkM-Exo induction of oxidative stress in HUVECs. miR-130a, an angiogenic miRNA, was highly expressed in SkM-Exo and successfully transferred to HUVECs. The potential angiogenic effect of skeletal muscle exosomes might provide an effective therapy for promoting skeletal muscle angiogenesis in diseases characterized by capillary rarefaction or inadequate angiogenesis.

29.0 FATIGUE

29.1

MECHANISMS FOR THE AGE-RELATED INCREASE IN POWER LOSS DURING FATIGUING DYNAMIC CONTRACTIONS IN MEN AND WOMEN

Christopher W. Sundberg[1], Hamidollah Hassanlouei[1], Andrew Kuplic[1], and Sandra K. Hunter[1]
[1]Physical Therapy, Marquette Univ., Cramer Hall, Rm., 215, 604 No. 16th St., Milwaukee, WI, 53233.

Old adults are typically more fatigable than young adults during high-velocity concentric contractions. The mechanisms for this

age-related increased fatigability, however, are not fully understood and have been investigated primarily in men. The purpose of this study was to compare the fatigability and the associated mechanisms between young and old men and women elicited by high-velocity concentric contractions of the knee extensor muscles. Fifteen young women (22.6±0.6 [SE] yrs), 14 young men (22.4±0.6 yrs), 29 old women (72.1±1.2 yrs) and 32 old men (70.8±1.2 yrs) performed 80 maximal velocity concentric contractions (1 every 3-s) with a load equivalent to 20% of the maximal voluntary isometric contraction (MVC) torque. Transcranial magnetic stimulation and electrical stimulation of the femoral nerve were used to quantify voluntary activation and the contractile properties, respectively, before and immediately (<10-s) following the fatiguing task. Old women generated 44% less power than old men (P<0.01) and young women 35% less power than young men (P<0.01), with the old generating 64% less power than the young (P<0.01). At the end of the fatiguing task, the relative loss in power was similar for the old men and women (P>0.05) and for the young men and women (P>0.05), but was ~2-fold greater in the old (33±2.5%) compared with the young (17±2.4%, P<0.01). In contrast, the relative loss in MVC torque was similar for the 4 cohorts (~24% reduction, P>0.05). Before fatigue, voluntary activation was similar at ~96% for the 4 cohorts (P>0.05), but was reduced only in the old women after the fatiguing task by 4 ± 1.3% (P<0.01). Regression analyses revealed that the reductions in power were best predicted by the reductions in the potentiated twitch amplitude (R^2=0.52). Similar to the reductions in power, the reductions in the twitch amplitude were ~2-fold greater in the old (31±2.3%) compared with the young (16±3.1%), with no sex differences for the young or old adults (P>0.05). These data indicate that the age-related increased power loss during high-velocity fatiguing contractions is similar for men and women and determined primarily by mechanisms originating within the muscle rather than the nervous system. Supported by NIA (R21 AG045766) to SK Hunter.

29.2

EFFECTS OF ACUTE DIGOXIN INTAKE ON SKELETAL MUSCLE NA^+,K^+-ATPASE CONTENT, PLASMA K^+ REGULATION AND FATIGUE DURING INTENSE EXCISE IN HEALTHY YOUNG ADULTS

Michael McKenna[1], Tania Atanasovska[1], Robert Smith[1,2], Chiew Wong[3,4], Andrew Garnham[1], Aaron Petersen[1], Trevor Farr[1], Mitchell Anderson[1,5], and Henry Krum[6]
[1]Inst. of Sport, Exercise and Active Living (ISEAL), Victoria Univ., PO Box 14428, Melbourne, 8001, Australia, [2]Anaesthesia, Western Hlth., Furlong Rd., Sunshine, Melbourne, Australia, [3]Cardiology, Western Hlth., Furlong Rd., Sunshine, Melbourne, Australia, [4]Cardiology, Univ. of Melbourne, Royal Parade, Parkville, Melbourne, Australia, [5]Heart and Diabetes Inst., Baker IDI, Commercial Rd., Prahran, Melbourne, Australia, [6]Dept. of Epidemiology and Preventive Med., Monash Univ., Alfred Hosp., Commercial Rd., Prahran, Melbourne, Australia.
Potassium (K^+) disturbances during intense exercise have been linked with fatigue. We investigated the effects of acute administration of digoxin, a specific Na^+,K^+-ATPase (NKA) inhibitor, on K^+ regulation, exercise performance and skeletal muscle NKA content and isoform abundance, in 10 healthy adults, in a randomised, crossover, double-blind, counterbalanced design study. Participants were orally administered 0.50 mg digoxin (DIG) or placebo (PLAC) and then 60 min later commenced cycling for 1 minute at 60% and 95%VO_2peak; then to volitional fatigue at 95%VO_2peak. Radial arterial plasma $[K^+]_a$ was measured at rest, during exercise, for up to 60 min in recovery. A vastus lateralis muscle biopsy was performed at rest and immediately post-exercise and analysed for NKA content via [^{3}H]-ouabain binding, without and with digoxin antibody Digi F(ab) ^{TM} to detect the fraction of NKA bound by digoxin; and for NKA isoform protein abundance. Serum digoxin concentration prior to exercise was 3.36±0.80 nM in DIG (below 0.2 nM detection limit in PLAC). Time to fatigue at 95%VO_2peak was 6.4% less during DIG than PLAC (233.7±46.0 vs 249.8±53.3, respectively, P=0.029). Muscle NKA content as determined by [^{3}H]-ouabain binding was unchanged with DIG; but separate [^{3}H]-ouabain binding analysis after removal of bound digoxin with DigiF(ab) ^{TM} antibodies revealed a 7.8% digoxin occupancy compared to PLAC (P=0.003), indicating a 7.8% increase in actual muscle NKA content after DIG. The NKA $\alpha_{1\text{-}3}$ and $\beta_{1\text{-}2}$ isoform protein abundances were unchanged with digoxin. Plasma $[K^+]_a$ increased during exercise and fell immediately in recovery, being lower than baseline at 10 min post-exercise (P=0.025). Plasma $[K^+]_a$ was greater in DIG than PLAC across all times (4.93±0.18 vs. 4.88±0.20, respectively, P=0.035). Thus acute digoxin treatment increased the number of apparently functional NKA complexes, as detectable by the 7.8% increase in [^{3}H] ouabain binding after DigiF(ab) ^{TM} pre-treatment, which occurred in the absence of any increase in α or β isoform abundances. This may indicate that acute digoxin-inhibition of NKA stimulated increased assembly of existing α and β subunits. This would act to rapidly recover the number of available NKA, thus preserving muscle NKA capacity in the face of acute NKA inhibition and consequent potential deleterious effects. Despite this, DIG perturbed arterial K^+ regulation and impaired muscle performance, with increased fatiguability during intense exercise.

30.0 MUSCLE INJURY

30.1

LEUCINE-ENRICHED ESSENTIAL AMINO ACIDS ATTENUATE INFLAMMATION AND ENHANCE MUSCLE REPAIR AFTER ECCENTRIC CONTRACTION IN RAT

Hiroyuki Kato[1], Kyoko Miura[1], Tomoko Takeda[1], Yoshiko Inoue[1], Sayako Nakano[1], Katsuya Suzuki[1], and Makoto Bannai[1]
[1]Inst. for Innovation, Ajinomoto Co., Inc., 1-1 Suzuki-cho Kawasaki-ku, Kawasaki, 210-8681, Japan.
Eccentric exercise results in prolonged muscle damage that may lead to muscle dysfunction. Although inflammation is essential to recovery from muscle damage, excessive inflammation may also induce secondary damage, and should thus be suppressed. In this study, we investigated the effect of leucine-enriched essential amino acids on muscle inflammation and recovery after eccentric contraction. These amino acids are known to stimulate muscle protein synthesis via mammalian target of rapamycin (mTOR), which, is also considered to alleviate inflammation. Five sets of 10 eccentric contractions were induced by electrical

stimulation in the tibialis anterior muscle of male Sprague–Dawley rats (8–9 weeks old) under anaesthesia. Rats received orally a 1 g/kg dose of a mixture containing 40% leucine and 60% other essential amino acids or distilled water once a day up to 14 days after eccentric contraction. Muscle dysfunction was assessed based on isometric dorsiflexion torque, while infiltration of inflammatory cells into muscle was evaluated by histochemistry. Gene expression of inflammatory cytokines and myogenic regulatory factors in skeletal muscle was also measured. mTOR signalling was assessed by immunoblotting 1, 3 and 5 hours after the administration of leucine-enriched essential amino acids on the day of eccentric contraction. We found that leucine-enriched essential amino acids restored full muscle function within 14 days after eccentric contraction, at which point rats treated with distilled water had not fully recovered. Indeed, muscle function was stronger 3 days after eccentric contraction in rats treated with amino acids than in those treated with distilled water. The amino acid mix also alleviated expression of interleukin-6 1 day after eccentric contraction and impeded infiltration of inflammatory cells into muscle 3 days after eccentric contraction, but did not suppress expression of myogenic regulatory factors. p70 S6K1 phosphorylation was increased 1 hour, but not 3 and 5 hours after the administration of the amino acids. These results suggest that leucine-enriched amino acids accelerate recovery from muscle damage by preventing excessive inflammation.

30.2

PATHOLOGICAL LIPID ACCUMULATION AFTER SKELETAL MUSCLE INJURY

Jonathan Gumucio[1], Brian McDonagh[2], and Christopher Mendias[1]
[1]Orthopaedic Surgery and Molecular & Int. Physiology, Univ. of Michigan, 109 Zina Pitcher Pl., BSRB 2017, Ann Arbor, MI, 48109, [2]Inst. of Ageing and Chronic Dise., Univ. of Liverpool, William Duncan Bldg., 6 W. Derby St., Liverpool, L7 9TX, UK.

Muscle fiber atrophy and fibrosis are commonly recognized pathological changes that occur after skeletal muscle injury. But many injured muscles also display an accumulation of lipid, a condition termed myosteatosis. Lipid accumulation in injured muscles can be grossly measured with MRI or CT imaging technology, and several epidemiological studies have demonstrated that the amount of lipid present in injured muscles correlates negatively with favorable functional outcomes. The molecular mechanisms that lead to this accumulation of lipid, and the roles that these lipid molecules play in regulating muscle degeneration and regeneration are largely unknown. To gain a greater understanding of the ontogeny of myosteatosis, we induced a severe injury to the supraspinatus muscle group in rats, isolated tissues 10, 30 or 60 days after tear, and used a combination of RNA sequencing and shotgun lipidomics to identify global changes in gene expression and lipid content in injured muscles, electron microscopy to identify ultrastructural changes in muscle fibers, and single muscle fiber contractility testing to assess functional changes after injury. Uninjured muscles served as controls. The RNA sequencing data and shotgun lipidomics results were then analyzed by Ingenuity Pathway Analysis (IPA) software to determine the biochemical pathways involved in myosteatosis. Following muscle injury, there was a time dependent increase in total lipid content, largely due to a marked rise in triacylglyceride species. Interestingly, genes related to lipid synthesis (DGAT1, DGAT2) and lipid breakdown (LPL, HSL) were largely downregulated over time. IPA results predicted increased mitochondrial dysfunction and oxidative stress, and decreased lipid oxidation to be highly associated with myosteatosis at earlier time points. Genes related to lipid utilization and mitochondrial function (CPT1/2, SDH, COXIV) were also decreased with time. Protein carbonylation was also increased at 60d. Electron micrographs demonstrated increased subsarcolemmal mitochondria at all time points after injury, and highly disordered sarcomere structure at 30d and 60d compared to controls, which corresponded with a time dependent decrease in muscle fiber force production. In summary, the accumulation of lipid that occurs after muscle injury is likely due to reduced lipid utilization and breakdown rather than an elevation in lipid synthesis. Oxidative stress and persistent mitochondrial dysfunction and may result in the elevated lipid infiltration and atrophy of muscle fibers over time.

30.3

MASSAGE-INDUCED CHANGES IN MEMBRANE PERMEABILITY ARE ASSOCIATED WITH ELEVATED SATELLITE CELLS AND MURF-1 PROTEIN

Emily Hunt[1], Amanda Hayek[1], Amy Confides[1], Sarah Abshire[1], Timothy Butterfield[1], and Esther Dupont-Versteegden [1]
[1]Rehabilitation Sci., Univ. of Kentucky, 900 S. Limestone St., Lexington, KY, 40503.

Introduction: Massage is a widely accepted manual therapy used to modulate inflammatory responses of muscle and restore function; however, prolonged compression of muscle potentially causes overt injury and damage to muscle fibers. Mechanical injury is induced when an excessive external load causes a disruption in the sarcolemma. Therefore, a balance exists between the positive effects of massage and the induction of mechanical damage and injury. In addition, skeletal muscle of aged individuals has increased stiffness and therefore the response to massage may be different compared to young. We hypothesized that aged skeletal muscle exhibits increased sarcolemmal permeability when subjected to massage compared to young skeletal muscle. **Methods:** Male Brown Norway/F344 rats, 10and 30 months of age, were each divided into control, non-massaged (n=8) and massaged (n=8) groups. The right gastrocnemius muscle received one bout of cyclic compressive loading (CCL) for 30 min at 4.5N as a massage-mimetic. Muscles were dissected and frozen 24 hours after massage. Immunohistochemistry was performed for determination of IgG inside fibers and Pax7+ cell number. Murf-1 protein abundance was assessed by Western analysis. **Results:** Average IgG infiltration was not different between control and massaged animals at either age. However, a significant shift to the right of the density histogram indicated that massaged animals had more fibers with higher IgG density than control at both ages. In addition, Pax7+ cell number and Murf-1 protein abundance was significantly elevated in massaged muscles compared to control at both ages. **Conclusions:**

One bout of massage did not induce overt muscle injury, but facilitated membrane permeability, which was associated with an increase in satellite cell number and muscle remodeling as indicated by Murf-1 expression. Data suggest that the load applied here, which was previously shown to induce immunomodulatory changes, does not induce overt muscle injury in young and old muscles but may result in muscle remodeling. Funded by NIH grant AG042699.

30.4

CIRCULATING MIRNAS AS EARLY BIOMARKERS OF SKELETAL MUSCLE DENERVATION IN RATS

Nathalie Koulmann[1,2], Julien Siracusa[1], Charles Chapus[3], Stéphanie Bourdon[1], Marie-Emmanuelle Goriot[4], and Sébastien Bandzet[4,5]

[1]Dépt. Environnements Opérationnels, Inst. de Res. Biomédicale des Armées, 1, Place Valérie André, Bretigny-Sur-Orge, 91223, France, [2]Dépt. Res., Ecole du Val-de-Grâce, 1 Place Alphonse Laverran, Paris, 75005, France, [3]Service de Biologie Moléculaire, Inst. de Rech. Biomédicale des Armées, 1 place Valérie André, , Bretigny-Sur-Orge 91223, France, [4]Ctr. de Transfusion Sanguine des Armées, Inst. de Res. Biomédicale des Armées, 101 Ave. Henri Barbusse, Clamart, 92410, France, [5]U 1197, INSERM, 101 Ave. Henri Barbusse, Clamart, 92410, France.

Skeletal muscle loss is a common feature during prolonged inactivity or aging, which can be at least partly attributed to denervation. Recently, circulating muscle-enriched miRNAs have been shown to be biomarkers of muscle damage, but whether they could be markers of early muscle loss is unknown. Our aim was to evaluate in rats, the use of single and combinational measurements of circulating miRNAs as an early diagnostic of muscle loss induced by denervation. **Methods:** Skeletal muscle denervation was induced by the section of the soleus muscle nerve (DNV, n = 32). Blood samples were drawn 6 h, 12 h, 24 h and 48 h post-denervation in DNV or sham operated rats (SHAM, n = 32) as well as in control rats (CON, n = 12) to measure levels of miR-1-3p, -133a-3p, -133b-3p, -206-3p, -208b-3p, -499-3p, -378a-3p and -434-3p by RT-qPCR. The diagnostic accuracy of each individual miRNA was assessed by a receiver-operating characteristic (ROC) curve analysis and the resulting area under the curve (AUC). DNV rats were considered positive, SHAM and CON were considered negative for muscle remodeling. Then, we sought to optimize the diagnostic accuracy by using a logistic regression analysis with a backward selection to identify the best miRNAs combination. **Results**: While we found no significant alteration of the circulating levels of miR-1-3p, -206-3p, -499-5p and -378a-3p in DNV and SHAM rats, miR-208-3p remained undetectable in most samples. Both miR-133a-3p and -133b-3p significantly increased at 12 h in DNV group compared to SHAM (1.9 and 3.4-fold, respectively) with a peak value at 24 h (3.4 and 4.6-fold, respectively), and returned to baselines at 48 h. MiR-434-3p transiently increased 6 h after the sham-operation but not in DNV. The ROC curve analysis revealed that miR-206-3p had the lower diagnostic accuracy (AUC = 0.472) while miR-133a-3p (AUC = 0.720) and miR-133b-3p (AUC = 0.842) had the higher. By using a logistic regression, we identified a model combining miR-133b-3p + miR-206-3p able to discriminate almost perfectly denervated rats from non-denervated rats (AUC = 0.929). **Conclusion**: We describe that individual circulating miRNAs could be useful biomarkers of early muscle remodeling in response to denervation. Furthermore, the combination of multiple biomarkers is an efficient strategy to greatly improve the diagnostic accuracy. This work was supported by contract PDH-1-SMO-2-0603 from the French "Direction Generale de l'Armement".

30.5

EARLY INFLAMMATORY CHEMOKINES AND MARKERS IN MUSCLE INJURY

Gengyun Le[1], Haley G Johnson[1], Matthew Jergenson[1], Megan Lenz[1], Gordon Warren[2], and Dawn Lowe[1]

[1]420 Washington Ave, SE, Univ, of Minnesota, MCB 7-210, Minneapolis, MN, 55455, [2]Physical Therapy, Georgia State Univ,, 293 Georgia Ave, SE, Atlanta, GA, 30312

Inflammation is a key component for skeletal muscle to recover from injury. Alterations of this response can lead to prolonged and even incomplete recovery which can have devastating effects. The very early inflammatory responses as well as the original source(s) of chemokines that are released following muscle injury have not been rigorously studied. Purpose: To determine the time of onset of inflammatory chemokines and markers after muscle injury in mice. Methods: Adult, female C57BL/6 mice had a freeze injury induced to both tibialis anterior (TA) muscles and at 0, 0.5, 1, 3, 5 or 12 h post-injury, mice were sacrificed and the muscles were excised. A group of uninjured mice served as controls. Gene expression for inflammatory chemokines and immune cell surface markers was assessed using real-time PCR. Results: Compared to uninjured muscles, expression of neutrophil-related chemokines (*Cxcl1* and *Cxcl5*) and the monocyte/macrophage-related chemokine (*Ccl2*) were upregulated as early as immediate to 1 h post-injury. The only marker that was significantly elevated immediately post-injury was *Cxcl5* (P=0.007); its expression increased steadily out to 12 h post-injury. *Ccl2* and *Cxcl1* were upregulated at 0.5-1 h post-injury ($P \leq 0.038$); their expressions increased out to 3 h post-injury and then declined thereafter. Neutrophil surface marker (*Ly6g*) was significantly increased at 0.5 h post-injury (P=0.031); its expression was increased further at 3 h and then was reduced to ~50% of peak levels by 12 h post-injury. The onset of increased expression of other cell surface markers including leukocytes (*CD11b*) and pro-inflammatory macrophages (*CD68*) was initially observed at 3 h ($P \leq 0.004$); their expressions increased steadily out to 12 h post-injury. The onset of expression of the anti-inflammatory macrophage markers (*CD163* and *CD206*) was at 3 h post-injury ($P \leq 0.024$) but expression decreased thereafter. Conclusions: These results indicate that inflammatory chemokines and markers, especially those related to neutrophils, are rapidly upregulated after muscle injury. Supported by NIH grant R01-AG031743.

31.0 EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE

31.1
SEX-BASED DIFFERENCES IN TENDON STRUCTURE AND FUNCTION

Dylan Sarver[1], Kristoffer Sugg[1], Yalda Ashraf Kharaz[2], Jonathan Gumucio[1], Eithne Comerford[2], and Christopher Mendias[1]
[1]Orthopaedic Surgery, Univ. of Michigan, 109 Zina Pitcher Pl., BSRB 2017, Ann Arbor, MI, 48109, [2]Inst. of Ageing and Chronic Dis., Univ. of Liverpool, William Duncan Bldg., 6 W. Derby St., Liverpool, L7 9TX, UK.

Tendons play a critical role in the transmission of forces between muscles and bones, and chronic tendon injuries and diseases are among the leading causes of musculoskeletal disability. For many types of tendinopathies, women have worse clinical outcomes than men. It is possible that sex-based differences in tendon morphology, composition and mechanical properties may explain the greater susceptibility of women to develop tendinopathies. Our objective was to evaluate the mechanical properties, biochemical composition and transcriptome of tendons from four month old male and female C57Bl/6 mice using in vitro biomechanics, mass spectrometry-based proteomics and genome-wide expression profiling. The plantaris and Achilles tendons, which act as ankle plantarflexors, were used in this study. While the plantaris tendons of male mice were approximately 17% larger than female mice ($P<0.05$), the cell density of female mice was around 15% larger than males ($P<0.05$). No significant differences in the length, peak force, peak stress or energy loss during stretch of plantaris tendons were observed. Mass spectrometry proteomics analysis revealed no significant difference between sexes in the abundance of major extracellular matrix (ECM) proteins like collagen types I and III, but female mice had approximately two-fold elevations ($P<0.05$) in different minor ECM proteins such as fibronectin 1, periostin and tenascin A. Using microarray analysis, there was no significant differences in the expression of most major and minor ECM genes. There was also no differences in the expression of genes involved in tendon fibroblast specification or proliferation. In summary, our results indicate that while male mice expectedly had larger tendons, male and female mice have very similar mechanical properties and biochemical composition, with small increases in minor ECM proteins and proteoglycans in female tendons. The role that these minor ECM proteins and proteoglycans play in tendon repair will be evaluated in future studies.

31.2
EFFECT OF ACETAMINOPHEN CONSUMPTION AND RESISTANCE EXERCISE ON EXTRACELLULAR MATRIX GENE EXPRESSION IN HUMAN SKELETAL MUSCLE

Shivam H. Patel[1,2], Andrew C. D'Lugos[3], Erica R. Eldon[2], Jared M. Dickinson[3], and Chad C. Carroll[1,2]
[1]Hlth. and Kinesiology, Purdue Univ., Lambert Fieldhouse, W. Lafayette, IN, 47906, [2]Physiology, Midwestern Univ., 19555 N. 59th Ave, Glendale, AZ, 85308, [3]Exercise Sci. and Hlth. Promotion, Arizona State Univ., 425 N. 5th St., Phoenix, AZ, 85004.

The cyclooxygenase (COX) inhibitor acetaminophen (APAP) has long been established as standard of care for pain-producing ailments, including musculoskeletal pain. Recent work has demonstrated that APAP consumption during resistance training leads to greater gains in muscle mass when compared to placebo. In contrast, APAP use during resistance training leads to a reduction in skeletal muscle collagen cross-linking while also limiting exercise training-induced increases in collagen content. The mechanisms contributing to these APAP mediated changes in the skeletal muscle extracellular matrix (ECM) remain largely unexplored. The purpose of this study was to evaluate the impact of APAP consumption during acute resistance exercise (RE) on the expression of extracellular matrix genes in human skeletal muscle**.** We proposed that APAP would alter mRNA expression of ECM regulatory proteins following RE. In a double-blinded, placebo controlled study; healthy men (n=8, 23-27 years) performed two trials of seated unilateral knee extension (8 sets x 10 reps) exercise. Subjects ingested either APAP (1000mg/6h) or placebo (PLA) for 24 hours prior to RE and an additional dose on the day of exercise immediately post RE. RT-qPCR was used to determine mRNA expression of ECM regulatory proteins in *vastus lateralis* biopsies obtained at rest, 1h, and 3h post RE. Relative to basal values, *MMP-9* mRNA expression was elevated at 3h post RE in the APAP and PLA group ($P<0.05$). *MMP-2* mRNA expression was unchanged in both groups at both time points ($P>0.05$). APAP treatment did not alter mRNA expression of MMPs when compared to PLA ($P>0.05$). During APAP consumption, TIMP-1 mRNA expression was reduced at 1h post-exercise but elevated at 3h ($P<0.05$) when compared to placebo. *LOX* mRNA expression was unchanged at both time points under placebo and APAP conditions ($P>0.05$). *COL1A1* and *COL3A1* mRNA expression were unchanged at both time points ($P>0.05$) during placebo or APAP consumption. These data indicate that APAP has minimal effects on the mRNA expression of key ECM regulatory proteins after acute resistance exercise in humans. While APAP did not strongly influence mRNA expression, APAP may still induce alterations to enzyme activity and protein phosphorylation in the ECM and skeletal muscle.

32.0 IMMUNOLOGY AND INFLAMMATION

32.1
T CELL ACTIVATION AND PROLIFERATION FOLLOWING ACUTE EXERCISE IN HUMAN SUBJECTS IS ALTERED BY STORAGE CONDITIONS AND MITOGEN SELECTION

Jacob Siedlik[1], Jake Deckert[2], Stephen Benedict[3], Anuja Bhatta[3], Amanda Dunbar[3], John Vardiman[4], and Philip Gallagher[2]
[1]Exercise Sci. and Pre-Health Professions, Creighton Univ., 2500 California Plaza, Omaha, NE, 68178, [2]Hlth., Sport, and Exercise Sci., Univ. of Kansas, 1301 Sunnyside Ave, Lawrence, KS, 66045, [3]Molecular Biosciences, Univ. of Kansas, 1200 Sunnyside Ave, Lawrence, KS, 66045, [4]Food, Nutrition, Dietetics and Hlth., Kansas State Univ., 1324 Lovers Ln., Manhattan, KS, 66506.

Recent work investigating exercise induced changes in immunecompetence suggests that some of the ambiguity in the literature is resultant from different cell isolation protocols and mitogen selection. To understand this effect, we compared post-exercise measures of T cell activation and proliferation using two differ-

ent stimulation methods (costimulation through CD3+CD28 or stimulation with phytohaemagglutinin [PHA]). Further, we investigated whether exercise induced changes are maintained when T cell isolation from whole blood is delayed overnight in either a room temperature (RT) or chilled (4˚C; CH) environment. As expected, an increased proliferation response was observed post-exercise in T cells isolated from whole blood immediately after blood collection. Also, cells stimulated with PHA after resting overnight in whole blood were not adversely impacted by the storage conditions. In contrast, allowing cells to rest overnight in whole blood prior to stimulation through CD3+CD28, lessened the proliferation observed by cells following exercise rendering both the RT and CH samples closer to the results seen in the control condition. Changes in early markers of activation (CD25), followed a similar pattern, with activation in PHA stimulated cells remaining fairly robust after overnight storage; whereas cell activation following stimulation through CD3+CD28 was disproportionately decreased by the influence of overnight storage. These findings indicate that decisions regarding cell stimulation methods need to be paired with the timeline for T cell isolation from whole blood. These considerations will be especially important for field based studies of immunocompetence where there is a delay in getting whole blood samples to a lab for processing as well as clinical applications where a failure to isolate T cells in a timely manner may result in loss of the response of interest. Supported, in part, by a grant through the Office of Naval Research and a University of Kansas Doctoral Student Research Fund award.

32.2

ACUTE INTERVAL EXERCISE DECREASES MONOCYTE AND NEUTROPHIL INTERLEUKIN-6 RECEPTOR ALPHA IN HEALTHY OLDER ADULTS AND IN INDIVIDUALS WITH TYPE 2 DIABETES

Cody Durrer[1], Monique Francois[1], Helena Neudorf[1], and Jonathan Little[1]
[1]Hlth. and Exercise Sci., Univ. of British Columbia, Okanagan, 3333 University Way, Kelowna, BC, V1V1V7, Canada.

Background: It is well established that an acute bout of strenuous exercise leads to elevations in circulating levels of interleukin (IL)-6, which is believed to promote subsequent elevations in IL-10 and IL-1Ra. This cytokine response is thought to be one of the key anti-inflammatory effects of exercise. IL-6 and IL-10 interact with specific receptor complexes on the surface of leukocytes in order to propagate their effects. While it is known that acute exercise impacts the expression of cell-surface receptors involved in inflammation, such as toll-like receptors, the effect of exercise on monocyte and neutrophil IL-6 receptor alpha (IL6Rα) and IL-10 receptor (IL10R) has not been previously studied. Aims: 1) To investigate the impact of a single session of high-intensity interval exercise on IL6Rα and IL10R expression on monocytes and neutrophils in patients with type 2 diabetes (T2D) and age-matched normoglycemic healthy controls; and 2) Determine any possible differences in response between T2D and healthy controls. Methods: Ten T2D patients (58 ± 5 y) and nine age-matched healthy controls (56 ± 9 y) underwent a baseline fitness test to assess maximal oxygen uptake (VO_{2PEAK}) prior to completing an acute cycling interval exercise trial involving 7 X 60-second intervals at ~85% of VO_{2PEAK} with 60-second rest periods in between. Venous blood samples were taken before, immediately after, and 60 minutes into recovery from the exercise session. Blood samples were stained with fluorescent-labelled antibodies specific for CD14, CD16, IL6Rα, and IL10R and were analyzed via flow cytometry. Median fluorescence intensity (MFI) of IL6Rα and IL10R were measured on $CD14^+$ classic monocytes, $CD16^+$ monocytes, and $CD16^+$ neutrophils. Results: There were no differences in baseline expression or exercise-induced changes in IL6Rα or IL10R between T2D and healthy controls on any cell type. There was a significant reduction in IL6Rα MFI on classic monocytes immediately after exercise ($p=0.035$), which persisted into one-hour of recovery ($p=0.035$). There was no effect of exercise on IL6Rα MFI on $CD16^+$ monocytes ($p>0.05$). IL6Rα MFI was significantly reduced on neutrophils immediately after exercise compared to baseline ($p=0.044$), and was further reduced at one-hour recovery ($p=0.015$). There was no effect of exercise on IL10R expression on any cell type ($p>0.05$). Conclusion: One session of high-intensity interval exercise led to a reduction in IL6Rα expression on monocytes and neutrophils in both T2D patients and healthy controls. Future work is required to determine if this impacts IL-6 signaling in the post-exercise period. Funding: NSERC (RGPIN 435807-13).

32.3

ENDURANCE EXERCISE TRAINING DECREASES MRNA EXPRESSION OF INFLAMMATORY GENES IN PERIPHERAL BLOOD MONONUCLEAR CELLS IN OVERWEIGHT AND OBESE ADULTS

Harkirat S. Jawanda[1], Douglas W. Van Pelt[1], Lisa M. Guth[1], and Jeffrey F. Horowitz[1]
[1]Sch. of Kinesiology, Univ. of Michigan, 401 Washtenaw Ave, Ann Arbor, MI, 48109.

Elevated inflammation in peripheral blood mononuclear cells (PBMC) is associated with obesity-related complications, such as atherosclerosis. Exercise can alleviate some of the adverse health effects associated with obesity, but the effect of exercise on the inflammatory profile of PBMC remains unclear. The purpose of this study was to examine the effect of exercise on mRNA expression of key markers of inflammation in PBMC. We recruited overweight/obese subjects who were either regular exercisers (EX; n=5) or habitually sedentary (SED; n=5) to examine the effects of both acute and chronic endurance exercise. The groups were well-matched for many physical characteristics (SED vs EX- age: 25±2 vs 27±1 years; BMI: 27±1 vs 29±2 kg/m^2; fat mass: 22±1 vs 24±3 kg, and fat free mass [FFM]: 62±3 vs 57±4 kg) but as expected, they differed in aerobic capacity (VO_2peak: 41.7±1.2 vs 50.5±3 ml/kg FFM/min; $p=0.04$). EX subjects did not exercise for 3 days before the trial. Both groups performed an acute, 1hr session of endurance exercise at ~65% VO_2peak, and blood samples were collected for isolation of PBMC before and immediately after exercise. Before the exercise session, we found lower mRNA expression of *TNFA* and *IL1B* in EX vs SED (both $p=0.01$). However, *TNFA*, *IL1B,*

NLRP3, and *MCP-1* mRNA expression did not change significantly in response to the single session of exercise. We also collected a blood sample 1h after exercise in a subset of subjects (n=4) and found no changes in PBMC mRNA expression of these inflammatory factors. Our findings suggest that regular endurance exercise training may induce adaptations that lower the expression of inflammatory genes in PBMC from overweight/obese adults, but a single session of moderate exercise did not change the mRNA expression of inflammatory genes in PBMC.

32.4

SHORT-TERM HIGH-INTENSITY INTERVAL TRAINING AND MODERATE-INTENSITY CONTINUOUS TRAINING ALTER CHEMOKINE RECEPTOR EXPRESSION IN OVERWEIGHT/OBESE ADULTS

Julianne Barry[1], Cody Durrer[1], Svetlana Simtchouk[2], Mary Jung[1], and Jonathan Little[1]

[1]Sch. of Hlth. and Exercise Sci., Univ. of British Columbia, 3333 University Way, Kelowna, BC, V1V1V7, Canada, [2]Irving K. Barber Sch. of Arts and Sci., Biology, Univ. of British Columbia, 3333 University Way, Kelowna, BC, V1V1V7, Canada.

A key player in the development of type 2 diabetes (T2D) is chronic low grade inflammation. One mechanism that drives this inflammatory state is the infiltration of immune cells into adipose and other tissues, a process mediated by chemotactic cytokines called chemokines that bind to specific chemokine receptors on the surface of leukocytes. Exercise demonstrates various anti-inflammatory effects yet it is unclear whether exercise modulates chemokine signaling and, if so, how different types of exercise compare. High-intensity interval training (HIIT) has been identified as a time-efficient exercise modality demonstrating equal or greater cardiometabolic benefits in healthy and clinical populations as compared to traditional moderate-intensity continuous training (MICT). The potential anti-inflammatory effects of HIIT are unclear. The purpose of this study was to examine the effects of a short-term, two week intervention of HIIT versus MICT, in the absence of weight loss, on circulating chemokines and leukocyte chemokine receptor levels in overweight/obese inactive adults. Forty-two overweight/obese and inactive adults were randomized to ten sessions of HIIT (N=22, 47.1 ± 8.8 yrs, 31.7 ± 8.1 kg/m²) or MICT (N=20, 44.0 ± 10.9 yrs, 30.1 ± 5.4 kg/m²) across a two-week intervention period. No changes were observed in circulating chemokine levels following either exercise intervention but training had a significant impact on surface protein expression of leukocyte chemokine receptors. CCR5 was increased on CD14+/CD16- monocytes after both HIIT (p=0.017) and MICT (p=0.047) and increased on CD16+ granulocytes following HIIT only (p=0.003). CXCR2 was reduced on CD14+/CD16+ monocytes after MICT (p=0.006). In addition, an interaction was seen for CCR2 expression (p=0.045), where CCR2 was higher following HIIT but lower following MICT on CD14+/CD16+ monocytes. In the absence of weight loss, short-term exercise training alters chemokine receptor levels on different leukocyte populations. Chemokine receptor responses differed following HIIT as compared to MICT, indicating that exercise intensity, duration and/or type may uniquely alter chemokine receptor levels in overweight/obese adults. Funding source: Canadian Institutes of Health Research, MOP-133581.

32.5

THE INFLUENCE OF PHYSICAL ACTIVITY AND MONOCYTE PHENOTYPE ON CIRCULATING PLATELET-MONOCYTE COMPLEXES IN OVERWEIGHT/OBESE PERSONS

Michael Levitt[1], Connor Glass[1], Cheryl Haston[1], Anthony Anzalone[1], Stephanie Turner[1], Michael Flynn[2], and Melody Phillips[1]

[1]Kinesiology Dept., Texas Christian Univ., 3005 Stadium Dr., Fort Worth, TX, 76129, [2]Hlth. and Human Performance, Coll. of Charleston, 24 George St., Charleston, SC, 29424.

Low-level systemic inflammation leads to platelet activation as well as an increase in circulating leukocyte number, adhesion molecules, and inflammatory cytokines. Activated platelets bind to circulating monocytes, forming platelet-monocyte complexes (PMC). Elevated PMCs promote atherosclerosis and are associated with type II diabetes mellitus and cardiovascular disease. It is unknown whether consistent physical activity decreases circulating PMCs. **Purposes:** 1) determine the monocyte phenotype most likely to form PMCs 2) examine the influence of PA on PMCs and their association with other inflammatory markers. **Methods:** Thirty-one overweight/obese subjects (44±5yr, BMI 34.2±5 kgâˆ™m^2) were divided into two groups: sedentary (SED, n=17) and physically active (PA, n=14). Flow cytometry was used to identify PMCs on the monocyte phenotypes: classical (CD14+CD16-), intermediate (CD14+CD16+), and non-classical (CD14+CD16++). Platelets were identified using the marker CD42a. All participants reviewed and signed an informed consent document approved by the TCU Institutional Review Board. **Results:** Monocyte phenotype significantly impacted both PMC percentage (%PMC) and platelet density per monocyte, as measured by median fluorescence intensity (MedFI) of CD42a, where lower CD16 expression led to a greater adhesion of platelets. There were no differences in %PMC (PA=25.3±3.86% SED=27.4±3.39%, p>0.05) between groups. HbA1c was greater (p=0.031) and L-selectin (p=0.019) was lower in SED compared to PA. HbA1c correlated with MFI of all PMCs (r=0.45, p = 0.015) and other PMC dependent variables. Platelet factor 4 was correlated with percent of classical (r=-0.482, p=0.031) and low inflammatory (r=0.473, p=0.035) monocytes. **Conclusions:** Classical monocytes appear to be more involved in PMC formation than do inflammatory monocytes in overweight/obese persons. This observation may be due to the shedding of adhesion molecules from platelets and monocytes during activation from a resting to a more inflammatory state. A minimum of three hours of moderate-high intensity PA per week in overweight/obese individuals did not influence %PMC or MedFI of CD42a. This lack of a difference may be attributed to the similarity in VO_2max between groups. Additionally, it is possible that moderate PA does not reduce PMC formation in obese persons. This work was supported by a Texas Christian University Research and Creative Activities Fund Grant.

32.6

NEUTROPHIL FUNCTIONAL CHANGES ARE ASSOCIATED WITH METABOLIC ALTERATIONS FOLLOWING TEN WEEKS OF HIGH INTENSITY INTERVAL EXERCISE TRAINING IN MEN AND WOMEN WITH PREDIABETES

David Bartlett[1,2], Cris Slentz[1], Leslie Willis[1], Kim Huffman[1], William Kraus[1], and Janet Lord[2]
[1]Duke Molecular Physiology Inst., Duke Univ., 300 N. Duke St., Durham, NC, 27701, [2]Inflammation and Ageing, Univ. of Birmingham, Coll. of Med. & Dental Sci., Birmingham, UK.

Introduction: With advanced age, dysfunctional neutrophils are a hallmark of immunesenescence and increased risk of infection. Further, neutrophil dysfunction is associated with increased systemic inflammation and insulin resistance. Improving neutrophil function in those at risk for diabetes may reduce disease risk. We have recently observed that neutrophil function in older individuals without disease is maintained better by engaging in regular physical activity. The aim of this study was to determine if neutrophil functions were improved by structured exercise in those at risk of diabetes. **Method**: Ten older (71±5 years) sedentary participants with prediabetes (HbA1c = 6.1±0.3%) completed 10-weeks of a high intensity interval training program with ten ≥60 second intervals of low intensity (50-60% heart rate reserve (HRR)) separated with bouts of high intensity intervals (80-90% HRR). Neutrophils were analyzed for chemotaxis, phagocytosis, oxidative killing and cellular metabolism before and after training. **Results**: Significant improvements were observed for relative peak VO_2 (p=0.004) and absolute peak VO_2 (p=0.01) with no change in body mass index (p=0.196) or body fat percent (p=0.574). Using live video-microscopy, compared to baseline, post training neutrophils migrated towards the chemokine IL-8 at a similar speed (p=0.857) but with improved velocity (p=0.01) and accuracy (p=0.008). Phagocytosis of opsonized *E.Coli* was enhanced on a per-cell basis (p=0.007), while oxidative killing capacity was slightly increased (p=0.05). Improved functions were not related to changes in the cell surface receptors CXCR2 or TLR-4 (both p>0.05). Using Seahorse technology, mitochondrial function was improved following training. Specifically, proton leak across the mitochondrial membrane was reduced (p<0.05), while basal and maximal respiration and ATP production were all improved (all p<0.05). **Conclusion:** Ten weeks of interval training in older individuals at risk for diabetes improved aerobic fitness with no change in body composition. Improved neutrophil functions were associated with mitochondrial improvements on a per cell basis. Ten weeks of interval training in persons with prediabetes alters neutrophil metabolism which is associated with improved primary functions, potentially reducing the risk of infection and inflammatory insult which can enhance diabetes risk. *This work was funded by an EU Marie Curie Outgoing Fellowship Grant (PIOF-GA-2013-629981).*

32.7

ASSOCIATION OF THE COMPOSITE INFLAMMATORY BIOMARKER, GLYCA, WITH EXERCISE-INDUCED CHANGES IN BODY HABITUS IN MEN AND WOMEN WITH PREDIABETES

David Bartlett[1], Cris Slentz[1], Margery Connelly[2], Lucy Piner[1], Leslie Willis[1], Lori Bateman[3], Esther Granville[1], Connie Bales[1], Kim Huffman[1], and William Kraus[1]
[1]Duke Molecular Physiology Inst., Duke Univ., 300 N. Duke St., Durham, NC, 27701, [2]LipoSci., Lab. Corp. of America Holdings, 2500 Sumner Blvd., Raleigh, NC, 27616, [3]Ctr. for Hlth. Promotion and Disease, Univ. of North Carolina, 1700 Martin Luther King, Chapel Hill, NC, 27514.

Introduction: Exercise interventions can reduce systemic inflammation and risk of inflammatory diseases, however it remains unclear specific exercise induced modifications. GlycA is a novel NMR measured composite measure of chronic systemic low grade inflammation, and is a good predictor of disease — including type-2 diabetes. The aim of this study was to determine the association of GlycA modifications in 4 different exercise intervention groups. **Method**: GlycA, fitness and body composition were measured longitudinally in 169 sedentary adults (45-75 years) with prediabetes. Participants were randomly assigned to one of four six-month exercise-based lifestyle interventions: 1) low-amount/moderate-intensity exercise; 2) high-amount/moderate-intensity exercise; 3) high-amount/vigorous-intensity exercise and 4) a combined diet and exercise intervention consisting of low-amount/moderate-intensity exercise plus weight-reduction diet designed to elicit a 7% body weight reduction. **Result**: Participants in the combined lifestyle (exercise + diet) group (p=0.007) and the vigorous intensity group (p=0.033) had a significant reduction in GlycA. The findings were similar for liver density — a surrogate measurement of liver fat content — wherein both the combined lifestyle and vigorous intensity exercise groups experienced reductions in liver density (both p<0.01). All four groups reduced total abdominal, subcutaneous and visceral adiposity (all p<0.05). When including individuals in all four interventions in the same analysis, GlycA reductions were associated with reductions in body fat percentage (p=0.028) and visceral adiposity (p=0.015), and improved fasting insulin (p=0.009). **Conclusion**: Exercise-based lifestyle interventions, including a vigorous intensity exercise-only intervention and a combined exercise and diet intervention, reduced GlycA concentrations through mechanisms that seem to be related to exercise-induced modulations in visceral adiposity and insulin production, but not through exercise-induced changes in liver fat content. *The study was funded by an NIH - NIDDK (R01DK081559) grant.*

32.8

ASPIRIN AS A COX INHIBITOR AND ANTI-INFLAMMATORY DRUG IN HUMAN SKELETAL MUSCLE

Todd Trappe[1], Steve Ratchford[1], Kaleen Lavin[1], Ryan Perkins[1], Bozena Jemiolo[1], and Scott Trappe[1]
[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave, Muncie, IN, 47306.

Although aspirin is one of the most common anti-inflammatory drugs in the world, the effect of aspirin on human skeletal muscle inflammation is almost completely unknown. This study examined the potential effects and related time course of an orally consumed aspirin dose on the inflammatory PGE_2/COX pathway in human skeletal muscle. Skeletal muscle biopsies were

taken from the vastus lateralis of 10 healthy adults (5M/5F, 25±2 y) before and 2, 4, and 24 h after consuming a standard dose of aspirin (975 mg) and partitioned for analysis of 1) *in vivo* PGE_2 levels in resting human skeletal muscle and 2) *ex vivo* skeletal muscle PGE_2 production when stimulated with the COX substrate arachidonic acid (5 μM). Both PGE_2 levels *in vivo* and PGE_2 production *ex vivo* were generally unchanged at each time point after aspirin consumption ($P>0.05$). However, most individuals clearly showed suppression of PGE_2, but at varying time points after aspirin consumption. When the maximum suppression after aspirin consumption, independent of time, was examined for each individual, both PGE_2 levels *in vivo* (Pre: 184±17, Post: 104±23 pg/g wet wt) and PGE_2 production *ex vivo* (Pre: 2.74±0.17, Post: 2.09±0.11 pg/mg wet wt/min) were reduced ($P<0.05$) by 44% and 24%, respectively. These results provide the first evidence that orally consumed aspirin can inhibit the COX pathway and reduce the inflammatory mediator PGE_2 in human skeletal muscle. Findings from this study highlight the need to expand our knowledge regarding the potential role for aspirin regulation of the deleterious influence of inflammation on skeletal muscle health in aging and exercising individuals. Sponsored by NIH grant R01 AG038576.

32.9

EXERCISE TRAINING REVERSES THE ACCUMULATION OF MARROW ADIPOSE TISSUE AND PRO-INFLAMMATORY CYTOKINES FOLLOWING DIET-INDUCED OBESITY.

Russell Emmons[1], Adam Kriska[2], Hong Chen[2,3], and Michael De Lisio[1,3]

[1]Dept. of Kinesiology and Community Hlth., Univ. of Illinois at Urbana-Champaign, 906 S. Goodwin Ave., Urbana, IL, 61801, [2]Dept. of Food Sci. and Human Nutrition, Univ. of Illinois at Urbana-Champaign, 905 S. Goodwin Ave, Urbana, IL, 61801, [3]Dept. of Nutritional Sci., Univ. of Illinois at Urbana-Champaign, 905 S. Goodwin Ave, Urbana, IL, 61801.

Obesity is associated with increased risk of developing colon cancer, potentially due to impairments to immune function. Hematopoietic stem and progenitor cells (HSPCs) within the bone marrow are responsible for maintenance of the mature immune and blood system throughout the lifespan. Marrow adipose tissue (MAT), a major constituent of the bone marrow niche, accumulates in obesity and is a negative regulator of hematopoiesis. Exercise training induces bone marrow remodeling; however, the impact of exercise on the bone marrow microenvironment in the context of obesity and cancer has not been examined. **Purpose:** To investigate the impacts of a progressive exercise training program on the bone marrow compartment following consumption of a high fat diet (HF) in a mouse model of colon cancer. **Methods:** C57Bl/6J mice were divided into three groups: control diet (CON n=5), high-fat sedentary (HF-SED, n=5), and high-fat exercise (HF-EX n=5). HF mice received a diet consisting of 45% fat for 8 weeks. All mice received 4 i.p. azoxymethane (AOM) injections to induce colon cancer and were returned to the control diet after the first injection. HF-EX mice underwent a 24-week progressive treadmill training program (1 hr/d, 3 d/wk) beginning after AOM injection. MAT was visualized in femurs via Xardia MicroCT. Inflammatory cytokine content was determined from whole bone marrow cell fractions using a multiplex array. **Results:** MAT was significantly increased in the HF-SED compared to CON (24.3 ± 2.3% vs 13.5 ± 2.3%, $p<0.05$). Exercise significantly reduced the increased MAT (24.3 ± 2.3% in HF-SED vs 11.9 ± 3.3% in HF-EX, $p<0.05$) and returned the MAT to a level that is similar to that of CON group (13.5 ± 2.3% vs 11.9 ± 3.3%). Increases in pro-inflammatory cytokines IL-1β (fold change: 1.0 in CON vs 1.8 in HF-SED, vs 0.56 in HF-EX), IFN-ϒ (fold change 1.0 in CON vs 1.3 in HF-SED vs 0.6 in HF-EX), and G-CSF (fold change: 1.0 in CON vs 1.3 in HF-SED vs 0.7 in HF-EX 0.7) were observed in HF-SED mice. These were decreased by exercise in HF-EX mice compared to CON. **Conclusions:** Our data suggest that a high fat diet increases the accumulation of MAT and pro-inflammatory cytokines within the bone marrow that persists even after return to a control diet. Exercise training completely reversed these changes. These data demonstrate the beneficial effects of exercise towards a healthier bone marrow compartment in the high fat-colon cancer model. Funding provided by UIUC Research Board.

32.10

A COMPARISON OF COLD WATER IMMERSION AND ACTIVE RECOVERY ON INFLAMMATION AND CELL STRESS RESPONSES IN HUMAN SKELETAL MUSCLE AFTER RESISTANCE EXERCISE

James Markworth[1], Jonathan Peake[2,3], Llion Roberts[3,4], Vandre Figueiredo[1], Ingrid Egner[5], Simone Krog[6], Sigve Aas[6], Katsuhiko Suzuki[7], Jeff Coombes[4], David Cameron-Smith[1], and Truls Raastad[6]

[1]Liggins Inst., Univ. of Auckland, Grafton, Auckland, New Zealand, [2]Sch. of Biomedical Sci. and Inst. of Hlth. and Biomedical Innovation, Queensland Univ. of Technology, Brisbane City, Brisbane, Australia, [3]Ctr. of Excellence for Applied Sport Sci. Res., Queensland Acd. of Sport, Brisbane, Australia, [4]Sch. of Human Movement and Nutrition Scie., Univ. of Queensland, St Lucia, Brisbane, Australia, [5]Dept. of Biosciences, Univ. of Oslo, Blindernveien 31, 0371, Oslo, Norway, [6]Dept. of Physical Performance, Norwegian Sch. of Sport Sci., Sognsveien 220, 0863, Oslo, Norway, [7]Fac. of Sport Sci., Waseda Univ., Tokorozawa, Saitama, Japan.

Cold water immersion and active recovery are common post-exercise recovery treatments. A key assumption about the purported benefits of cold water immersion is that it reduces inflammation in skeletal muscle. However, no data are currently available from humans to support this notion. We compared the effects of cold water immersion versus active recovery on inflammatory cells, pro-inflammatory cytokines, neurotrophins and heat shock proteins (HSPs) in skeletal muscle after intense resistance exercise. Nine active men performed unilateral lower-body resistance exercise on separate days, at least 1 wk apart. On one day, they immersed their lower body in cold water (10degC) for 10 min after exercise. On the other day, they cycled at a low intensity for 10 min after exercise. Muscle biopsies were collected from the exercised leg before, 2, 24, and 48 h after exercise in both trials. Exercise induced a strong inflammatory response, with increased intramuscular neutrophil and mac-

rophage counts, and corresponding muscle mRNA expression levels of MAC1, CD163, IL1β, TNF, IL6, and CCL2 ($P<0.05$). As evidence of hyperalgesia, the expression of NGF and GDNF mRNA increased after exercise ($P<0.05$). The cytosolic protein content of αB-crystallin and HSP70 protein content decreased after exercise ($P<0.05$). This response was accompanied by increases in the cytoskeletal protein content of αB-crystallin and the percentage of type II fibres stained for αB-crystallin. Changes in inflammatory cells, cytokines, neurotrophins, and HSPs did not differ significantly between the recovery treatments. These findings indicate that cold water immersion is no more effective than active recovery for reducing inflammation or cellular stress in muscle after a bout of resistance exercise.

32.11

MENOPAUSAL STATUS IMPAIRS TRANSIENT INFLAMMATORY RECOVERY AFTER ACUTE HYPERTROPHIC RESISTANCE EXERCISE

Christopher Axelrod[1], Emily Kullman[1], Kenneth Sparks[1], and Kathleen Little[1]

[1]Dept. of Hlth. and Human Performance, Cleveland State Univ. Coll. of Edu. and Human Services, 2121 Euclid Ave., Julka Hall 164, Cleveland, OH, 44115.

Loss of ovarian function is associated with elevated risk of osteoporosis, cardiovascular disease, gastrointestinal distress, and chronic low-grade inflammation (1-3). It has been previously reported that estrogen promotes inflammatory recovery in response to macrophages treated with lipopolysaccharide *in vitro* (4). However, there is little *in vivo* evidence supporting this notion. Thus, the purpose of this investigation was then to determine the effects of menopausal status on acute hypertrophic exercise-induced inflammatory recovery in humans. Twenty healthy, sedentary women aged 18-65 years completed a session of submaximal, full body resistance exercise. Subjects were categorized as either pre- (n=10) or post-menopausal (n=10) based upon history of menopausal status and follicle stimulating hormone (FSH) levels. On a separate day, at least two weeks prior to testing, one repetition maximum (1RM) was determined for the chest and leg press, leg and biceps curl, vertical pull down, triceps and leg extension exercises. On the day of testing, subjects performed 3 sets of 10 repetitions at 75% 1RM for all exercises. Blood samples were obtained from the antecubital vein prior to, immediately after, and one hour after the termination of exercise. Changes in plasma concentrations of interleukin-6, -10, -13, and transforming growth factor beta (IL-6, -10, -13, and TGF-β1) were determined via enzyme-linked immunosorbent assays (ELISA). Post-menopausal women had lower ($p<0.05$) absolute and fat free mass-adjusted 1RM's. IL-6 concentrations increased ($p<0.05$) over time, with no difference between groups. Pre-menopausal IL-10 levels increased ($p<0.05$) pre- to immediately post-exercise, whereas post-menopausal displayed no change. There was a significant ($p<0.05$) difference in IL-10 levels between groups immediately post-exercise. Thus, menopause diminished IL-10 stimulated inflammatory recovery without significantly altering the magnitude of response. **References:** 1. Abu-Taha M, Rius C, Hermenegildo C, Noguera I, Cerda-Nicolas JM, Issekutz AC, Jose PJ, Cortijo J, Morcillo EJ, Sanz MJ. Menopause and ovariectomy cause a low grade of systemic inflammation that may be prevented by chronic treatment with low doses of estrogen or losartan. J Immunol. 2009;183(2):1393-402. doi: 10.4049/jimmunol.08031

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32.12

DOXORUBICIN ATTENUATES PROINFLAMMATORY MEDIATOR EXPRESSION IN BRAIN AND PIAL ARTERIES FROM OVARIECTOMIZED FEMALE RATS FOLLOWING HIGH INTENSITY EXERCISE

Nirmal Vijayavel[1], Puneet Raman[1], Mei So[1], Jared Dickinson[2], Chad Carroll[3], Siddhartha Angadi[2], and Rayna Gonzales[1]

[1]Basic Med. Sci., Univ. of Arizona, 425 N. 5th St., Phoenix, AZ, 85004, [2]Sch. of Nutrition and Hlth. Promotion, Arizona State Univ., 425 N. 5th St., Phoenix, AZ, 85004, [3]Physiology, Midwestern Univ., 19555 N. 59th Ave, Glendale, AZ, 85308.

Doxorubicin (DOX) is a highly effective chemotherapy agent used to reduce reoccurrence and mortality in breast cancer patients. Its use is hampered however, owing to severe dose-dependent cardiovascular toxicity in cancer survivors. Multiple mechanisms have been implicated in the pathogenesis of DOX cardiotoxicity, one of which involves inflammation mediated by activation of the NFκB/TLR4/COX-2 pathway. The purpose of this study was to determine the effect of DOX on TLR4 and COX-2 levels in cortex and pial arteries isolated from ovariectomized female Sprague-Dawley rats. In addition, we determined if high-intensity interval exercise before and during biweekly DOX treatments would impact the adverse effects of DOX. We hypothesized that DOX would increase proinflammatory markers COX-2 and TLR4 levels, both of which are under the transcriptional regulation of NFκB. We further hypothesized that exercise would attenuate this response. Rats were randomized to one of four treatments: Sedentary vehicle (Sed+Veh); (Sed+DOX); Exercise+Vehicle (Ex+Veh); and Ex+DOX). The exercise group underwent high intensity (85-95 %VO2peak) interval exercise (4×4 min bouts) 5d/wk starting 1 week prior to the first injection and continued throughout study duration. DOX (4 mg/kg; cumulative dose 12mg/kg) or vehicle (saline) injections were administered i.p. and animals were euthanized 5 days after the last dose. Tissues were isolated, homogenized, and lysates analyzed for COX-2 and TLR4 levels via western analysis. Nuclear fractionation was used to determine NFκB activation. Basal levels of COX-2 and TLR4 protein were detected in brain cortex and pial artery lysate from vehicle-treated rats. However, contrary to our hypothesis, levels of COX-2 and TLR4 were decreased following DOX ($p<0.05$ vs. SED+VEH or VEH+EX) independent of DOX-induced NFκB

activation. Exercise did not alter COX-2 or TLR4 expression in vehicle or drug treated animals. In conclusion, these preliminary data suggest that long term administration of DOX may elicit anti-inflammatory actions, particularly in female cohorts with low circulating levels of gonadal hormones.

33.0 STEMS CELLS AND REGENERATION

33.1
BED REST FOR 5-DAYS IS ACCOMPANIED BY ROBUST SATELLITE CELL DEPLETION IN SKELETAL MUSCLE OF OLDER ADULTS

Alec McKenzie[1], Paul Reidy[1], Daniel Nelson[2], Katherine Barrows[1], Preston Brunker[1], Paul LaStayo[1], and Micah Drummond[1]
[1]Dept. of Physical Therapy and Athletic Training, Univ. of Utah, 520 Wakara Way, Salt Lake City, UT, 84108, [2]Dept. of Nutrition and Int. Physiology, Univ. of Utah, 250 S. 1850 E., Salt Lake City, UT, 84108.

Short-term disuse (i.e. bed rest) often leads to pronounced losses in skeletal muscle mass and function. Compared to their younger counterparts, older adults are more susceptible to sudden periods of disuse that result in muscular deficits and a risk of impaired recovery of physical function/independence. Skeletal muscle satellite cells (SCs) play an important role during muscle recovery following a physiological insult, and are likely affected during a period of muscle disuse especially in this vulnerable population. The existing body of literature regarding the short term SC response (e.g. 5-14 days) to disuse (i.e., bed rest, cast immobilization) is inconclusive, and is likely due to dissimilar methodologies (i.e. study duration, varying inactivity models, etc.). We aimed to address whether or not the SC population in older adults is altered by a period of short-term bed rest, and if these alterations are accompanied by a loss of muscle fiber cross-sectional area (CSA). Skeletal muscle biopsies were collected from 17 healthy older adults (14M, 3F; 70.2 ± 5.6 y; 25.7 ± 2.9 kg/m²) prior to (Pre), and immediately following (Post) 5 consecutive days of supervised bed rest. Immunofluorescent microscopy was used to quantify SC content and fiber CSA in a myosin heavy chain I/IIa (MyHC I/IIa) dependent manner. Short-term bed rest resulted in a 25% ($p=0.02$) and 14% ($p=0.04$) decrease in both MyHC I & IIa SC content, respectively. Fiber CSA decreased in both MyHC I (Pre: 4527 ± 359 to Post: 3670 ± 278 μm^2, $p=0.03$) and MyHC IIa (Pre: 4159 ± 436 to Post: 3427 ± 177 μm^2, $p=0.05$) following short-term bed rest. SC content of MyHC IIa fibers positively correlated with MyHC IIa CSA ($r^2=0.13$, $p=0.05$). Short-term bed rest also tended to result in a 7% ($p=0.13$) and 11% ($p=0.11$) decrease in the myonuclear content of MyHC I and IIa fibers, respectively. Our data support that even as few as 5-days of bed rest can significantly reduce the SC population in skeletal muscle of older adults. Given the crucial role of SCs in the context of muscle maintenance and regeneration, these data underscore the importance of interventional strategies designed to preserve/enhance the SC population during inactivity and disuse. Currently we are exploring mechanisms underlying SC loss with bed rest as well as interventions to preserve SCs and lean mass in older adults on bed rest. *Funding was provided by NIH* R03AG047308 and from the University of Utah Funding Incentive Seed Grant Program.

33.2
CYCLE TRAINING ALTERS SATELLITE CELL AND TRANSCRIPTIONAL RESPONSES TO A BOUT OF RESISTANCE EXERCISE

Kevin Murach[1], Grace Walton[1], Christopher Fry[2], Sami Michaelis[1], Jason Groshong[1], Brian Finlin[3], Philip Kern[3], and Charlotte Peterson[1]
[1]Dept. of Rehabilitation Sci., Univ. of Kentucky, 900 S. Limestone, C.T. Wethington Bldg., Lexington, KY, 40536, [2]Dept. of Nutrition and Metabolism, Univ. of Texas Med. Branch, 301 University Blvd., Galveston, TX, 77555, [3]Dept. of Med., Univ. of Kentucky Med. Ctr., MN 150, Lexington, KY, 40563.

This investigation evaluated whether increased satellite cell density and hypertrophy from moderate-intensity cycle ergometer training would affect satellite cell and transcriptional responses to acute maximal concentric/eccentric resistance exercise. Baseline and 72 hour post resistance exercise *vastus lateralis* biopsies were obtained from seven healthy middle-aged women (56±5 y, BMI 26±1, VO_2max 27±4) before and after 12 weeks of cycle training. Myosin heavy chain (MyHC) I- and II-associated satellite cell density and cross sectional area were determined via immunohistochemistry. Expression of 93 genes representative of the muscle-remodeling environment was also measured via NanoString. Overall fiber size increased ~20% with cycle training ($P=0.052$). MyHC I satellite cell density increased 29% in response to acute resistance exercise and 50% with endurance training ($P<0.05$). When endurance trained, MyHC I satellite cell density was attenuated by 10% following acute resistance exercise (acute resistance x training interaction, $P<0.05$). Genes with an interaction effect tracked with satellite cell changes, increasing in the untrained state and decreasing in the endurance trained state in response to resistance exercise. Similar satellite cell and gene expression response patterns suggest coordinated regulation of the muscle environment to promote adaptation. The acute response to a robust concentric/eccentric stimulus is altered subsequent to satellite cell and molecular adaptations following moderate-intensity concentric cycle training. Cycle training is an effective endurance exercise modality for promoting growth, specifically in middle-aged women who are highly susceptible to muscle mass loss as age progresses.

33.3
SKELETAL MUSCLE PERICYTES TRANSITION TO A MESENCHYMAL STROMAL CELL PHENOTYPE FOLLOWING AN ACUTE BOUT OF ELECTRICAL STIMULATION

Svyatoslav Dvoretskiy[1], Koyal Garg[1], Michael Munroe[1], Yair Pincu[1], Ziad Mahmassani[1], and Marni Boppart[1]
[1]Kinesiology & Community Hlth., Univ. of Illinois, Urbana-Champaign, 405 N. Mathews Ave, MC-251, Champaign, IL, 61801.

Pericytes are mural cells that are located on the outer surface of blood capillaries where they attach to endothelial cells and regulate vascular function. Recent studies suggest that pericytes in skeletal muscle may contribute to myofiber repair in response to injury. However, the pericyte response to exercise remains largely unexplored. The purpose of this study was to evaluate pericyte quantity and gene expression following electrical stim-

ulation. Hindlimbs of WT mice were subjected to bilateral electrical stimulation protocol that results in 20 eccentric and 20 concentric contractions during a single session or (n=5; n=4 sham). A separate cohort was subjected to electrical stimulation twice weekly for 4 weeks (n=4; n=4 sham). Gastrocnemius-soleus complexes were dissected 24h following the final stimulation. Pericyte quantity was assessed by multiplex flow cytometry in all samples. $NG2^+CD45^-CD31^-$ and $CD146^+CD45^-CD31^-$ pericytes were isolated and gene expression was evaluated using high throughput qPCR. Acute electrical stimulation resulted in a significant increase in the percentage of $NG2^+CD45^-CD31^-$ pericytes expressing the mesenchymal stem/stromal cell (MSC) /fibroadipogenic (FAP) marker PDGFRα. Isolation of pericytes based on CD146 revealed a population of cells highly engaged in the synthesis of factors necessary for myogenesis, satellite cell activation, and extracellular matrix remodeling post-acute stimulation. Finally, a similar pericyte to MSC transition was observed with 4 weeks of stimulation, but no changes in overall pericyte quantity were noted. This study provides evidence that resistance exercise promotes a pericyte to MSC transition, an event that may be necessary for pericytes to engage in skeletal muscle repair and adaptation.

34.0 PHYSICAL INACTIVITY AND CHRONIC DISEASE

34.1
BREAKING UP PROLONGED SITTING ALTERS THE POSTPRANDIAL PLASMA LIPIDOMIC PROFILE IN ADULTS WITH TYPE 2 DIABETES

Megan Grace[1], Paddy Dempsey[1], Jacquelin Weir[2], Natalie Mellett[2], Parneet Sethi[1], Piyush Mundra[2], Neville Owen[3], David Dunstan[1], Peter Meikle[2], and Bronwyn Kingwell[4]
[1]Physical Activity Lab., Baker IDI Heart and Diabetes Inst., Level 4, Alfred Ctr., 99 Commercial Rd., Melbourne, VIC, 3004, Australia, [2]Metabolomics Lab., Baker IDI Heart and Diabetes Inst., 75 Commercial Rd., Melbourne, VIC, 3004, Australia, [3]Behavioural Epidemiology Lab., Baker IDI Heart and Diabetes Inst., Level 4, Alfred Ctr., 99 Commercial Rd., Melbourne, VIC, 3004, Australia, [4]Metabolic and Vascular Physiology Lab., Baker IDI Heart and Diabetes Inst., Level 4, Alfred Ctr., 99 Commercial Rd., Melbourne, VIC, 3004, Australia.

Background: In addition to their role as energy substrates, lipids are important inflammatory and signalling mediators. Evidence suggests that postprandial lipemia, such as that associated with type 2 diabetes (T2D), may trigger inflammation and oxidative stress, contributing to disease progression. Studies have demonstrated that acute dietary and exercise interventions can affect lipidomic profiles. However, many with T2D have poor diet quality and spend many hours sitting daily. Brief active interruptions in sitting are associated with more favourable cardiometabolic risk profiles. We investigated the effects of regular light intensity activity breaks, in comparison to prolonged sitting, on the postprandial plasma lipidome in adults with T2D. **Methods:** In a randomized cross-over trial[1], 21 inactive overweight/obese adults with T2D underwent 3 x 8h conditions: (i) uninterrupted sitting (SIT); (ii) sitting interrupted by 3min of light walking every 30min (3.2km/h; LW); or (iii) sitting interrupted by 3min of simple body weight resistance activities every 30min (SRA). Standardized breakfast and lunch meals were consumed. Baseline (fasting) and 8h plasma samples were analyzed for 363 lipid species using mass spectrometry. Using mixed model analysis (controlling for baseline lipids, sex and BMI), the percentage change in lipid species across the day (from baseline to 8 h) was compared between conditions. **Results:** After Benjamini Hochberg correction for multiple comparisons, 35 lipids were significantly different between conditions ($p<0.05$). Compared to SIT, the elevation in postprandial saturated and shorter chain diglycerides, triglycerides and phosphatidylethanolamines were attenuated in LW and SRA ($p<0.05$). Plasmalogens and lysoalkylphosphatidylcholines were reduced in SIT, compared to being either elevated or unchanged in LW, or reduced to a lesser extent in SRA. Phosphatidylserines were elevated with LW, compared to a reduction in SIT and SRA. **Conclusions:** The postprandial plasma lipidome is differentially altered with regular LW or SRA breaks, compared to SIT. The smaller postprandial increase in diglyceride and triglyceride species is likely due to the oxidation of lipids for ATP production in skeletal muscle. Moreover, compared to SIT, LW and SRA interruptions were associated with reduced pro-inflammatory lipids and increased concentrations of lipids with antioxidant capacity. Breaking up prolonged sitting may impart beneficial effects on postprandial plasma lipidomic profile in adults with T2D. 1. Dempsey, et al. Diab Care 2016; 39:964-72.

34.2
INDUCED URINARY BLADDER DISTENSION AND PHYSICAL ACTIVITY PATTERNS IN MICE

Robert Bowen[1], Brittany Cates[1], Bryce Dillard[1], Brittany Foster[1], Shawnee Patterson[1], and Thomas Spivey[1]
[1]Lab. of Applied and Exercise Endocrinology, Truett McConnell Univ., 100 Alumni Dr., Cleveland, GA, 30528.

Habitually low physical activity levels result in a "couch potato" phenotype riddled with adverse health outcomes. Understanding the mechanisms that control physical activity is an important healthcare-related goal.The estrogens exhibit control over activity patterns in both humans and rodents. Estrogens target many different tissues and some dosing strategies might result in ancillary effects that adversely mask the true hormonal regulation pattern. The purpose of this paper was to assess the effects of estrogen (a known influencer of activity) and estrogen-induced urinary bladder distension (a postulated mechanical inhibitor of activity) on the recovery of orchidectomy-suppressed physical activity patterns in mice. All aspects of this study adhered to humane animal care and use guidelines. Eight week old male C57BL/6j mice (n = 28) where acquired for this study. Mice acclimate to the wheel running environment in standard rat sized cages. Solid surface running wheels (circumference = 450 mm) were interfaced to computers to track daily distance, duration, and speed. Two mice were excluded from further study after acclimation due to illness; the remaining mice underwent baseline activity assessment for one week. Following baseline data collection, mice were subjected to a sham gonadectomy (n = 8) or bilateral orchidectomy to eliminate the sex hormones (n = 18). Several mice were assessed for depletion of sex hormones following the surgical recovery period (n = 3 sham; n = 3 orchidec-

tomized). Wheel running was observed for another week under low estrogen levels. Lastly, mice received Silastic implants containing estrogen at varying dosage regimens: low (n = 5), moderate (n = 5), and high (n = 5) doses. Sham mice (n = 5) received capsules without estrogen. Caudal pressure was used to express urinary bladder contents and urine volume was assessed following a final seven-day observation period during estrogen treatment. Urinary volume was elevated in mice exposed to high levels of estrogen, but physical activity appeared unaffected in all mice regardless of estrogen status. Furthermore, estrogen replacement failed to elicit recovery of the pattern to pre-surgical levels. In conclusion, estrogen-induced urinary bladder distension did not mechanically influence physical activity. These findings indicate that urinary bladder distension is not a major concern to the study of physical activity with estrogen treatment and results can be interpreted directly.

34.3

PHYSICAL INACTIVITY MAY DECREASES INSULIN SENSITIVITY THROUGH THE ACCUMULATION OF INTRAMYOCELLULAR DIACYLGLYCEROL, AND IT IS FURTHER FACILITATED BY HIGH FAT DIET

Saori Kakehi[1], Yoshifumi Tamura[1,2], Ryuzo Kawamori[1], and Hirotaka Watada[1,2]

[1]Sportology Ctr., Juntendo Univ., 2-1-1 Hongo Bunkyo, Tokyo, 1138421, Japan, [2]Dept. of Metabolism & Endocrinology, Juntendo Univ., 2-1-1 Hongo Bunkyo, Tokyo, 1138421, Japan.

Intramyocellular lipid accumulation especially diacylglycerol and ceramide has been reported as one of the causes of decreased insulin sensitivity in skeletal muscle. However, they were not clear whether intramyocellular lipid is involved in decreased insulin sensitivity by physical inactivity in skeletal muscle, and whether physical inactivity and high fat diet (HFD) has combined effect of decrease insulin sensitivity in skeletal muscle. To elucidate them, 24hours hind-limb cast immobilization (HCI), which was reported to decrease insulin sensitivity in skeletal muscle, had been used for insulin resistance model induced by physical inactivity. C57BL6J mice were randomly assigned to four groups; control group, 24h HCI group, short-term (2wk) HFD group, and 24h HCI after 2wk HFD group. As a result, 24h HCI significantly decreased insulin-stimulated 2DG-uptake by ~40%, while 2wk HFD did not alter 2DG-uptake. On the other hand, 24h HCI after 2wk HFD dramatically decreased insulin-stimulated 2DG-uptake by ~75%. Then, we examined intracellular fat composition and protein level of lipid metabolizing enzyme. Intriguingly, we found that 24h HCI increased intramyocellular diacylglycerol (IMDG) in soleus by ~190%, while the amount of intramyocellular triglycerol (IMTG) was not changed. Moreover, whereas IMDG and IMTG were not changed by 2wk HFD, 24h HCI after 2wk HFD dramatically increased IMDG by ~330%. In parallel with IMDG accumulation, PKCε activity and oxidative stress were increased, and insulin signaling was reciprocally impaired. The IMDG accumulations were also accompanied by increased muscle mRNA of adipose triglyceride lipase (ATGL) and Lipin1, enzymes for diacylglycerol synthesis. In addition, we identified oxidative stress increased ATGL and Lipin1 mRNA in vitro. Finally, we applied 24h leg cast immobilization in human and found increased IMDG accumulations and mRNA of ATGL and Lipin1 in skeletal muscle. These results suggested that 24h HCI decrease insulin sensitivity in skeletal muscle, which is furthered by HFD. Increased IMDG and oxidative stress might be involved in the mechanisms. Taken together, this might be regarded as one of the mechanisms decreased insulin sensitivity independent with obesity.

34.4

EXAMINATION OF PHYSICAL ACTIVITY AND FAMILY HISTORY OF TYPE 2 DIABETES ON SERUM FGF21

Greggory Davis[1], Joshua Guillory[2], Tiffany Deville[1], David Bellar[1], and Arnold Nelson[3]

[1]Sch. of Kinesiology, Univ. of Louisiana at Lafayette, 225 Cajundome Blvd., Lafayette, LA, 70503, [2]Kinesiology, Louisiana Tech Univ., 305 Wisteria St, Ruston, LA, 71272, [3]Kinesiology, Louisiana State Univ., 112 Huey P. Long Fieldhouse, Baton Rouge, LA, 70803.

The objective of the study was to determine if physical activity (PA) levels in individuals with (FH+) and without (FH-) a first degree family history of type 2 diabetes (T2D) affect serum FGF21. Additional serum biomarkers as well as clinical, metabolic, and anthropometric measures were analyzed as potential co-variables. Healthy male and female participants between the ages of 18-35 were recruited, FH+ n = 18, FH- n = 17. All participants reported to the lab following an overnight fast. Female participants had to report to the lab within seven days of starting the follicular phase of the menstrual cycle. PA levels were determined via the Leisure and Physical Activity Survey. Body composition, resting metabolic rate, gender, age, body mass index, waist circumference, and blood pressure measurements were collected. Serum biomarkers included FGF21, adiponectin, resistin, C-reactive protein, and interleukin-6. FGF21 concentrations were determined via commercially available immunoassay kit and all other biomarkers were determined via a multiplex assay kit. The FGF21 assay was read on a microplate absorbance reader and the multiplex assay was analyzed using chemilumenesence imaging. All samples were analyzed in duplicate. A one-way ANOVA revealed that differences between groups for FGF21 were not significant (FH+ = 266 pg/ml ± 51.4, FH-= 180 pg/ml ± 29; $F = 2.04$, $p = 0.16$). PA did not significantly affect FGF21 regardless of family history (High PA = 200.01 pg/ml ± 190.37, Low PA = 235.87 pg/ml ± 178.01; $F = 0.29$, $p = 0.59$). Adiponectin values were lower in FH+ (8.81 µg/ml ± 2.14) compared to FH- (10.65 µg/ml ± 1.44) ($F = 8.83$, $p = 0.01$). No other variables were significantly different between groups. Regression analysis revealed that resistin was negatively correlated with FGF21 for all participants ($r = -0.38$, $p = 0.03$), but no other clinical, metabolic, or serum markers were predictive for serum FGF 21 in FH+ or FH-. Serum FGF21 is not significantly different between FH+ and FH- in young, healthy individuals, regardless of PA levels. In addition, the inability of clinical, anthropometric, metabolic, and serum markers to predict serum FGF21 make this protein an unlikely candidate as a predictive marker for T2D.

34.5 Withdrawn

34.6

BREAKING SITTING WITH LIGHT ACTIVITIES VERSUS STRUCTURED EXERCISE: BENEFITS FOR GLYCEMIC CONTROL AND INSULIN SENSITIVITY IN TYPE 2 DIABETES

Bernard M. F. M. Duvivier[1,2], Nicolaas C. Schaper[2], Matthijs K. C. Hesselink[1], Linh van Kan[1], Nathalie Stienen[2], Bjorn Winkens[3], Annemarie Koster[4], and Hans H. C. M. Savelberg[1]

[1]Human Biology and Movement Sci., Maastricht Univ. Med. Ctr., P. O. Box 616, Maastricht, Netherlands, [2]Int. Med., Div. Endocrinology, Maastricht Univ. Med. Ctr., P. O. Box 616, Maastricht, Netherlands, [3]Methodology and Statistics, Maastricht Univ. Med. Ctr., P. O. Box 616, Maastricht, Netherlands, [4]Social Med., Maastricht Univ. Med. Ctr., P. O. Box 616, Maastricht, Netherlands.

Objective: Mounting evidence suggests that sitting has adverse health effects. The purpose of this study was to examine the effects of breaking up sitting time with standing and light-intensity walking vs. an equicaloric bout of structured exercise on 24-h glucose levels and insulin sensitivity in adults with type 2 diabetes. **Methods:** In a randomized cross-over study, 19 adults with type 2 diabetes with a mean (±SD) age of 63 ± 9 years, BMI 30.5 ± 3.3 kg/m^2 and HbA1c 49.5 ± 8.8 mmol/mol were included. Each participant followed three activity regimes for four days in free-living conditions: 1) 'Sitting': sitting 14h/day; 2) 'Exercise': 1h/day of sitting replaced with moderate to vigorous cycling ; 3) 'Sit Less': 5h/day of sitting replaced with standing (3h) and light-intensity walking (2h). Meals were standardized; physical activity and glucose levels were assessed 24h/day by accelerometry and a glucose sensor respectively. Incremental area under the curve for 24-h glucose and the HOMA2-insulin resistance index (HOMA2-IR) were assessed. The study has been conducted in accordance with the principles of the Declaration of Helsinki. **Results:** Incremental area under the curve for 24-h glucose (mean ± SEM; min.mmol/L) during Sit Less was significantly lower compared to Sitting (546 ± 312 vs. 1573 ± 362); p=0.001) and was similar between Sit Less and Exercise (Exercise: 790 ± 255; p=0.415). Exercise failed to improve HOMA2-IR compared to Sitting (2.06 ± 0.28 vs. 2.16 ± 0.26; p=0.177), Sit Less (1.89 ± 0.26) significantly reduced HOMA2-IR, compared to Exercise (p=0.015) as well as Sitting (p=0.001). **Conclusions:** In adults with type 2 diabetes, breaking up sitting time with standing and light-intensity walking improved 24-h glucose levels effectively and reduced insulin resistance to an even greater extent than structured exercise. Thus, our results suggest that breaking up sitting time with standing and light-intensity walking may be an alternative to structured exercise to promote glycemic control in adults with type 2 diabetes. *Funding sources:* Novo Nordisk B.V., Medtronic and Roche.

34.7

INTRINSIC HIGH AEROBIC CAPACITY IS ASSOCIATED WITH PROTECTION OF MITOCHONDRIAL RESPIRATORY CAPACITY AND DECREASED INFLAMMATION FOLLOWING CHRONIC HIGH-FAT/HIGH-CHOLESTEROL DIET CHALLENGE

E. Matthew Morris[1], Colin McCoin[1], Lauren Koch[2], Steven Britton[2], and John Thyfault[1,3]

[1]Molecular & Integrative Physiology, Univ. of Kansas Med. Ctr., 3901 Rainbow Blvd., G011 Wahl Hall E., Mail Stop 3043, Kansas City, KS, 66160, [2]Anesthesiology, Univ. of Michigan, 1500 E. Medical Ctr. Dr., Ann Arbor, MI, 48109, [3]Res., Kansas City VA Med. Ctr., 4801 Linwood Blvd., Kansas City, KS, 64128.

We previously reported a novel model in which rats were artificially selected over several generations to produce high and low capacity runners (HCR and LCR) with contrasting intrinsic aerobic capacities. This divergent aerobic capacity produces increased hepatic fatty acid oxidation (FAO), maximal mitochondrial respiratory capacity, and decreased liver triacylglycerol (TAG) accumulation in the HCR compared to LCR rats. A body of evidence suggests that a western diet results in alterations in mitochondrial function facilitating increased oxidative stress, which can produce elevated expression of pro-inflammatory genes. Herein we examined the hypothesis that increased aerobic capacity associated with increased hepatic FAO/mitochondrial respiratory capacity of the HCR rat would protect against development of hepatic inflammation following a chronic high-fat/high-cholesterol diet challenge. HCR/LCR rats were fed open source low-fat diet (LFD, 10% kcal fat/3.5% kcal sucrose Research Diet) prior to initiation of a 45% kcal fat/1% cholesterol (gram)/17% kcal sucrose diet (Research Diet) for 16 weeks. Both HCR and LCR rats demonstrated increased weight gain following HFHC, with only the LCR having increased fat mass gain compared to LFD. Both strains were observed to have reduced hepatic complete FAO due to HFHC; however, HCR complete FAO was greater than LCR regardless of diet. The HFHC resulted in reduced state 3 hepatic mitochondrial respiration of glutamate and pyruvate in both strains, with LCR also having reduced state 3 respiration of palmitoyl-carnitine (L-PC). However, HCR was observed to have greater hepatic mitochondrial state 3 and uncoupled respiration of glutamate, pyruvate, and L-PC compared to LCR regardless of diet. The differences in state 3 mitochondrial respiration due to diet are inversely associated with increased mRNA expression of hepatic inflammation markers (MCP-1, TLR4, TLR2, IL-b, and F4/80). However, HCR rats on HFHC demonstrate significantly lower expression of these markers compared LCR. In conclusion, HCR rats are partially protected against chronic HFHC diet induced hepatic inflammation, which is associated with greater mitochondrial respiratory capacity compared to LCR.

34.8

EFFECT OF A NOVEL WORKSTATION DEVICE ON INCREASING METABOLIC RATE

Craig Horswill[1], Haley Scott[1], and Danel Voorhees[1]

[1]Kinesiology and Nutrition, Univ. of Illinois at Chicago, 337 PEB, 901 W. Roosevelt Rd., Chicago, IL, 60608.

Sedentary lifestyle is implicated in the development of chronic disease and early mortality. Occupations that require sitting at a desk for long periods contribute to the problem. Even subtle increases in the demand on skeletal muscle, e.g., standing at a desk, may be beneficial in elevating metabolic rate and reducing some risk factors for chronic disease. This study examined the

effect of three different types of a workstation: sitting, standing, and use of a device to promote leg movement while seated (Hovr'®) – on metabolic rate. Subjects (13 females, 3 male; age, 26.1 ±6.0 y; BMI, 24.7 ±4.3) performed for 15 min at three stages that represented each workstation. To minimize inter-day variability, the three stages were performed at one lab session in the following order: sitting only, sitting using the Hovr', and standing. To keep fine motor-skill activities consistent, subjects performed their choice of intellectual work and did the same type of desk work during all three stages of their measurements. After 5 min of working at a stage to establish a steady state, respiratory gases (VO_2 and VCO_2) and heart rate (HR) were measured for 10 min as the stage continued. To assure steady state values and consistency of the activity in each stage, only the final five min of data were averaged for data analyses. The Stroop word-color test was administered after VO_2 assessment (mouthpiece and nose clips removed) as the stage continued. One-way ANOVA with repeated measures was used to compare stages for VO_2 (L/min; primary outcome), METs, RER, and HR ($p<0.05$). The ANOVA was significant for each dependent variable ($p<0.05$). Post hoc tests indicated VO_2 differed for each stage (mean ±SD in L/min: sitting, 0.286 ±0.040; sitting with Hovr', 0.337 ±0.064; standing, 0.315 ±0.054; $p<0.05$). METs followed a similar pattern (sitting, 1.19 ±0.16; sitting with Hovr', 1.39 ±0.20; standing, 1.29 ±0.16; $p<0.05$). For RER and HR, mean values during standing differed from the other two stages ($p<0.05$). An increase in Stroop Test scores was found as the stages progressed ($p<0.05$). Modest movement while seated, i.e., use of Hovr', elevated metabolic rate by 17.6% compared to sitting and by 7% compared to standing. Funded in part by Active Ideas, LLC, Chicago, IL.

34.9

BRAIN SEROTONINERGIC SYSTEM HAS AN ESSENTIAL ROLE IN REGULATING PHYSICAL INACTIVITY IN RATS

Shinya Yanagita[1], Natsuko Kubota[1], Masakazu Umezawa[1], and Ken Takeda[1]

[1]Sci. and Technology, Tokyo Univ. of Sci., 2641 Yamazaki Noda, Chiba, 2788510, Japan.

Daily physical activity can influence various brain functions, and lead to some beneficial effects for our physical and mental health. It is also well known that amount of daily physical activity (i.e. exercise volume) is an important factor for regulating beneficial effects of exercise. On the other hands, numerous studies have shown that physical inactivity induce several harms for our health. Therefore, it is important to conduct the methods that enhances our daily physical activity in order to keep healthy life. Thus, we have tried to find the central regulator of voluntary physical activity using our original rat models. Because brain serotonergic systems have a crucial for various physiological functions, in the present study, we focused on the relationships between amount of daily spontaneous wheel running and brain serotonergic systems using c-DNA microarray and High performance liquid chromatography (HPLC) analysis in the rat models. Male Wistar rats housed in the cages with attached running wheel for 4 weeks to divide into high (HR) and low active runners (LR). Following a 4-week running session, we compared gene expression patterns in the hypothalamus between high and low runners using c-DNA microarray. Furthermore, the microarray results were validated by quantitative RT-PCR. The results of microarray analysis showed that 184 genes were differentially expressed between HR and LR. Annotation analysis using Gene Ontology revealed that the differentially expressed genes between HR and LR were enriched in "serotonin transporter" function. Slc6a4 was extracted as a candidate of regulatory gene to regulate the phenotype. However, a significant difference in Slc6a4 was not be able to be confirmed by quantitative RT-PCR using TaqMan probe, due to an irreducible minimum sample quantities. The results of HPLC analysis indicated that neurotransmitter levels of serotonin in LR were significantly higher than that in HR. Furthermore, serotonin precursor injections to high runners actually decreased their running distances in the dark phase. Our findings suggest that the function of serotonin transporters and serotonin levels have a crucial role in regulating physical activity levels, and regulation of brain serotonergic systems may be essential targets to resolve the problems related to physical inactivity.

34.10

SKELETAL MUSCLE AUTOPHAGY AND MITOPHAGY IN ENDURANCE-TRAINED RUNNERS, AND IN RESPONSE TO A HIGH-FAT MEAL

Michael D. Tarpey[1], Ryan P. McMillan[1], Suzanne Bowser[1], Tanya M. Halliday[1], Nabil E. Boutagy[1], Kevin P. Davy[1], Madlyn I. Frisard[1], and Matthew W. Hulver[1]

[1]Human Nutrition, Foods and Exercise, Virginia Tech, 1981 Kraft Dr., Blacksburg, VA, 24060.

We tested the hypothesis that skeletal muscle adaptations within endurance-trained male runners would promote autophagy and mitophagy, which would be associated with greater metabolic flexibility in response to a high-fat meal (HFM). Muscle biopsies were collected to determine differences in metabolic flexibility and protein markers of autophagy and mitophagy under fasting conditions and 4h post-HFM between groups of endurance-trained male runners (VO_{2max}: 65.8 ± 2.3 ml·kg·min^{-1}) and sedentary, healthy, non-obese controls (VO_{2max}: 43.1 ± 3.4 ml·kg·min^{-1}). Blood samples were taken each hour for 4h post-HFM. All study procedures were approved by the Virginia Polytechnic Institute and State University Institutional Review Board and all participants provided consent. Endurance-trained runners displayed significantly greater VO_{2max}, and significantly lower percent body fat and fasting plasma triglycerides compared to sedentary controls. No significant differences were found in fasting skeletal muscle metabolic flexibility between groups, although metabolic flexibility was significantly increased post-HFM in skeletal muscle of endurance-trained runners, but not sedentary controls. The plasma glucose AUC was significantly lower in endurance-trained runners following a HFM, implying a greater glucose tolerance. We found no significant differences within or between groups for skeletal muscle content of autophagy proteins LC3, p62, ULK1/pULK1^{Ser556}, FoxO3a/pFoxO3a^{Thr32}, Bcl-2 and Beclin-1, when fasted or following a HFM. Protein markers of mitophagy (pPink1^{Thr257} and pParkin^{Ser65}) and mitochondrial dynamics (pDrp1^{Ser616} and Mfn2) were significantly greater in skeletal muscle of en-

durance-trained runners compared to sedentary controls, but were unaffected by a HFM. Mitophagy and mitochondrial dynamics markers were positively correlated with each other, and with VO_{2max} and electron transport chain (ETC) protein content. No correlations existed between autophagy or mitophagy markers and metabolic flexibility or plasma glucose AUC. In conclusion, mitophagy activity may be enhanced in endurance-trained runners based on elevated markers of mitophagy and mitochondrial dynamics, which were associated with a greater VO_{2max} and ETC protein content. The absence of a relationship between metabolic flexibility and mitophagy markers may suggest that mitophagy is not a key determinant of metabolic flexibility in a healthy population, but further investigation is required. This research was funded by ADA-07-12 (MWH)

35.0 AGING

35.1 Withdrawn

35.2
EFFECTS OF ENDURANCE AND RESISTANCE EXERCISE ON BONE TURNOVER IN PRE-MENOPAUSAL WOMEN UNDERGOING OVARIAN HORMONE SUPPRESSION

Sarah Wherry[1], Pamela Wolfe[2], Ellie Gibbons[1], Rebecca Boxer[1], and Wendy Kohrt[1]
[1]Dept. of Med., Univ. of Colorado, Anschutz Med. Campus, 12631 E. 17th Ave., Rm. 8111, Mail Stop B179, Aurora, CO, 80045, [2]Preventive Med. and Biometrics, Univ. of Colorado, 2AMCA, Anschutz Administration, 13001 E. 17th Pl., Aurora, CO, 80045.

Declines in ovarian hormones during menopause accelerate bone loss, but epidemiological evidence suggests exercise may attenuate the loss. However, data are limited on bone turnover changes during exercise training in menopausal women. Because menopause occurs over time, factors other than ovarian hormones may influence bone metabolism. Gonadotropin releasing hormone agonist ($GnRH_{ag}$) isolates the suppression of ovarian hormones from other factors related to aging. Therefore, the purpose of this study was to investigate how exercise influenced markers of bone turnover in premenopausal women on $GnRH_{ag}$. **Methods:** Samples came from two $GnRH_{ag}$ studies in which participants were randomized to resistance (RT) or endurance training (ET). The RT protocol included 32 women (aged 21-49y) randomized to no-exercise control (RT-C, n=20) or RT (RT-E, n=12) for 5 months. The ET protocol included 15 women (aged 41-54y) randomized to no-exercise control (ET-C, n=7) or ET (ET-E, n=8) for 6 months. Blood was taken at baseline and the end of the intervention to measure markers of bone resorption (c-terminal collagen crosslinks; CTX) and formation (procollagen type 1 N-terminal propeptide; P1NP). Changes in CTX and P1NP (ΔCTX, ΔP1NP) within each study and differences in changes between studies were evaluated by t-tests. **Results:** When studies were pooled, exercisers had a non-significantly (p=0.06) greater ΔCTX (mean±SD, 0.41±0.23 ng/mL) than controls (0.30±0.39 ng/mL). Across modes of exercise, ET-E had a non-significantly (p=0.22) greater ΔCTX than RT-E (ET-E: 0.52±0.22 ng/mL; RT-E: 0.33±0.22 ng/mL). Pooled ΔP1NP was non-significantly (p=0.21) greater in exercisers (23.4±24.8 ng/mL) than controls (12.1±33.6 ng/mL). ΔP1NP was non-significantly (p=0.59) greater for ET-E than RT-E, (ET-E: 28.05±27.56 ng/mL; RT-E: 20.28±23.53 ng/mL). **Conclusion:** There were no significant effects of endurance or resistance training to alter the increase in bone turnover that occurs in response to ovarian hormone suppression. ΔCTX and ΔP1NP were greater in exercisers than controls, but were not significant. Trends for ΔCTX and ΔP1NP to be higher in ET than RT suggests that there could be differential effects on bone mineral density. Given the convenient samples, small sample size, and limited time points, future studies are needed to investigate the potential benefits of endurance vs resistance training to mitigate menopause-related bone loss. Funding: P50 HD073063, R01 AG018198, ULI TR001082.

35.3
ENDURANCE EXERCISE PROMOTES TELOMERE TRANSCRIPTION

Louise Deldicque[1], Aurélie Diman[2], Joanna Boros[2], Florian Poulain[2], Julie Rodriguez[1], Marin Purnelle[1], Harikleia Episkopou[2], Luc Bertrand[3], Marc Francaux[1], and Anabelle Decottignies[2]
[1]Inst. of Neuroscience, Univ. Catholique de Louvain, Place Pierre de Coubertin, 1, Box L08.10.01, Louvain-la-Neuve, 1348, Belgium, [2]de Duve Inst., Univ. Catholique de Louvain, Ave Hippocrate 75, Box B1.75.02, Woluwé-Saint-Lambert, 1200, Belgium, [3]Cardiovascular Res. Unit, Univ. Catholique de Louvain, Ave Hippocrate, 55, Box B1.55.05, Woluwé-Saint-Lambert, 1200, Belgium.

Persistent DNA breaks activate the DNA damage response and trigger cellular senescence. Telomeres are specialized nucleoprotein structures that protect chromosome ends from being recognized as broken DNA. Whether and how chromosome end protection can be enhanced to counteract the age-dependent decline in telomere integrity is a challenging question. Recently, Telomeric Repeat-containing RNA, TERRA, transcribed from subtelomeric promoters, emerged as important player in telomere integrity. How human telomere transcription is regulated is however still largely unknown. Here, we tested whether endurance exercise could regulate telomere integrity and TERRA expression. Ten healthy young volunteers (S1-S10) were submitted to a cycling endurance exercise of either low (50% VO_2 peak) or high (75% VO_2 peak) intensity and three muscle biopsies were taken according to a standardized protocol either before (B1), directly after (B2), or 2h30 after (B3) exercise. Blood lactate was measured immediately at the end of the exercise. Based on the lactate concentration at the end of exercise, the individual response was classified as low, medium or high. Fitting with post-exercise blood lactate levels, acetyl-coenzyme A carboxylase (ACC) phosphorylation was induced by, respectively, ~9-fold in B2 and B3 of S5 (high lactate), ~7 and 6-fold in B2 and B3 of S6 (medium lactate) and only ~4-fold in B2 of S12 (low lactate), returning to basal levels in B3. Similarly, nuclear translocation of peroxisome proliferator-activated receptor gamma coactivator 1ï ¡ (PGC-1α) was more prominent in S5 than in S12 biopsies but, in all cases, was already detected in B2. TERRA levels were up-regulated in 50 to 90% of B2 samples and in 80 to 100% of B3 samples, depending on the chromo-

some end tested. TERRA up-regulation in B3 reached an average of 1.9-fold in the high intensity exercise group (P<0,0001) and of about 1.3-fold in the low intensity group (P=0,0007). Plotting TERRA induction in B3 against post-exercise blood lactate concentration revealed a clear correlation that was highly significant for 16p TERRA (R^2=0.788, P=0,003). Together with our demonstration that telomeres from muscle biopsies are covered with TERRA, our results suggest that, while cycling cells naturally renew TERRA pools after S phase completion, exercise-induced telomere transcription may provide a general mechanism of TERRA renewal and telomere protection in non-dividing tissues. The data further support the idea that endurance exercise may protect against cellular ageing.

35.4

THE RELATIONSHIP BETWEEN COGNITIVE FUNCTION, HEART RATE VARIABILITY, INSULIN AND GHRELIN IN OLDER ADULTS: A PILOT STUDY

David Bellar[1], Ellen Glickman[2], and John Gunstad[3]
[1]Sch. of Kinesiology, Univ. of Louisiana at Lafayette, 225 Cajundome Blvd., Lafayette, LA, 70506, [2]Sch. of Hlth. Sci., Kent State Univ., Gym Annex 162, Kent, OH, 44243, [3]Dept. of Psychological Sci., Kent State Univ., Gym Annex 162, Kent, OH, 44243.

The objective of the present pilot investigation was to examine the relationship of heart rate variability, insulin, ghrelin and cognitive function in a sample of older adults. The participants in the present investigation were 13 older adults (3 male, 10 female, 74.2±9.8 yrs). After giving informed consent, a fasted blood sample was obtained via venipuncture and baseline heart rate variability (HRV) was determined. Following these assessments the participants filled out the Rapid Assessment of Physical Activity survey (RAPA), and Trail Making Test (TMT) part A and B were administered. At the conclusion of the study blood samples were analyzed for Insulin (INS) and Ghrelin (GHR). The data was analyzed via multiple regression analysis for the association between the cognitive tests (TMT A and B) and the RAPA aerobic score and strength scores, INS, GHR and the standard deviation of the baseline HRV. Regression analysis was controlled for Age and Body Mass Index (BMI). The regression model for TMT A was not significant (r^2=0.729, p=0.355). However, the model for TMT B was significant (r^2=0.957, p=0.014) with Age (β =1.09, p=0.004), BMI (β =-0.79, p=0.008), GHR (β = 0.851 p=0.002), INS (β = 0.488 p=0.038), and SD HRV (β = 0.763 p=0.008), all being significant predictors in the model. RAPA aerobic (β = -.0387 p=0.080) and RAPA strength (β = 0.059 p=0.776) measures failed to attain significance. It appears that HRV, INS and GHR are related to measures of cognitive function in a pilot sample of older adults. Based upon these pilot data, further work should be done in a larger cohort to evaluate the relationship between heart rate variability, hormones and cognitive function in older adults.

35.5

EFFECT OF LIFELONG EXERCISE-TRAINING ON MITOCHONDRIAL QUALITY CONTROL MECHANISMS IN AGED HUMAN MUSCLE

Jens Frey Halling[1], Henrik Møller[1], Peter Plomgaard[2,3], Birgitte Regenberg[1], and Henriette Pilegaard[1]
[1]Dept. of Biology, Univ. of Copenhagen, Universitetsparken 13, Copenhagen, 2100, Denmark, [2]Dept. of Clinical Biochemistry, Rigshospitalet, Blegdamsvej 9, Copenhagen, 2100, Denmark, [3]Ctr. for Physical Activity Res., Rigshospitalet, Univ. of Copenhagen, Ole Maaløes Vej 24, Copenhagen, 2200, Denmark.

Exercise training is known to promote healthy aging, in part through improving skeletal muscle mitochondrial oxidative capacity. Skeletal muscle mitochondria form dynamically regulated networks controlled by fission and fusion proteins. Mitochondrial fission proteins mediate the exclusion of damaged mitochondria for subsequent autophagic degradation (mitophagy) and mitochondrial fusion has been shown to be required for normal mitochondrial oxidative function as well as maintaining redox balance in skeletal muscle. Recent evidence suggests that lifelong exercise-training prevents mitochondrial fragmentation in mouse skeletal muscle by suppressing mitochondrial fission protein expression, which may be a mechanism to protect muscle function during aging. The aim of this study was to examine the effects of lifelong exercise-training on mitochondrial quality control mechanisms in aged human skeletal muscle. Therefore, healthy aged (60-65 years old) men who had either stayed sedentary or performed regular exercise their entire lives were recruited, and vastus lateralis biopsy samples were analyzed for markers of oxidative capacity, protein oxidation, antioxidant enzymes, auto-/mitophagy markers and mitochondrial fission/fusion proteins. Trained men tended to have ≈30% higher (p=0.053) citrate synthase activity and had 1.5-2-fold higher (p<0.05) content of OXPHOS complex I-IV than sedentary. Protein carbonyl content was ≈30% lower (p<0.05) in trained than sedentary, which correlated inversely with a ≈1.5-fold higher (p<0.05) content of antioxidant enzymes (Catalase and SOD2) in trained than sedentary. Markers of auto-/mitophagy, p-ULK1 ser317 (p<0.05) and BNIP3 (p=0.058) were 2-3-fold higher in trained than sedentary, while the marker of autophagosome content LC3II was similar. The contents of mitochondrial fusion proteins MFN1 (p=0.072) and MFN2 (p<0.05) were 2-2.5-fold higher in trained than sedentary, while mitochondrial fission protein content (FIS1 and DRP1) was similar. A mitochondrial fusion index (MFN2/DRP1) tended to be higher (p=0.061) in trained than sedentary. In conclusion, the present results suggest that the higher oxidative capacity observed in lifelong exercise-trained than sedentary men is associated with improved antioxidant capacity, higher content of markers of auto-/mitophagy and increased mitochondrial fusion protein expression all of which are potential mechanisms to protect muscle function during aging.

35.6

SESTRIN, A NOVEL TARGET IN THE MTOR PATHWAY THAT EXTENDS HEALTHSPAN AND MOBILITY

Alyson Sujkowski[1], Myungjin Kim[2], Boyoung Kim[2], Jun-Hee Lee[2], and Robert Wessells[1]
[1]Physiology, Wayne State Univ., 5275 Scott Hall, 540 E. Canfield St., Detroit, MI, 48221, [2]Molecular Int. Physiology, Univ.

of Michigan, 3358 BSRB 109 Zina Pitcher Pl., Ann Arbor, MI, 48109.

Modern lifestyle, often characterized by over-nutrition and lack of exercise, causes prolonged activation of mTOR complex 1 (mTORC1)/S6K and chronic suppression of mTORC2/AKT, which together promote age-related muscle pathologies including insulin resistance, fat accumulation, mitochondrial dysfunction and functional decline. Using *Drosophila* as a model organism, we recently found that Sestrin acts as an important regulator of both mTOR complexes, and that the absence of Sestrin brings about several age-associated pathologies including fat accumulation, mitochondrial dysfunction and skeletal/cardiac muscle degeneration. In diverse tissues including skeletal muscle, Sestrin strongly potentiates the activity of mTORC2/AKT signaling, while slightly downregulating mTORC1/S6K signaling. mTORC2/AKT signaling is essential for proper metabolic regulation, as well as for cell survival and growth, while chronic mTORC1/S6K activation can be detrimental to muscle metabolism and physiology. Sestrin dependent regulation of mTOR complexes is important for maintaining muscle health throughout life. We hypothesize that Sestrin can be a novel molecular target in the mTOR signaling network that can limit chronic mTORC1 activation and preserve mTORC2 activity in muscle, thereby promoting life- and healthspan. Transgenic induction of Sestrin in skeletal and cardiac muscle can prevent age-dependent loss of endurance and mobility. Importantly, endurance exercise induces Sestrin expression, while Sestrin deficiency nullifies the effects of long-term exercise in improving mobility and metabolism. These data suggest that Sestrins may mediate the beneficial effects of exercise in preserving muscle health. We reveal the beneficial effects of Sestrin in protection against aging and age-associated functional and structural degeneration of skeletal and cardiac muscle. We identify the Sestrin protein family as a potential therapeutic target for the prevention of age-associated mobility decline, ultimately enabling the development of innovative methods for preserving mobility and improving quality of life in later ages.

35.7

METABOLIC CHANGES UNDERPINNING AGING FLIGHT MUSCLES IN THE HAWK MOTH, *MANDUCA SEXTA*

Beate Wone[1], Elana R. Kaup[1], Jason M. Kinchen[2], and Bernard W. M. Wone[1]

[1]Biology, Univ. of South Dakota, 414 E. Clark St., CL 191, Vermillion, SD, 57069, [2]Academic & Government, Metabolon Inc., 800 Capitola Dr., Ste. 1, Durham, NC, 27713.

Aging muscle in vertebrates has parallels with aging muscle in insects. To better understand and characterize the metabolic basis of muscle aging, we conducted a time course metabolic profiling of middle-age to aged dorsolateral flight muscle in the hawk moth, *Manduca sexta*. These muscle samples were analyzed using non-biased, global metabolomics profiling technology based on UHLC/MS/MS^2 and GC/MS platforms. A total of 535 metabolites were characterized across diel time (daytime/nighttime) and from middle-age to aged. Significant metabolite changes were detected between male and female metabolic profiles, revealing both similarities and differences across diel time and ages. Interestingly, in females 43 metabolites have diel oscillations in their abundance levels and this rhythm, as well as their overall abundance is attenuated as they age. Males do not show diel oscillations in metabolite abundance levels regardless of age. Metabolite over representation analyses indicated a greater than 2-fold enrichment in the following metabolic pathways: methionine, glycerolipid; biotin; glutathione; alpha linolenic acid and linoleic acid; betaine; aspartate; and glutamate. Overall, our results provide an unprecedented view into the complex biochemical regulatory events coordinating senescence in muscle.

35.8

PROTEIN TRANSLATIONAL RESPONSES TO HEALTHSPAN-EXTENDING TREATMENTS IN SKELETAL MUSCLE

Christopher Wolff[1], Carol Wilusz[2], Alan Schenkel[2], Frederick Peelor[1], Benjamin Miller[1], and Karyn Hamilton[1]

[1]Hlth. and Exercise Sci., Colorado State Univ., 1582 Campus Delivery, Fort Collins, CO, 80523-1582, [2]Microbiology, Immunology, and Pathology, Colorado State Univ., 1682 Campus Delivery, Fort Collins, CO, 80523-1682.

During periods of energetic stress (e.g., during exercise), cellular resources are diverted away from energetically costly processes, such as protein translation, to maintain ATP homeostasis. Chronic activation of energetic stress signaling (activated AMPK and inhibited mTOR) by rapamycin treatment, metformin and rapamycin co-treatment, or caloric restriction increases lifespan and healthspan in mice. We have previously shown that while chronic rapamycin and caloric restriction decrease cytoplasmic and myofibrillar protein synthesis rates, mitochondrial protein synthesis rates are maintained. Furthermore, we have shown that skeletal muscle protein homeostasis (proteostasis) is increased in these and other long-lived murine models as assessed by a ratio of protein to DNA synthesis rates. The purpose of the current investigation was to assess, in cultured myotubes, global skeletal muscle protein translation as well as mitochondrial and cytoplasmic protein synthesis rates, and DNA synthesis rates to examine proteostatic mechanisms in response to healthspan extending treatments. Global protein translation was assessed by the sequencing-based ribosome profiling technique, while mitochondrial and cytoplasmic protein synthesis rates, and DNA synthesis rates were assessed using deuterium oxide enriched medium containing rapamycin (RAP; 5nM), metformin+rapamycin (MET+RAP; 2mM+5nM), DMSO (0.01%) or Control (CON). Preliminary ribosome profiling data revealed a reduced number of actively translating mRNAs following healthspan-extending treatments, indicating a global decrease in translation. Additionally, cytoplasmic and mitochondrial protein synthesis rates were decreased ($P<0.05$) following RAP and MET+RAP treatments compared to DMSO and CON. However, cytoplasmic proteostasis was increased ($P<0.05$) following RAP treatment compared to MET+RAP, DMSO, and CON. RAP treatment also increased ($P<0.05$) mitochondrial proteostasis 45±4% compared to CON, while MET+RAP and DMSO were not different from CON. These data suggest that the impact of energetic stress signaling on increased healthspan may by mediated, in part, through a decrease in cellular proliferation

in order to maintain protein turnover in existing cells. Research is ongoing to determine the selectively translated proteins following RAP treatment, as they may provide insight into the mechanisms responsible for proteostasis and healthspan extension. This project is supported by NIH R01-AG042569.

35.9

AGE-RELATED RESPONSES TO HINDLIMB UNLOADING AND RE-AMBULATION RESULT IN DIVERGENT SKELETAL MUSCLE MACROPHAGE POLARIZATION PATTERNS AS DETERMINED BY FLOW CYTOMETRY

Paul Reidy[1], Daniel Nelson[1], Alec Mckenzie[1], Catherine Lindsay[1], James Gardner[1], Alexandra Keefe[2], Gabrielle Kardon[2], Thomas Huffaker[3], Ryan O'Connell[3], and Micah Drummond[1,3]
[1]Physical Therapy, Univ. of Utah, Salt Lake City, UT, 84108, [2]Human Genetics, Univ. of Utah, Salt Lake City, UT, 84132, [3]Pathology, Univ. of Utah, Salt Lake City, UT, 84112.

The pro- (M1) and anti-inflammatory (M2) polarizations of macrophages mediate timely skeletal muscle regeneration. Since skeletal muscle regeneration following disuse is impaired with aging we sought to examine skeletal muscle resident immune cells (macrophages) after a period of hindlimb unloading and after re-ambulation in mice. For this experiment, old (25-26 month; n=16) and young (3-4 month; n=21) mice underwent 2 weeks of ambulation or hindlimb unloading (HU) or 2 weeks HU followed by 4d of re-ambulation (R4). We demonstrated that young and old mice experience a similar level of muscle atrophy in soleus muscle (~35%) following 2 weeks of HU while soleus muscle size in older mice was not recovered at R4. Single cell suspensions were generated from gastrocnemius muscle samples. Following antibody labeling, the samples were run on a BD FACSAria for detection of immune cells and cell populations were analyzed with FlowJo. After forward and side scatter exclusion of debris and doublets, DAPI was used to gate-out dead and the live cells, $CD45^+CD11b^+$ gate was used to quantify monocytes/macrophages as either $F4/80^+$ (all macrophages), $F4/80^+$,$Ly6c^-$ (mature anti-inflammatory macrophages) or $F4/80^{+/-}$,$Ly6c^+$ (pro-inflammatory monocytes/macrophages). Old mice had increased $F4/80^{+/-}$,$Ly6c^+$ cells after HU (p=0.056) compared to ambulatory controls and this response was higher than young mice (p<0.001). $F4/80^{+/-}$,$Ly6c^+$ cells were also higher in the old (vs young) at R4 (p<0.02). Additionally, old mice had less $CD45^+CD11b^+F4/80^+$ macrophages during HU compared to young (p<0.05). Next, we examined $MHCII^+$ (M1) and $CD206^+$ (M2) mature anti-inflammatory macrophage populations. Young mice increased $CD206^+$ cells following HU (p<0.001) and this response was greater than the old mice (p<0.01). In all conditions, the young had higher proportions of $MHCII^+$ mature macrophages compared to the old (p<0.003). Finally, in the young, MHC II^+ cells significantly decreased following HU (p<0.03) yet increased (p<0.04) at R4 compared to ambulatory controls. Together, these data indicate that older mice demonstrate less macrophage polarization plasticity following hindlimb unloading and re-ambulation compared to young mice, which may contribute to impaired muscle recovery with aging. *Funding was provided by NIH: R01AG050781 and* R56AG050781 *to M.D. and 5P30CA042014-24 and 1S10RR026802-01 to University of Utah Flow Cytometry Facility.*

35.10

PGC-1A AND P53 INTERACTION: THE IMPACT OF AGE AND LIFELONG EXERCISE TRAINING

Maja Munk Nielsen[1], Stine Ringholm[1], and Henriette Pilegaard[1]
[1]Biology, Univ. of Copenhagen, Universitetsparken 13, Copenhagen, 2100, Denmark.

Background: Aging is associated with loss of skeletal muscle mass and oxidative capacity. Previous studies have shown that exercise training can reduce age associated loss of skeletal muscle mass and maintain muscle function. The transcriptional coactivator peroxisome proliferator activated receptor-γ coactivetor (PGC)-1α, is known as a master regulator of mitochondrial biogenesis and has been suggested to mediate exercise training adaptations. Furthermore, recent studies encompass the tumor suppressor protein 53 (p53), as a regulator of metabolic processes in addition to the extensive role of p53 in regulating cell cycle arrest, senescence and apoptosis. Additionally, p53 has been suggested to mediate exercise training adaptations. Moreover, PGC-1α and p53 have been shown to interact during metabolic stress. However, the interplay between PGC-1α and p53 during aging with and without exercise training has not been resolved. **Aim:** Therefore the aim of the present study was to test the hypothesis that life-long exercise training prevents an age-associated decrease in PGC-1α and p53 mRNA in skeletal muscle in a PGC-1α dependent manner. **Methods:** Quadriceps muscles were obtained from young (3 months) and 15 month old whole body PGC-1α knockout (KO) mice and littermate wildtype (WT) control. The 15 month old mice were either exercise trained by wheel running from 3 months of age or remained untrained. In addition, skeletal muscle from young and 15 month old muscle specific PGC-1α overexpression (MCK) mice and littermate WT mice were obtained. **Results:** Quadriceps PGC-1α and p53 mRNA content was lower in 15 month old WT than in 3 month old WT mice and exercise training prevented these decreases. The p53 mRNA content was similar in young and 15 month old PGC-1α KO mice and p53 mRNA content was lower in young and higher in 15 month old untrained PGC-1α KO mice than corresponding WT mice. Quadriceps mouse double minute 2 homolog (MDM2) mRNA content was higher in untrained and exercise trained 15 month old PGC-1α KO mice than corresponding WT mice, but young mice were unaffected by genotype. Quadriceps PGC-1α mRNA was 12-60 fold higher in MCK than WT mice. PGC-1α mRNA content was 84% lower in untrained 15 month old, than young MCK mice. p53 mRNA content was lower in untrained 15 month old MCK than young MCK mice, while p53 mRNA content was unaffected by age in WT mice. Moreover p53 mRNA was unaffected by overexpression of PGC-1α. The MDM2 mRNA content was unaffected by age and genotype in the PGC-1α MCK strain. **Conclusion:** Lifelong exercise training prevented an age-associated decrease in skeletal muscle PGC-1α and p53 mRNA content. PGC-1α was required for the age effect and exercise training effect on p53 mRNA, while overexpression of PGC-1α did not prevent the decrease with aging. Taken together this sup-

ports a related regulation of PGC-1α and p53 in skeletal muscle with aging and lifelong exercise training.

35.11

THE AGING ATHLETE: DNA CONTENT IN SLOW- AND FAST-TWITCH SKELETAL MUSCLE FIBERS

Gwenaelle Begue[1], Ulrika Raue[1], Bozena Jemiolo[1], Kiril Minchev[1], Holmes Finch[1], Todd Trappe[1], and Scott Trappe[1]
[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave, Muncie, IN, 47306.

The purpose of this phase of the investigation was to evaluate the potential benefits of lifelong aerobic exercise on fiber-type specific (MHC I and IIa) DNA content. To accomplish this goal, we examined old lifelong exercisers (LLE; n=8 M, 74±4 y), old healthy individuals (OH; n=9 M, 75±2 y) and young exercising individuals (YE; n=8 M, 25±1 y). Single muscle fibers were separated from vastus lateralis muscle bundles (~5-6 mm length) under a light microscope. The fiber type (MHC) was determined using SDS-PAGE before fiber-type specific DNA extractions. Single muscle fiber size and length were used to normalize DNA content per fiber volume (fiber length x CSA), and fiber-type specific DNA content was assessed in approximately 64 pooled MHC I and 57 pooled MHC IIa muscle fibers per subject. In MHC I fibers, DNA content tended to be elevated (+31%, P=0.1) in OH (234±20 ng/mm^3) compared to YE (171±21 ng/mm^3), and this increase was prevented (P<0.05) with LLE (139±21 ng/mm^3). In MHC IIa fibers, DNA content was 35% higher (P<0.05) in OH (192±15 ng/mm^3) compared to YE (126±16 ng/mm^3), and this increase was attenuated in LLE (157±16 ng/mm^3) given the similarity (P>0.05) to OH and YE. In summary, these data show an increased DNA content in slow and fast muscle fibers with aging, which is completely (slow fibers) or partially (fast fibers) attenuated with lifelong aerobic exercise. Further research is warranted to investigate the relationship between muscle fiber DNA content and the impact on skeletal muscle health with aging and lifelong aerobic exercise. Sponsored by NIH grant R01 AG038576.

35.12

THE AGING ATHLETE: GENERAL HEALTH AND EXERCISE PROFILE

Adam Voss[1], Kevin Gries[1], Ulrika Raue[1], Bruce Graham[1], Lenny Kaminsky[1], Holmes Finch[1], Todd Trappe[1], and Scott Trappe[1]
[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave, Muncie, IN, 47306.

The purpose of this phase of the investigation was to evaluate the potential benefits of lifelong aerobic exercise on the general health profile. To accomplish this goal, we examined old lifelong exercisers (LLE; n=23 M, 74±1 y), old healthy individuals (OH; n=11 M, 75±1 y) and young exercising individuals (YE; n=10 M, 25±1 y). For this study, 420 old individuals were interviewed after responding to advertisements, and based on their exercise habits and overall health, 105 individuals (37 LLE and 68 OH) were invited to attend information sessions. The exercise history and general health profile of the subjects was extensively evaluated using a variety of measures including: anthropometric data, resting and exercising cardiovascular data, pedometer data, blood draws, a dual-energy x-ray absorptiometry (DXA) scan, and a medical and exercise history questionnaire. The two exercising cohorts, YE and LLE, were cyclists and/or runners and exhibited similar exercise routines of ~5 days/week of moderate to high intensity. The exercise routines resulted in a substantially greater activity status (after correcting for non-ambulatory exercise) in LLE (14,037±1,264 steps/day) and YE (14,605±1,225 steps/day) compared to OH (6,183±551 steps/day). As expected, YE demonstrated superior values to LLE and OH in nearly all general health measures. Evaluation of the older subjects showed that many aspects of the metabolic profile (HDL, triglycerides, %fat, BMI, waist circumference) were indicative of superior health status in LLE compared to OH (p<0.05), but OH did not exhibit any values suggestive of metabolic disease. On average, LLE (3±1) took one less prescription medication than OH (4±1), both of which were less than the national average of 5 for males over 65 y. In summary, the LLE and OH groups are both representative of successful aging, with lifelong aerobic exercise providing additional metabolic and health benefits. Sponsored by NIH grant R01 AG038576.

35.13

EFFECT OF AGE ON MUSCLE SYMPATHETIC NERVE TRAFFIC DURING DYNAMIC AND STATIC EXERCISE

Catherine Notarius[1], Philip Millar[2], Connor Doherty[2], Anthony Incognito[2], Nobuhiko Haruki[1], Emma O'Donnell[1], and John Floras[1]
[1]Cardiology, UHN and Mt. Sinai Hosp., Univ. of Toronto, 6ES 414, 200 Elizabeth St., Toronto, ON, M5G 2C4, Canada, [2]Human Hlth. and Nutritional Sci., Univ. of Guelph, Gordon St., Guelph, ON, N1G 2W1, Canada.

Resting muscle sympathetic nerve activity (MSNA) increases with age. The effect of aging on MSNA elicited by dynamic leg exercise is unknown. We compared contralateral fibular nerve MSNA during one-leg cycling in 18 young (22±1 years [mean±SE]) and 18 older (57±2 years) sex-matched healthy subjects whose peak oxygen uptake (VO2peak) was assessed on enrolment. We hypothesized that MSNA elicited by mild (0 load) and moderate (30-40% of peak work rate) cycling changed with age. Subjects cycled for 2 minutes each at both work rates and as an internal control performed 2 minutes each of static handgrip (HG) and post-HG ischemia (PHGI) to activate the muscle metaboreflex. Mean height, weight, resting heart rate (HR), systolic blood pressure (BP) and percent predicted VO2 peak did not differ between groups. Older subjects had higher resting diastolic BP (P=0.01) and MSNA burst frequency and incidence (P<0.001). There was no age effect on HR or MSNA responses during mild cycling (P>0.05). In contrast, during moderate cycling the mean change in HR was blunted (young: +19±2 vs. old: +15±2 bpm; interaction P=0.03) and MSNA burst incidence decreased more in the older group (-11±2 vs.-19 ± 2 bursts/100heartbeats; P=0.01). During PHGI after static exercise, HR remained slightly elevated in the older group (interaction P=0.02) whereas MSNA remained elevated in the young group (4.6±2 vs 9.5±2 during HG, P=0.1; old: 1.6±2 vs 10.8±1, P<0.001). An age-related impairment in the

sympatho-excitatory muscle metaboreflex may contribute to the greater inhibition of MSNA documented when older subjects perform moderate leg cycling. PJM is supported by a NSERC Discovery grant. JSF holds the Canada Research Chair in Integrative Cardiovascular Biology.

35.14

THE AGING ATHLETE: CIRCULATING INFLAMMATORY REGULATORS OF SKELETAL MUSCLE HEALTH

Ryan Perkins[1], Kaleen Lavin[1], Tim Burnett[1], Ulrika Raue[1], Todd Trappe[1], and Scott Trappe[1]
[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave, Muncie, IN, 47306.

The purpose of this phase of the investigation was to evaluate the potential benefits of lifelong aerobic exercise on circulating inflammatory factors known to influence skeletal muscle mass and health. To accomplish this goal, we examined old lifelong exercisers (LLE; n=21 M, 74±1 y), old healthy individuals (OH; n=10 M, 75±1 y), and young exercising individuals (YE; n=10 M, 25±1 y). Fasted, resting blood draws were obtained for measurements of serum C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α. Muscle size of the quadriceps was determined by MRI. Aging resulted in an elevation of IL-6 (YE: 0.9±0.1; OH: 3.8±1.0 pg/mL, $P<0.05$), and lifelong exercise attenuated this increase (LLE: 1.9±0.2 pg/mL, $P=0.057$ vs OH). Aging and lifelong exercise had no influence ($p>0.05$) on CRP (YE: 0.6±0.2, OH: 0.9±0.1, LLE: 0.8±0.1 mg/L) or TNF-α (YE: 1.7±0.2, OH: 1.5±0.3, LLE: 1.7±0.1 pg/mL). Higher quadriceps muscle size (YE>LLE>OH, $P<0.05$) corresponded with lower systemic IL-6 levels (YE<LLE<OH). In summary, these data show that some of the lifelong aerobic exercise benefits for skeletal muscle may be obtained through attenuation of the age-related increase in circulating inflammatory regulators (i.e., "inflammaging"). Further examination of the effects of aging and lifelong exercise on inflammatory pathways in skeletal muscle is warranted. Sponsored by NIH grant R01 AG038576.

35.15

THE AGING ATHLETE: SINGLE MUSCLE FIBER SIZE AND CONTRACTILE FUNCTION

Greg Grosicki[1], Kiril Minchev[1], Ulrika Raue[1], Holmes Finch[1], Todd Trappe[1], and Scott Trappe[1]
[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave, Muncie, IN, 47306.

The purpose of this phase of the investigation was to evaluate the potential benefits of lifelong aerobic exercise on single muscle fiber performance. To accomplish this goal, we examined old lifelong aerobic exercisers (LLE; n=21 M, 74±1 y), old healthy individuals (OH; n=11 M, 75±1 y) and young exercising individuals (YE; n=10 M, 25±1 y). Muscle biopsies were obtained from the vastus lateralis for the measurement of myosin heavy chain (MHC) I and IIa single muscle fiber size (cross-sectional area), strength (P_o), speed (V_o), power and normalized power (i.e. muscle quality). MHC I muscle fibers in LLE (7623±603 μm^2) were ~30% larger ($P<0.05$) than OH (5476±744 μm^2) and YE (5690±603 μm^2). LLE MHC I fibers were also were also stronger ($P<0.05$) and more powerful ($P<0.05$) compared to OH and YE. In contrast, MHC IIa fibers were ~20% larger ($P<0.05$) in YE (7681±612 μm^2) compared to LLE (6466±580 μm^2) and OH (6237±762 μm^2), with no difference among the older cohorts. The performance of the MHC IIa fibers was variable, with normalized power showing a hierarchical pattern (OH>LLE>YE, $P<0.05$) among OH (16.7±1.9 W/L), LLE (13.9±1.0 W/L) and YE (12.3±1.1 W/L). These data show that lifelong aerobic exercise appears to provide benefits for size and function of slow muscle fibers that are not apparent in the fast muscle fibers. Furthermore, lifelong aerobic exercise appears to attenuate the improved normalized power in fast muscle fibers that is typically observed with aging. Sponsored by NIH grant R01 AG038576.

35.16

THE AGING ATHLETE: CARDIOVASCULAR FITNESS WITH EXERCISE INTENSITY

Kevin Gries[1], Adam Voss[1], Brittany Overstreet[1], Bruce Graham[1], Lenny Kaminsky[1], Holmes Finch[1], Todd Trappe[1], Ulrika Raue[1], and Scott Trappe[1]
[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave, Muncie, IN, 47306.

The purpose of this phase of the investigation was to evaluate the potential benefits of lifelong aerobic exercise on cardiovascular fitness. To accomplish this goal, we examined whole body aerobic capacity in old lifelong exercisers (LLE; n=23 M, 74±1 y), old healthy individuals (OH; n=11 M, 75±1 y) and young exercising individuals (YE; n=11 M, 25±1 y). Each subject performed a graded maximal exercise test on a cycle ergometer to assess aerobic capacity (VO_2max) and related variables (see Table).

	VO_2max (L/min)	VO_2max (ml/kg/min)	HRmax (beats/min)	Max O_2 Pulse (ml O_2/beat)	V_Emax (L/min)	Peak Power (Watts)
YE	3.9±0.2*	52.9±2.5*	193±8*	20.4±0.9*	139±6*	332±11*
LLE	2.6±0.1*	33.2±1.1*	157±5	16.9±0.6*	100±3*	219±8*
OH	1.9±0.2	21.9±1.2	146±5	13.5±1.1	73±5	152±8

Values are mean±SE. *P<0.05 vs LLE and OH, #P<0.05 vs OH

Based upon exercise training intensity and engagement in competitive events, the LLE group was sub-divided into Elite (n=5, 73±2 y), Vigorous (n=9, 75±1 y), and Fitness (n=7, 75±1 y) categories. Both Elite (41.3±0.5 ml/kg/min) and Vigorous (35.3±2.2 ml/kg/min) had superior aerobic capacity compared to Fitness (27.2±1.6 ml/kg/min) ($P<0.05$), that may be due to a greater preservation of maximal heart rate (25% and 18% greater vs. Fitness, respectively) ($P<0.05$) as maximal oxygen pulse (a surrogate for maximal stroke volume) was not different among the LLE sub-groups. In summary, these data suggest maximal stroke volume is partially preserved with lifelong aerobic exercise, contributing to the attenuation of the age-related decline in aerobic capacity. Moreover, high-intensity lifelong aerobic exercise may expand upon this benefit by mitigating the age-related decline of maximal heart rate, thus further enhancing cardiovascular fitness with age. Sponsored by NIH grant R01 AG038576.

35.17

THE AGING ATHLETE: WHOLE MUSCLE SIZE AND FUNCTION

Tim Burnett[1], Ulrika Raue[1], Gary Lee[1], Holmes Finch[1], Todd Trappe[1], and Scott Trappe[1]

[1]Human Performance Lab, Ball State Univ., 2000 W. University Ave, Muncie, IN, 47306.

The purpose of this phase of the investigation was to evaluate the potential benefits of lifelong aerobic exercise on skeletal muscle size and function. To accomplish this goal, we examined old lifelong exercisers (LLE; n=23 M, 74±1 y), old healthy individuals (OH; n=11 M, 75±1 y), and young exercising individuals (YE; n=10 M, 25±1 y). Magnetic resonance imaging (MRI) was used to determine quadriceps muscle cross-sectional area (CSA). Intermuscular adipose tissue (IMAT) was determined from a single mid-thigh MRI slice. Quadriceps muscle function was comprehensively evaluated for: strength, knee extension 1-repetition maximum (1RM); speed, knee extension velocity (Vmax); force, 90° knee angle maximal isometric voluntary contraction (MVC); and power. Quadriceps CSA showed a hierarchical pattern (YE>LLE>OH, $P<0.05$) among YE (7793±896 mm^2), LLE (6717±735 mm^2) and OH (5484±803 mm^2). Similarly, thigh IMAT showed a hierarchical pattern (YE<LLE<OH, $P<0.05$) among YE (5.0±1.6%), LLE (8.3±2.4%) and OH (10.7±2.6%). Knee extensor muscle function was greater ($P<0.05$) for all variables in YE compared to LLE and OH. MVC was 16% greater ($P<0.05$) in LLE (487±75 N) compared to OH (389±76 N). These data suggest that lifelong aerobic exercise enhances thigh muscle size, decreases thigh IMAT and has some functional benefit. These findings highlight the potent therapeutic potential of lifelong aerobic exercise for skeletal muscle health. Sponsored by NIH grant R01 AG038576.

35.18

MITOCHONDRIAL PROTEINS IN HUMAN SKELETAL MUSCLE: THE EFFECT OF AGING AND 12 WEEKS HIGH-INTENSITY INTERVAL TRAINING IN AGED INDIVIDUALS

Victoria Wyckelsma[1,2], Luke Formosa[3], Michael Ryan[3], Itamar Levinger[1], Michael McKenna[1], and Robyn Murphy[2]

[1]Inst. of Sport, Exercise and Active Living (ISEAL), Victoria Univ., PO BOX 14428, Melbourne, 3003, Australia, [2]Dept. of Biochemistry and Genetics, La Trobe Inst. for Molecular Sci., La Trobe Univ., Kingsbury Dr., Bundoora, 3083, Australia, [3]Dept. of Biochemistry, Monash Univ., 10 Ancora Imparo Way, Monash Univ., Melbourne, 3800, Australia.

Aging is a natural process of life. Inevitable, serious consequences of aging include progressive loss of skeletal muscle mass and function, known as sarcopenia. Sarcopenia leads to increased falls, loss of independent living and quality of life, as well as a propensity for metabolic disease. Skeletal muscle is a metabolically active tissue comprising 40% of the body's total mass. Mitochondria are important in skeletal muscle as the major site of energy production and healthy mitochondria are crucial to overall muscle health. We aimed to explore whether skeletal muscle mitochondria respond to exercise training in old individuals, in a similar, positive manner to which they are known to respond in young individuals. In this study, we examined skeletal muscle biopsy samples obtained from healthy old (69 ± 3 yrs, n=8) and young (18-30 yrs, n=8) individuals, with similar physical activity levels. We found that the mitochondrial markers cytochrome oxidase IV (COXIV) and NDUFA9 are unchanged when measured in whole muscle preparations from young and old individuals, however analyses of mitofusin 2 (Mfn2) and the mitochondrial dynamics protein 49 (MiD49) revealed 1.5-2.5-fold increases in these proteins, respectively. We also examined the older cohort of individuals before and after 12 weeks of high-intensity interval training (HIIT, 4x4 min at ~95% peak heart rate, 3x/week for 12 wks). The training protocol increased aerobic capacity (16%) and work rates (25%). There were increases in the abundance of mitochondrial respiratory chain subunits COXIV (37%) and NDUFA9 (48%), and whilst smaller, a still significant increase in MiD49 (12%) but not Mfn2. Analysis of mitochondrial proteins using Blue Native PAGE revealed increases in Complexes 1-2, 4-5 following exercise training. We hypothesise that the upregulation of Mfn2 and MiD49 in skeletal muscle from aged compared with young individuals is an attempt to compensate for the loss of mitochondrial function that inevitably occurs with aging. The upregulation of mitochondrial proteins in response to exercise training in older individuals suggests a robust, adaptable cellular system in skeletal muscle of the elderly.

35.19

RESISTANCE TRAINING PREVENTS AGING-INDUCED MUSCLE FIBROSIS IN MICE

Naoki Horii[1], Shumpei Fujie[1,2], Natsuki Hasegawa[1,2], Masataka Uchida[1], Takeshi Hashimoto[1], Eri Oyanagi[3], Hiromi Yano[4], and Motoyuki Iemitsu[1]

[1]Fac. of Sport and Hlth. Sci., Ritsumeikan Univ., 1-1-1, Nojihigashi, Kusatsu, 525-8577, Japan, [2]DC, Res. Fellow of Japan Soc. for the Promotion of Sci., 5-3-1, Kojimachi, Chiyoda, Tokyo, Japan, [3]Dept. of Hlth. Promotion and Exercise, Natl. Inst. of Hlth. and Nutrition, 1-23-1, Toyama, Shinjuku-ku, Tokyo, Japan, [4]Dept. of Hlth. and Sports Sci., Kawasaki Univ. of Med. Welfare, 288, Matsushima, Kurashikishi, Okayama, Japan.

Aging is accompanied by a progressive decline of muscle mass, quality and strength. In recent studies, the loss of muscle mass with aging is associated with the replacement of muscle fiber mass by fibrous connective tissue and adipose tissue. Resistance training increases muscle mass and muscle strength in elderly people. However, it is still unclear whether resistance training prevents aging-induced muscle fibrosis. Purpose: The purpose of this study was to investigate whether resistance training prevents aging-induced muscle fibrosis in mice. Methods: Male 13-week-old SAMP1 mice (Young) and 38-week-old SAMP1 mice (Aged) were randomly divided into two groups per each age group; sedentary control young (Young-Con) and resistance training young (Young-RT) groups and sedentary control aged (Aged-Con) and resistance training aged (Aged-RT) groups (n=7 each group). Resistance training was performed 3 days a week on alternate days for 12 weeks using a climbing ladder inclined at 80° with tail weight. Cross-sectional area (CSA) and muscle fibrosis area in tibialis anterior muscle were measured by masson trichrome stain. Evaluation of muscle strength is defined

as the maximal amount of tail weight, which can perform a single climbing ladder. Results: Aged-Con mice had significantly lower muscle mass and CSA in the tibialis anterior muscle and muscle strength than those in Young-Con mice ($p<0.05$). However, the resistance trained-aged and young groups showed significantly increased muscle mass, CSA, and muscle strength compared with Aged-Con and Young-Con groups respectively ($p<0.05$). Aged-Con mice showed a higher muscle fibrosis area compared with Young-Con mice ($p<0.05$), whereas Aged-RT mice exhibited a reduction of muscle fibrosis area compared with Aged-Con mice ($p<0.05$). Furthermore, muscle strength was negatively correlated with muscle fibrosis area ($r = -0.741$, $p<0.05$) and positively correlated with CSA in the tibialis anterior muscle ($r = 0.794$, $p<0.05$). Conclusions: These results suggest that resistance training may prevent aging-induced muscle fibrosis with muscle loss, leading to the increase in muscle strength in mice.

35.20

EFFECT OF RESISTANCE EXERCISE TRAINING ON AMINO ACID SENSING AND ANABOLIC RESISTANCE IN OLDER ADULTS

Tatiana Moro[1,2], Rachel R. Deer[2], Theodore G. Graber[1], Elena Volpi[1,2], and Blake B. Rasmussen[1]

[1]Dept. of Nutrition and Metabolism, UTMB, 301 University Blvd., Galveston, TX, 77555, [2]Sealy Ctr. on Aging, UTMB, 301 University Blvd, Galveston, TX, 77555-1124.

Aim: Anabolic resistance is the reduced capacity of skeletal muscle to increase protein synthesis rates in response to appropriate anabolic stimuli such as exercise and nutrient intake. This condition could explain the physiological decline of structural and functional characteristics in skeletal muscle that occurs with aging. However, the molecular mechanisms underlying anabolic resistance are unknown. Acute bouts of physical activity can improve the ability of amino acids to stimulate mTORC1 signaling, which is the primary contributor to muscle protein synthesis, in older adults. It is not known whether chronic exercise training will reverse anabolic resistance. Therefore, the aim of this study was to determine if resistance exercise training in older adults improves mTORC1 signaling, restores amino acid sensing, and reverses anabolic resistance. **Methods**: To test our hypothesis 20 healthy older adults (65-80 years old) were trained for 12 weeks (3 days per week) with a progressive resistance exercise training program. Pre and post-training measurements of muscle mass, strength, and metabolic health (i.e., lipid profile, insulin sensitivity/OGTT) were obtained. Pre and post study days also included a stable isotope infusion trial wherein subjects ingested an essential amino acids (EAA) mixture and skeletal muscle biopsies were taken at rest, 1 hr and 3 hr after EAA ingestion. Muscle biopsies were used to measure markers of amino acid sensing (e.g., mTORC1 activation) via immunoblotting and to assess protein synthesis. **Results**: We report preliminary data as all subjects have not completed the training protocol. Final data will be presented during the IBE meeting. RT increased muscle mass and strength and improved metabolic parameters such as the lipid profile (e.g., TC, LDL, HDL, VLDL) and insulin sensitivity (e.g., OGTT). RT enhanced mTORC1 activation as indicated by a post-training increase in the phosphorylation status of Akt, 4E-BP1, p70S6K, and rpS6 in response to EAA. **Conclusion**: Our preliminary data suggest that resistance exercise training can improve amino sensing in skeletal muscle and may be an effective therapeutic strategy to overcome anabolic resistance in older adults. This work was supported by NIH R56 AG051267.

35.21

DYSREGULATION OF CIRCULATING MICRO RNA EXPRESSION AFTER RESISTANCE EXERCISE IN OLDER MEN ASSOCIATED WITH ANABOLIC RESISTANCE

Donato Rivas[1], Lee Margolis[1], Sarah Lessard[2], Yassine Ezzyat[1], and Roger Fielding[1]

[1]Nutrition, Exercise Physiology and Sarcopenia Lab., Tufts Univ., 711 Washington St., Rm. 1302, Boston, MA, 02111, [2]Clinical Res., Joslin Diabetes Ctr., 1 Joslin Place, Boston, MA, 02215.

The plasticity and adaptability of skeletal muscle to anabolic stimuli such as resistance-exercise (RE) is a fundamental physiological event leading to larger and more robust skeletal muscle. However, muscle growth in response to RE, like other anabolic stimuli, is attenuated in older adults. The inability of aged skeletal muscle to adapt to RE may be a crucial factor that contributes to sarcopenia (the loss of skeletal muscle mass and function with aging). The physiological responses to RE have largely been characterized by observational clinical outcomes and/or highly invasive molecular analyses using muscle biopsies to determine factors underlying muscle adaptation. Recent work has revealed a novel role for circulating small non-coding RNAs, called microRNAs (miRNA) as predictive biomarkers for multiple diseases such as, muscular dystrophy, COPD, cancer and cardiovascular disease. However, the utility of using changes in the expression of circulating miRNA (c-miR) as a predictive tool to determine skeletal muscle adaptations to an anabolic event is not known. Following RE, principal component analysis revealed a divergent response in expression of 10 c-miR, where expression profiles were upregulated in younger and downregulated in older participants. Using Ingenuity Pathway Analysis to test c-miR-to-mRNA interactions in skeletal muscle, it was found that response of c-miR to exercise was indicative of an anabolic response in younger but not older participants. This finding was corroborated with a positive association observed with the phosphorylation status of Akt and S6K1 and expression of miR-19a-3p, miR-19b-3p, miR-20a-5p, miR-26b-5p, miR-143-3p, and miR-195-5p. These important findings provide compelling evidence that dysregulation of c-miR expression after RE with aging may reflect underlying molecular mechanisms resulting in age-associated declines in skeletal muscle mass and 'anabolic resistance'.

35.22

MITOPHAGY FLUX WITH AGING AND CHRONIC EXERCISE IN SKELETAL MUSCLE

Heather Carter[1,2], Dorrin Zarrin-khat[1], Yuho Kim[1], Avi Erlich[1], and David Hood[1]

[1]Sch. of Kinesiology and Hlth. Sci., York Univ., 4700 Keele St., Toronto, ON, M3J1P3, Canada, [2]Muscle Hlth. Res. Ctr., York Univ., 4700 Keele St., Toronto, ON, M3J 1P3, Canada.

The molecular mechanisms that govern mitochondrial turnover during aging and exercise remain incompletely described. Vital to maintaining a healthy population of organelles in muscle is the balance between synthesis (biogenesis) and degradation (mitophagy). While acute exercise is known to stimulate signaling toward biogenesis as well as mitophagy, little is known regarding the effect of chronic exercise on mitophagic flux, or how aging may impact this process. Thus, we examined autophagic and mitophagic flux in tibialis anterior muscle basally, as well as following adaptation to unilateral chronic contractile activity (CCA; 9 days; 3hrs/day) in both 6 month and 35 month old FBN344F1 hybrid rats. During the last three days of CCA, colchicine (0.4mg/kg/day) or saline was administered to measure autophagic flux. In young muscle, CCA resulted in a 1.7-fold increase in COX activity, an estimate of mitochondrial content, while aged animals exhibited a modest 1.3-fold increase. Basally, aged muscle showed an ~20% lower mitochondrial content, as well as a 44% decrease in State III respiration. CCA increased respiration by 25% and 32% in young and aged muscle, respectively. To evaluate mitophagic flux, SS and IMF mitochondria were isolated and analyzed for LC3-II and p62 localization. Flux was calculated as the difference in LC3-II and p62 between colchicine and vehicle-treated animals. Basally, mitophagy flux was higher in SS and IMF mitochondria from aged, compared to young muscle. With CCA, SS mitochondria exhibited reduced LC3-II and p62 flux in both age cohorts, albeit to a lesser degree in the aged. However, IMF mitochondrial flux remained unaffected by CCA in both young and aged muscle. Examination of whole muscle LC3-II and p62 as markers of autophagic flux revealed reduced turnover of LC3-II with CCA in both age groups. However, p62 flux was elevated with age and remained unchanged following CCA in both young and old muscle. Collectively, these data reveal that the reduced mitochondrial content observed in aged muscle may be, in part, due to the high levels of mitophagic flux. With chronic exercise, young muscle adapts readily to increase mitochondrial mass, which ultimately reduces the drive for mitophagic flux in the more labile SS mitochondrial pool. Interestingly, aged muscle does not enhance mitochondrial mass to the same degree as young muscle, and this may be due to the continued elevation in mitophagy that remains following chronic exercise.

36.0 BRAINS, BLOOD VESSELS, AND HEARTS: CAN EXERCISE TREAT THE MOLECULAR MECHANISMS UNDERLYING CARDIOVASCULAR DISEASE?

36.1
UTILIZING EXERCISE TO TREAT THE CARDIOMYOCYTE

Tim Domeier[1]
[1]Med. Pharmacology and Physiology, Univ. of Missouri, 1 Hospital Dr., M472 Med. Sci. Bldg., Columbia, MO, 65212.

Half of all heart failure patients are diagnosed with heart failure with preserved ejection fraction (HFpEF). While exercise training has been shown to improve cardiac function and clinical outcomes in heart failure with reduced ejection fraction (HFrEF), the effects of exercise in the setting of HFpEF are less clear. The goal of this research was to examine the effects of chronic exercise training on cardiomyocyte function in aortic-banded (AB) mini-swine displaying cardiac hypertrophy and functional characteristics of HFpEF. Intracellular calcium homeostasis (fura-2) and contractile function (sarcomere shortening) were assessed in myocytes isolated from the left ventricle of three groups of miniature swine: sedentary control (CON), sedentary aortic-banded (AB), and low-intensity moderate continuous exercise trained aortic-banded (AB-ET; treadmill walking, 3 days/wk, 2.5 mph for 45 min). Action-potential induced calcium transient amplitude and associated myocyte shortening were reduced in AB versus CON ($P<0.05$), consistent with impaired myocyte function. Exercise training partially restored calcium transient amplitude in the setting of AB ($P<0.05$, AB-ET vs. AB), although myocyte shortening was not improved. Following treatment with the beta-adrenergic agonist dobutamine (1 uM), myocytes from AB animals exhibited a prolonged time to maximum inotropic response that was restored with exercise training ($P<0.05$, AB vs. CON and AB-ET). Further, in the presence of dobutamine calcium transient and shortening amplitude were reduced in the AB group ($P<0.05$ vs. CON) and restored with exercise training ($P<0.05$, AB-ET vs. AB). Biochemical examination of calcium handling proteins revealed complex expression changes, including a decrease in the L-type calcium channel in AB and AB-ET ($P<0.05$ vs. CON), an increase in the Ryanodine Receptor in AB and AB-ET ($P<0.05$ vs. CON), a decrease in phosphorylation of threonine-17 on Phospholamban (PLB) in AB and AB-ET ($P<0.05$ vs. CON), a decrease in phosphorylation of serine-16 of PLB in AB ($P<0.05$ vs. CON and AB-ET), and an increase in Sodium-Calcium exchanger in AB-ET ($P<0.05$ vs. CON and AB). Expression of the Sarco/endoplasmic reticulum calcium ATPase and PLB were unchanged among all groups. In conclusion, exercise training improves cardiomyocyte calcium handling and contractile function in a large animal model of pressure-overload heart failure, largely due to increased responsiveness following beta-adrenergic stimulation.

36.3
EXERCISE AND STEM CELLS IN THE HEART

Joseph Libonati[1]
[1]Sch. of Nursing, Univ. of Pennsylvania, Fagin Hall, 418 Curie Blvd., Philadelphia, PA, 19104.

Studies have shown that the heart contains a population of progenitor cells that can form new cardiac tissue, albeit at very low rates. Thus, while most cardiac myocytes in the adult heart are terminally differentiated, some new cardiac myocytes and endothelial cells can be formed from endogenous sources. It is well accepted that stem cells initiate growth factor paracrine signaling to host myocardium, and it is feasible that stem cell paracrine signaling is altered by exercise, which in its own right, activates insulin-like growth factor signaling and is seminal in the development of physiologic-induced cardiac hypertrophy. Aerobic exercise training may alter this dynamic, as training has been reported to increase the myocardial abundance of endogenous stem cells ($c\text{-}kit^{+}$ cells), increase the rate of cardiac myocyte proliferation, and attenuate cardiomyocyte death. Moreover, several studies have shown that aerobic exercise stimulates the mo-

bilization and circulation of endogenous progenitors. Our recent work has shown that treadmill exercise can increase the retention of exogenous stem cells while also increasing myocardial proliferative activity post-MI (1). Our findings are similar to another study showing that swimming improved left ventricular ejection fraction and provided a more favorable post MI remodeling profile compared to sedentary animals following bone marrow mononuclear cell transplantation (2). Thus the idea of using exercise as a vector to improve cell therapy may be a novel, safe, inexpensive, and necessary clinical adjuvant. (NIH 1R21HL11377). References: 1) Chirico E, Ding D, Muthukumaran G, Houser SR, Starosta T, Mu A, Margulies KB, Libonati JR (2015). Acute aerobic exercise increases exogenously infused bone marrow cell retention in the heart. Physiol Rep. doi: 10.14814/phy2.12566. PMID: 26486160; 2) Cosmo S., Francisco J. C., Cunha R. C., Macedo R. M., Faria-Neto J. R., Simeoni R., Carvalho K. A., Olandoski M., Miyague N. I., Amaral V. F., Guarita-Souza L. C. (2012). Effect of exercise associated with stem cell transplantation on ventricular function in rats after acute myocardial infarction. Rev Bras Cir Cardiovasc. Dec;27(4):542-51.

36.4
CONNECTING THE BRAIN TO THE HEART: CARDIOGENIC DEMENTIA AND EXERCISE THERAPY

T. Dylan Olver[1]
[1]Biomedical Sci., Univ. of Missouri, 1600 E. Rollins, Columbia, MO, 65211.

Among patients with heart failure and preserved ejection fraction (HFpEF), cognitive decline is associated with increased hospitalization, the loss of independence and increased risk of mortality.[1,2] Deficient cerebral blood flow may contribute to this phenomenon, however, this has not been studied rigorously in HFpEF patients possibly because cardiac output and ejection fraction (EF%) are maintained at rest. Swine represent a gold standard regarding translational relevance for human cardiovascular[3] and cognitive function,[4] as both the pig heart and brain share similar anatomical, biochemical, and functional similarities with humans. In a novel, translational cardiac pressure-overload (aortic-banding; AB) swine model reminiscent of human HFpEF, cerebral perfusion, autoregulation and cognition are impaired. Despite similar cardiac output and a higher perfusion pressure, resting carotid artery blood flow is reduced by ~25% in AB pigs and decreases in perfusion are accompanied by an inability to maintain cranial blood flow during experimental reductions in blood pressure (i.e. rightward shift in the autoregulation curve). Carotid artery vascular stiffness is also increased in AB pigs. Both cranial hypoperfusion and carotid arterial stiffening appear to mediate the relationship between AB and accelerated cognitive decline. Extending on these observations, cranial hypoperfusion, altered blood flow control, carotid artery vascular stiffening and cognitive impairment can be treated effectively with a low-intensity exercise intervention, highlighting the efficacy of exercise therapy for treating cardiogenic dementia in an experimental setting of HFpEF. These findings: 1) reveal cardiogenic dementia is associated with peripheral vascular dysfunction independent of resting cardiac systolic dysfunction (i.e. preserved EF%); and 2) support the use of carotid artery stiffness as a biomarker and/or risk factor for vascular cognitive dysfunction in HFpEF that can be treated effectively with a low-intensity exercise intervention. (NIH RO1HL112998, CAE). 1) Hajduk AM, et al. Circulation. 2013;6(4):451–60. 2) VanDen Hurk K, et al. European Journal of Heart Failure. 2011;13(12):1362–1369. 3) Dixon JA, Spinale FG. Circulation: Heart Failure. 2009;2(3):262–271.4) Kornum BR, Knudsen GM. Neurosci and biobehav rev. 2011;35(3):437–51.

37.0 EXERCISE AND AGING: RESPONSIVENESS OF SKELETAL MUSCLE TO EXERCISE TRAINING AS A FUNCTION OF AGE

37.1
IMPACT OF VOLUNTARY EXERCISE ON FRAILTY IN OLD MICE

LaDora V. Thompson, PhD,Haiming Liu, PhD and Ted G. Graber, PhD
Univ. of Minnesota Med. Sch., Minneapolis, MN 55455.

Background: Frailty is a clinical syndrome associated with declining muscle strength and reduced metabolic quality that leads to increased morbidity and disability. We previously developed a frailty index (FI) based on four clinically relevant criteria: grip strength, walking speed, endurance score and physical activity to identify frail mice and a Frailty Intervention Assessment Value (FIAV) to test the efficacy of interventions. Effective exercise interventions to reverse frailty and the cellular pathways involved have not been fully elucidated. Therefore, the aim of this study was to investigate the effect of aerobic exercise on frailty in mice at the physical and cellular levels. We hypothesized that 4-weeks of aerobic exercise (voluntary wheel running) would be able to prevent and/or reverse frailty, improve physical measures (FI and FIAV), improve muscle contractility (force, power), increase metabolic quality (PGC-1α content, a biomarker for mitochondrial biogenesis), and increase activation of the Akt pathway (Akt phosphorylation). **Methods:** Adult and old mice (6 and 28+ months, respectively) were housed individually in cages with running wheels for 4 weeks. Control mice were housed without wheels. Each mouse was tested on the four frailty criteria before and after the 4-week exercise period. The soleus and EDL muscles of each mouse were tested for contractility, the total PGC-1α, Akt, p-Akt (Thr308), and p-Akt (Ser473) in hindlimb muscles was determined after the 4-week exercise period. **Results:** We found old mice deemed frail by FI were rescued by the aerobic exercise intervention. The adult mice demonstrated a far greater positive response to the exercise, though both age groups benefited significantly. Overall, aerobic exercise was able to produce improvements in muscle contractility. Exercise induced more relative PGC-1α content ($p=0.016$). In addition, the adult exercise group exhibited higher p-Akt (Thr308 and Ser473) relative protein content compared to the control mice ($p<0.05$), though no difference in Akt phosphorylation was found after exercise in the old group. **Conclusion:** Collectively, we conclude that the aerobic exercise reversed frailty and improved functional parameters. Although only of short-term duration, the intervention served as a positive

exercise stimulus to activate the Akt anabolic pathway and initiate improved oxidative metabolism.

37.2

NOVEL ROLES FOR SATELLITE CELLS IN MUSCLE HYPERTROPHY AND AGING

Charlotte Peterson[1], Christopher Fry[2], Tyler Kirby[3], and John McCarthy[3]

[1]Coll. of Hlth. Sci., Univ. of Kentucky, 900 S. Limestone, CTW105, Lexington, KY, 40536, [2]Sch. of Hlth. Professions, Univ. of Texas Galveston, 301 University Blvd., Galveston, TX, 77555, [3]Dept. of Physiology, Univ. of Kentucky, 900 S. Limestone, Lexington, KY, 40536.

Satellite cells are the primary stem cell in skeletal muscle, required for postnatal muscle growth and adult muscle regeneration. Satellite cells are activated to proliferate and normally contribute nuclei to growing myofibers in response to hypertrophic stimuli, although considerable growth can occur in the absence of myonuclear accretion through the expansion of the myonuclear domain. We utilized the discrete expression of Pax7 in satellite cells to develop the Pax7-DTA mouse, whereby the use of *Cre*-lox technology allows for the specific and inducible depletion of satellite cells following tamoxifen-induced expression of diphtheria toxin. Depleting satellite cells in adult sedentary mice neither accelerated nor exacerbated sarcopenia. Synergist ablation surgery, where removal of synergist muscles places mechanical overload on the plantaris, was used to stimulate robust hypertrophy. Depletion of satellite cells in the adult mouse prior to mechanical overload of muscle resulted in extracellular matrix (ECM) dysregulation and muscle fibrosis. In aged mice, growth of the plantaris in response to mechanical overload was severely blunted, regardless of satellite cell content. We characterized interactions of activated satellite cells and their daughter cells, myogenic progenitor cells (MPCs), with muscle fibroblasts, which are responsible for the majority of ECM accumulation in muscle. We found that MPC-derived exosomes are capable of down-regulating fibroblast collagen expression. Interfering with microRNA processing, resulting in loss of microRNAs in MPC exosomes, reduced their ability to downregulate fibroblast ECM gene expression. These findings provide the first evidence for a new role for satellite cells in the regulation of fibroblast ECM production and suggest MPCs are actively involved in the remodeling of the skeletal muscle extracellular environment during muscle hypertrophy. Support: AR060701 and AG049806. References: Fry et al. (2014) Regulation of the muscle fiber microenviroment by activated satellite cells during hypertrophy. FASEB J 28, 1654-1665; Fry et al. (2015) Inducible depletion of satellite cells in adult, sedentary mice impairs muscle regenerative capacity without affecting sarcopenia. Nature Med 21, 76-80; Lee et al. (2016) Aged muscle demonstrates fiber type adaptations in response to mechanical overload, in the absence of myofiber hypertrophy, independent of satellite cell abundance. J Gerontol. 71A: 461-467.

37.3

METABOLIC AND MOLECULAR NETWORKS OF HUMAN ADAPTATION TO EXERCISE AND AGE

Philip Atherton[1]

[1]Clinical, Metabolic & Molecular Physiology, Univ. of Nottingham, Grad. Entry Med. Sch., The Sch. of Med., Royal Derby Hosp., Uttoxeter Rd., Derby, DE22 3DT, UK.

While aging has negative consequences for skeletal muscle (e.g. sarcopenia, dynapenia and metabolic dysfunction), exercise positively influences muscle mass, muscle function and whole-body metabolic health. Given epidemiological and physiological links between "skeletal muscle health" and organismal health, understanding interactions between exercise, ageing and skeletal muscles are of paramount importance. Nonetheless, this is a challenging area given intrinsic variations in genetics and environment that exert influences upon human skeletal muscle. For instance, marked inherent heterogeneity of exercise adaptation in humans in addition to unpicking the impacts of biological aging from age-related sedentarism, poly-pharmacy, and [sub]-clinical co-morbidities. Recently we have conducted numerous clinical studies with contemporary stable isotopic, metabolic and molecular approaches in attempts to yield insight into human aging and exercise biology. A number of themes have emerged. Firstly, on a molecular level exercise does not appear to "reverse" or oppose human muscle aging. Nevertheless, exercise may offset deconditioning associated with aging thereby reversing molecular signatures resulting from sedentarism. Resistance exercise training (RET) arguably remains the most [cost]-effective countermeasure for age-related musculoskeletal decline - hence is a hotbed of research. Successful hypertrophy in response to RET in younger age is associated with rapid onset cumulative increases in muscle protein synthesis (MPS), ribosomal biogenesis (RNA accumulation) and anabolic signaling (e.g. mTORc1) that generally subside after just 3-4 weeks of training. Paradoxically the apparent longer-term downregulation of "growth genes" likely occurs as a result of negative feedback programming relating to plateauing muscle growth and re-establishment of a new steady-state proteostasis. With aging, responses to key anabolic environmental influences - nutrition and exercise - are blunted (vs. young) in human muscle. This so-called "anabolic resistance", detected using short-term stable isotope protocols, is thought to be an incipient driver of sarcopenia. Recently, using longer-term deuterated water (D2O) approaches we have taken this a step further to reveal that blunted hypertrophy associated with aging is synchronous to sustained deficits in cumulative MPS during RET. Moreover, this is concomitant to impaired ribosomal biogenesis and blunted activation of molecular transducers of translational capacity (e.g. MYC) and efficiency (e.g. mTORc1). This blunted acute signaling may be connected to unfavorable hormone profiles (e.g. lower serum testosterone/IGF-1, not increased myostatin) in older age. Emerging evidence of the role of DNA turnover [satellite cells] in anabolic responses to RET in youth and aging is underway and will be presented. Despite age-related anabolic resistance, RET induces functional improvements likely due to small changes in myo-architecture and neuromuscular adaptations. In sum, RET remains a positive but dampened anabolic stimuli in aging via multiple mechanisms.

39.0 LATE-BREAKING ABSTRACTS

39.1
EXERCISE INCREASES RESTING-STATE BRAIN ACTIVITY IN PARKINSON'S DISEASE

K. H. Wood[1,2], N. A. Kelly[2,3], J. B. Allendorfer[1,2], M. P. Ford[4], C. S. Bickel[2,5], J. Marstrander[6], A. W. Amara [1,2], T. Anthony[6], M. M. Bamman[2,3], and F. M. Skidmore[1, 2]
[1]Univ. of Alabama at Birmingham (UAB), Dept. of Neurology, [2]Univ. of Alabama at Birmingham, Ctr. for Exercise Med., [3]Univ. of Aalabama at Birmingham, Dept. of Cell, Developmental, and Integrative Biology, [4]Dept. of Physical Therapy, Samford Univ., [5]Univ. of Alabama at Birmingham, Department Physical Therapy, [6]Univ. of Alabama at Birmingham, Dept. of Engineering.

Purpose: Parkinson's disease (PD) is a multisystem disorder that results in progressive deterioration of multiple structures in the brain/nervous system. As a result, PD presents clinically with both motor and non-motor deficits. The positive effect of exercise on the human brain, even among older adults, is well established, as are the beneficial effects of exercise on motor and non-motor symptoms in PD. Since physical exercise alters resting-state brain activity in non-PD populations and improves PD symptoms, we assessed the effects of exercise on resting-state brain activity in individuals with PD. The present study was designed to better understand the effects of exercise on resting-state brain activity in PD and potentially elucidate mechanisms behind common symptomatic and functional improvements seen in response to exercise training in PD patients. **Methods:** Individuals with PD underwent 16 weeks of high-intensity exercise training. Resting-state fMRI was performed post-training (after the 16th week) 1 hour before a single bout of exercise and again 1 hour after the exercise session. Amplitude of the low-frequency fluctuation (ALFF) signal was used to evaluate the effect of exercise on brain activity. **Results:** Increased resting-state brain activity after exercise was observed within the left ventromedial prefrontal cortex (PFC), right dorsolateral PFC, and bilaterally within the substantia nigra (SN). **Conclusions:** Given the role of the SN and PFC in motor and non-motor symptoms in PD, increases in brain activity within these regions, if repeated frequently over time (i.e., exercise training), may serve as a potential mechanism underlying exercise-induced PD-specific clinical benefits. **Future directions:** Assess chronic changes in regional brain activity due to long-term exercise training compared to non-PD participants. Investigate changes in resting-state functional connectivity linked to clinical and behavioral outcomes in PD. **Acknowledgements:** UAB School of Medicine, UAB Center for Exercise Medicine, National Institutes of Health [1T32 HD071866 (KHW, NAK), 5K23NS083620 (FMS) K23NS080912 (AWA)], and the UAB Center for Clinical and Translational Science [UL1 TR000165].

39.2
ACUTE MENTAL STRESS AND ITS IMPACT ON SYSTEMIC VASCULAR ENDOTHELIAL FUNCTION IN OBESE ADULTS

Julien V. Brugniaux[1,2], Danielle Hodson[1], Christopher J. Marley[1] and Damian M. Bailey[1].
[1]Neurovascular Res. Lab., Fac. of Life Sci. and Education, Univ. of South Wales, Wales, UK. [2]Sch. of Sci. & Hlth., Western Sydney Univ., NSW, Australia.

Background and aims: Everyday life stressors such as acute mental stress can result in transient impairments in vascular endothelial function (2). Similarly, obesity is known to impair arterial smooth muscle function (1). However, their combined effect remains unknown. To investigate this, we determined to what extent a battery of neuropsychometric tests further compounded vascular endothelial dysfunction in obese adults related to non-obese controls. **Methods**: Eight obese [26 (mean) ± 8 (SD) years old; BMI = 33 ± 4] and 8 non-obese (21 ± 4 years old; BMI = 25 ± 3) male participants were recruited. Brachial artery flow-mediated dilatation (FMD, Acuson P50, Siemens) was measured 1 hour before and immediately following a standardised battery of neuropsychometric tests. Following a 1-min baseline, the occluding cuff (distal) was inflated (>250mmHg) for 5 min and a subsequently released for 5-min into recovery. Brachial artery diameter and flow were recorded continuously throughout the test. Baseline data correspond to the 1-min average pre cuff inflation and peak diameter was measured as the average of the highest 3 values recorded. Data were analysed using automated edge-detection and wall-tracking software (Brachial Tools, Medical Imaging Application). Following confirmation of distribution normality (Shapiro-Wilk *W* tests), data were analysed using a 2-way (Time *x* Group) repeated measures ANOVA. Data are expressed as mean ± SD with significance set at $P < 0.05$. **Results**: Psychometric stress was shown to impair FMD (Pre: 5.3 ± 1.4% vs. Post: 4.4 ± 1.4%, $P < 0.05$). The obese group also displayed a lower FMD than their non-obese peers during both FMD tests ($P<0.05$). The obese further exhibited a decrease in baseline flow from 0.11 ± 0.02 m/sec before to 0.08 ± 0.02 m/sec after acute mental stress ($P<0.05$). **Conclusion**: The present results confirmed that acute mental stress impairs systemic vascular endothelial function. Contrary to our original hypothesis, this impairment was not further compounded by obesity. **References: 1. Ayer JG, Harmer JA, David C, S Steinbeck K, Seale JP, Celermajer DS.** *Obesity* 19, 54-60, 2011. **2. Ghiadoni L, Donald AE, Cropley M, Mullen MJ, Oakley G, Taylor M, O'Connor G, Betteridge J, Klein N, Steptoe A, Deanfield JE.** *Circulation* 102, 2473-2478, 2000.

39.3
METABOLIC BENEFITS OF ENDURANCE EXERCISE TRAINING IN PREGNANCY FOR FEMALES BORN SMALL ON HIGH FAT DIET

Glenn D. Wadley[1,2], Dayana Mahizir[2], Kristina Anevska[2], Andrew J. Jefferies[2], Karen M. Moritz[3] & Mary E. Wlodek[2]
[1]Inst. for Physical Activity and Nutrition, Sch. of Exercise and Nutrition Sci., Deakin Univ., Burwood, Victoria, Australia, [2]Dept. of Physiology, Univ. of Melbourne, Parkville, Victoria, Australia and [3]Sch. of Biomedical Sci., Univ. of Queensland, St. Lucia, Queensland, Australia.

Intrauterine growth restriction programs adult metabolic disease, which is exacerbated with "second hits" such as pregnancy and obesity in females born small. Importantly, exercise is reported to have a positive effect in those born small. This study deter-

mined if a high fat diet (HFD) exacerbates metabolic dysfunction in pregnant females born small and whether exercise before and during pregnancy is more beneficial in preventing these complications than exercise during pregnancy alone.The study was approved by the University of Melbourne ethics committee and conformed to the APS Guiding Principles for the Care and Use of Animals. Uteroplacental insufficiency resulting in growth restriction was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery on embryonic day 18 (E18) in Wistar-Kyoto rats. Female offspring consumed a Chow or HFD (43% kcal from fat) from 5 weeks and were mated at 20 weeks. Female rats were exercised on treadmills for 4 weeks before pregnancy and throughout pregnancy or during the last two thirds of pregnancy only. A glucose tolerance test was performed at E18 and plasma, pancreas and skeletal muscle were collected at E20. Control and Restricted rats exposed to a HFD were heavier with higher plasma leptin concentrations compared to Chow-fed rats irrespective of exercise interventions. HFD exacerbated the pre-existing glucose intolerance in Restricted female rats and importantly exercise before and during pregnancy prevented the development of glucose intolerance (p<0.05). These females on a HFD who exercised before and during pregnancy had increased pancreatic β-cell and islet mass (p<0.05). Compared to Control counterparts, exercise before and during pregnancy reduced intramuscular triglyceride in Restricted Chow-fed females (p<0.05). However, no difference in mitochondrial biogenesis markers (peroxisome proliferator-activated receptor gamma coactivator 1-α and citrate synthase activity) were detected across the groups. Metabolic dysfunction was not impacted by exercise in pregnancy alone. In conclusion, females born small are at a greater risk of glucose intolerance when exposed to a HFD and this was prevented by the lifestyle intervention of exercise potentially due to improved β-cell mass but muscle mitochondrial biogenesis was not affected. This study also suggests that exercise prior to and during pregnancy is more beneficial in preventing metabolic disease than exercise during pregnancy only.

39.4

LONG-TERM CARDIAC PROGRAMMING BY SHORT-TERM JUVENILE EXERCISE TRAINING

Glenn D. Wadley[1,2], Mary E. Wlodek[2], Mary J. Black[3], Aaron P. Russell[1], Paul. Soeding[4] and Yasmin. Asif[1].

[1]Inst. for Physical Activity and Nutrition, Sch. of Exercise and Nutrition Sci., Deakin Univ., Burwood, Victoria, Australia, [2]Dept. of Physiology, Univ. of Melbourne, Parkville, Victoria, Australia, [3]Dept. of Anatomy & Developmental Biology, Monash Univ., Clayton, Melbourne, Victoria, Australia and [4]Dept. of Pharmacology, Univ. of Melbourne, Parkville, Victoria, Australia.

Background: Wadley et al. (2016) recently reported a sustained 10% increase in the heart mass of adult rats who underwent a few weeks of endurance training in juvenile life. Therefore, the aim of this study was to investigate if short-term endurance training during juvenile life (5-9 wks of age) results in sustained improvements in adult heart structure, function, and morphology. **Methods:** The study was approved by the University of Melbourne ethics committee and conformed to the APS Guiding Principles for the Care and Use of Animals. Training was conducted on a motorized treadmill 1h/day, 5 days/wk in either juvenile (training from 5-9 wks of age), or adult (20-24 wks of age) male Wistar-Kyoto rats, and compared to sedentary rats. Cardiac structure and function were assessed at 9 and 24 wks of age using transthoracic echocardiography with hearts being perfusion-fixed for cardiomyocyte analysis or frozen in liquid nitrogen for miRNA analysis by PCR. **Results:** When compared to 24 wk old sedentary rats, juvenile exercise training led to long-term increases in left ventricle (LV) mass (+18%; P<0.05), wall thickness (+11%; P<0.05), the longitudinal area (LA) of binucleated cardiomyocytes (P<0.05), cardiomyocyte number (+36%, P<0.05), and doubled the proportion of mononucleated cardiomyocytes (from 7% to 14%; P<0.05). Adult exercise training also increased LV mass (+11%; P<0.05), wall thickness (+6%; P<0.05) and the LA of binucleated cardiomyocytes (P<0.05), despite no change in cardiomyocyte number or the proportion of mono and binucleated cardiomyocytes. Resting cardiac function, LV chamber dimensions and fibrosis levels were not altered by juvenile or adult exercise training (P>0.05). At 9 wks of age juvenile exercise significantly reduced the expression of miR-1 and increased miR-133b. However, at 24 wks of age miR-1 expression was unaltered following juvenile exercise but significantly increased following adult exercise. At 24 wks of age, adult exercise significantly reduced the expression of miR-208b and miR-222. **Conclusion:** The juvenile period of life is a stage of developmental plasticity that is amenable to long-term, beneficial cardiac programming by short-term endurance training. **References:** Wadley, Laker, McConell & Wlodek. Endurance training in early life results in long-term programming of heart mass in rats. 4(4): 1-14, 2016. Physiological Reports. Supported by the Institute for Physical Activity and Nutrition (IPAN), Deakin University.

39.5

PHYSIOLOGICAL RESPONSES TO TREADMILL RUNNING IN TRAINED COLLEGE AGED AND MASTER LEVEL FEMALE RUNNERS

Leo J. D'Acquisto, Ryan Perkins, Vincent Nethery, Robert Pritchett, Debra D'Acquisto, Amber Brown, Colin Carriker, Sophia Liu, and Amanda Layton.

Central Washington Univ., Dept. of Hlth. Sci., Ellensburg, WA 98926, Ball State Univ., Human Performance Lab., Muncie, IN. 47306, Central Washington Univ., Dept. of Physical Education, Sch. of Hlth. and Movement Studies, Ellensburg, WA. 98926, Good Samaritan Hosp., Sioux Falls, SD 57108, High Point Univ., High Point, NC 27268, Univ. of Washington, Sch. of Med., Dept. of Radiology, Seattle, WA, Central Oregon Comm. Coll,, Bend, OR 97703.

There is a paucity of research on key performance parameters such as maximal oxygen uptake (VO_2 max) and running economy (RE) in highly trained young and masters female runners. Thus, the purpose of this study was to investigate physiological responses in similarly trained, competitive young and masters female runners. As a secondary intent, stride length (SL) and rate (SR) were measured to assess running kinematics. Thirteen young (Y; 20.1±0.4 yr) and fourteen masters (M; 45.6±1.1 yr)

trained female runners performed a series of submax and one max treadmill run to volitional exhaustion. Metabolic (open-circuit spirometry), HR (telemetry) and blood lactate (finger stick) responses were monitored. SR was measured by timing 50 stride cycles over the last minute of each submaximal effort while SL was computed by dividing running velocity by SR. A similar VO_2 max was noted between groups (2.95±0.11 (M) vs. 2.92±0.10 $l \cdot min^{-1}$ (Y); 49.9±0.9 (M) vs. 48.8±1.0 $ml \cdot kg^{-1} \cdot min^{-1}$ (Y); P>0.05) while a lower HR max (174±3 vs.193±2 bpm) and peak lactate (8.3±0.4 vs. 10.7±0.9 mM) was found in the masters runners (P<0.05). Maximal O_2 pulse, a surrogate of maximal stroke volume, was greater in the masters runners (~11%; P<0.05). VO_2 (relative to body wt.), blood lactate, HR, SL and SR at common submaximal running speeds was similar between M and Y. Aerobic demand relative to distance covered ($ml\ O_2 \cdot kg^{-1} \cdot km^{-1}$) at given metabolic efforts (70 to 100% VO_2 max) was independent of running velocity and similar between M and Y (P>0.05). In conclusion, highly trained masters female runners have the same maximal aerobic power and running economy as their younger counterparts of 25 years. Furthermore, both groups displayed the same kinematic profile as noted by similar SL and SR values regardless of submax running velocity. Our findings indirectly suggest that performing a high level of training consistently into the fifth decade of life results in a greater stroke volume to offset the decline in HR max**.** Lastly, the fitness level of our groups, especially the masters runners, is noteworthy when comparing their VO_2 max to values obtained from cardiopulmonary maximal exercise testing in females (Kaminsky et al. (2015)). Our young and masters runners rank at ~85th and above the 95th percentile, respectively, in measured VO_2 max.

39.6

DECREASED HETE-12 AND -15 ARE ASSOCIATED WITH GLUCOSE REGULATION FOLLOWING HIGH INTENSITY EXERCISE IN PEOPLE WITH PREDIABETES

Steven K. Malin[1,2,3,4], Corey A. Rynders[5], Judy Y. Weltman[3], Eugene J. Barrett[2,4], Jerry Nadler[6], and Arthur Weltman[1,2,3]
[1]Dept. of Kinesiology, Univ. of Virginia, Charlottesville VA, [2]Div. of Endocrinology and Metabolism, Univ. of Virginia, Charlottesville VA, [3]Exercise Physiology Core Lab., Univ. of Virginia, Charlottesville VA, [4]Robert M. Berne Cardiovascular Res. Ctr., Univ. of Virginia, Charlottesville VA, [5]Div. of Geriatrics and Ctr. on Aging, Univ. of Colorado, Denver CO, [6]Dept. of Med., Eastern Virginia Med. Sch., Norfolk, VA.

Purpose: We previously reported that high intensity exercise (HIE) lowered circulating post-prandial glucose more than moderate intensity exercise (MIE) in people with prediabetes, and this may have been related to insulin action. Hydroxyeicosatetraenoic acid [12- and 15-HETE] is an inflammatory mediator of insulin resistance and secretion, but the effects of exercise are unknown. Here we tested the hypothesis that exercise intensity may differentially impact HETE in relation to glucose control in adults with prediabetes. **Methods**: Thirteen subjects (Age: 51.5±4.0 yr; BMI: 32.6±1.6kg/m^2; VO_2peak: 22.9±1.3 mg/kg/min) with prediabetes (ADA criteria, 75g OGTT screening) underwent 3 randomly assigned conditions: time-course matched control (CON), and exercise at isocaloric (~200kcal) MIE (at lactate threshold (LT) and HIE (75% of difference between LT and VO_2peak). One-hour post-exercise, a 120-minute 75g OGTT was performed, and plasma glucose, insulin, and C-peptide were determined for calculations of glucose tolerance (total area under the curve (AUC)), insulin sensitivity (Oral Minimal Model (OMM) and HOMA-IR), glucose-stimulated insulin secretion (Deconvolution modeling; Insulin secretion $rate_{AUC\ 0\text{-}120}$/$Glucose_{AUC\ 0\text{-}120}$; GSIS), disposition index (peripheral and hepatic DI) and hepatic insulin extraction (C-$pep_{AUC\ 0\text{-}120}$/$Insulin_{AUC\ 0\text{-}120}$). Urinary HETE-12 and -15 corrected for creatinine were collected post-OGTT. **Results**: Although exercise intensity had no statistical effect on HETE-12 or -15 compared with CON, decreased HETE-15 was related to improved hepatic insulin extraction following HIE (r=-0.47, P=0.09) and MIE (r=-0.61, P=0.02). Interestingly, reductions in HETE-12 and -15 were only correlated with improved glucose tolerance (r=0.52, P=0.07) and insulin sensitivity (OMM; r=-0.68, P=0.01) following HIE. Consistently, decreased HETE-12 also correlated with reduced GSIS (r=0.70, P<0.01) and hepatic DI (r=0.54, P=0.06) following HIE only. **Conclusion**: HETE-12 and -15 responses appear related to improvements in glucose and insulin metabolism following higher intensities of exercise. Together, these data suggest exercise intensity may influence inflammatory responses that impact glucose homeostasis in people with prediabetes.

39.7

HIT DOES NOT ALLEVIATE INTENSIFIED TRAINING-INDUCED REDUCTIONS IN MUSCLE CYTOKINE RESPONSE TO ACUTE EXERCISE

Maria A. Cardenas, Michael Levitt, Melody D. Phillips, Brooke Burgess, and Cheryl Haston.
Texas Christian Univ., Exercise Physiology Lab., Fort Worth, TX.

High intensity training programs (HIT) induce comparable endurance performance adaptations to those of continuous long slow distance training (LSD). The use of HIT has increased, as athletes are able to maintain their VO_2 max or performance with less time, and reduced training volume. **Purpose:** examine the cytokine (IL-6,IL-8,TNFα) response to HIT and LSD during 4 days intensified training volume. **Methods**: Eight endurance-trained males (23.1±2.0yr,VO_2 max 53.9±5.3 $ml \cdot kg^{-1} \cdot min^{-1}$) performed two, four-day intensified training protocols: HIT and LSD conditions (≥ 21 days between conditions). Both conditions included 2 exercise sessions / day (morning (AM) and late afternoon (PM)). LSD consisted of 50 min cycle ergometery in the AM (70% VO2max) and 90 min running in the PM (70% VO2max). The AM UHIT session included 8 all-out, 30 sec cycling sprints (resistance=0.075$kg \cdot kg^{-1}$ body mass) with 4.5-8.5 min active recovery. The PM session in UHIT was the same as that for LSD. Plasma cytokines were assessed both before and after the morning exercise sessions (pre-(PR), post(PO)-exercise) in both conditions on the first (before training; BT) and fourth (after training; AT) day of intensified training. Cytokines were analyzed in duplicate using Millipore multiplex kits. **Results:** IL-6 % change from PR to PO was greater (p=0.036;

main effect-condition) in HIT (93±26%) vs. LSD (17±16%) and greater (p=0.01; main effect-intense training) BT (87±18%) vs. AT (23±19%). There was a main effect of acute exercise for IL-8 (p=0.001), where PO (5.1±1.0pg·ml^{-1}) was greater than PR (3.6±0.80pg·ml^{-1}) in both conditions collapsed. IL-8 % change from PR to PO was greater (p=0.041; main effect-condition) in HIT (35±13%) vs. LSD (-2.0±8.9%) and greater (p=0.004) BT (42±7.8%) vs. AT (-9.1±12%). There was no difference in % change TNF-α (HIT 189±94% LSD 19±19% p>0.05) between conditions. The observed decline in Il-6 and Il-8 responses to acute exercise, regardless of exercise condition, may be partially consequent to the intensified training-induced elevations in resting values at the ATPR time point [IL-6: BTPR=3.0±1.2, BTPO=5.2±1.8, ATPR=9.7±4.9, ATPO= 7.4±2.6pg·mL^{-1}; IL-8: BTPR=3.6±0.8, BTPO=5.2±1.0, ATPR=8.7±3.8, ATPO=6.8± 2.0pg·mL^{-1}]. **Conclusions:** Acute exercise-induced IL-6 and IL-8 response is dependent on exercise intensity. How-ever, four days of exhaustive exercise training reduced the mag-nitude of the acute exercise IL-6 and IL-8 responses in both con-ditions.

39.8
ENERGY SUBSTRATE OXIDATION DURING CYCLING AND RUNNING IN THE COLD AND HEAT

Dominique D. Gagnon, Lina Perrier, Michelle Laurence, Sandra Dorman, Céline Larivière, and Olivier Serresse
Sch. of Human Kinetics, Laurentian Univ., Sudbury, ON, Canada.

Introduction: The examination of energy substrate oxidation under thermal stress has previously demonstrated an increase in lipid utilization during walking and running in the cold (Gagnon et al. 2013) but not during cycling (Layden et al. 2002) at fixed intensities. No exercise thermophysiology study has comprehensively examined metabolic differences between exercise modalities nor has addressed the fundamental metabolic changes across exercise intensities. The aim of the study was to examine the influence of environmental temperature on energy substrate oxidation in a cold and warm environment across a range of exercise intensities during running and cycling. **Methods:** Nine male subjects (21.2±1.4 yrs, 84.0±14.6 kg, 1.76±0.07 m, 10.6±5.7 %BF) dressed in shorts and t-shirt, completed 4 trials, one week apart, during which they performed an incremental maximal oxygen consumption (VO_{2max}) test on a cycle ergometer or treadmill in a cold (4.6°C) or warm environment (34.1°C) which was designed to include 6 to 15 three-min stages. VO_{2max}, maximal fat oxidation rate (MFO), and exercise intensity where MFO occurs (Fat_{max}) were assessed. Data was analyzed using a two-way ANOVA (factors: temperature, exercise modality) for repeated measures with significance at $p<0.05$. **Results:** VO_{2max} in the treadmill condition was 47.2 ± 5.9 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ and 39 ± 6.8 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ in cycling. MFO was greater in the cold *vs*. warm (0.55 g•min^{-1} vs. 0.38 g•min^{-1}; p=0.016) as well as during running *vs.* cycling (0.57 g•min^{-1} vs. 0.37 g•min^{-1}; p=0.028). Analyses further revealed that environmental temperature had no influence on MFO during cycling (p=0.071). Fat_{max} was also greater in the cold *vs*. warm (60% vs. 37% of VO_{2max}; p=0.004) with no factorial interactions within groups (p=0.451). **Conclusions:** We examined thermal influences on energy metabolism across a wide range of intensities during running and cycling. We demonstrated that running in a cold environment increases maximal fat oxidation rate which peaked at a higher exercise intensity compared to a warm environment. These results further validate the implication of environmental temperature on energy metabolism during exercise and could serve as a reference for training designs. This study was supported by an NSERC Discover Grant and a Laurentian University Research Grant. **References:** Gagnon DD, et al. (2013). *Front. Physiol.* 4 (99)**,** Layden et al. (2002). *Med. Sci. Sports Ex.* 34 (5), 774-779.

39.9
RANDOMIZED, FOUR-ARM, DOSE-RESPONSE CLINICAL TRIAL TO OPTIMIZE RESISTANCE EXERCISE TRAINING FOR OLDER ADULTS WITH AGE-RELATED MUSCLE ATROPHY

Brandon M. Roberts,[1,2] Michael J. Stec,[1,2] Anna Thalacker-Mercer,[1,2] David L. Mayhew,[1,2] Neil A. Kelly,[1,2] S. Craig Tuggle,[1,2] Edward K. Merritt,[1,2] Cynthia J. Brown,[1,3,6] Samuel T. Windham,[1,4] Louis J. Dell'Italia,[1,5,7] C. Scott Bickel,[8] Kristina M. Vaughn,[1,2] Irina Isakova-Donahue,[1,2] Gina Many,[1,2] and Marcas M. Bamman,[1,2,6]
[1]UAB Ctr. for Exercise Med., Univ. of Alabama at Birmingham, Birmingham, AL 35294, [2]Dept. of Cell, Developmental, and Integrative Biology, Univ. of Alabama at Birmingham, Birmingham, AL 35294, [3]Div. of Gerontology, Geriatrics, and Palliative Care, Dept. of Med., Univ. of Alabama at Birmingham, Birmingham, AL 35294, [4]Dept. of Surgery, Univ. of Alabama at Birmingham, Birmingham, AL 35294, [5]Div. of Cardiovascular Dis., Dept. of Med., Univ. of Alabama at Birmingham, Birmingham, AL 35294, [6]Geriatric Res., Education, and Clinical Ctr., Veterans' Affairs Med. Ctr., Birmingham, AL 35233, [7]Res. Service, Veterans' Affairs Med. Ctr., Birmingham, AL 35233, [8]Dept. of Physical Therapy, Univ. of Alabama at Birmingham, Birmingham, AL 35294.

Background. There are numerous consequences of age-related muscle atrophy including reduced muscular strength, power, and mobility; increased risk of falls, disability, and metabolic disease; and compromised immune function**.** Ultimately, aging muscle atrophy results from a loss of myofibers and atrophy of the remaining type II myofibers. The purpose of this trial (NCT02442479) was to titrate the dose of resistance training (RT) in older adults in an effort to maximize muscle regrowth and gains in muscle function. The goal was to identify a prescription that sufficiently loaded muscle to promote myogenic processes, while allowing adequate recovery between bouts to limit muscle inflammation signaling. **Methods.** The design was a randomized, four-arm efficacy trial in which four, distinct RT prescriptions varying in intensity, frequency, and contraction mode/rate were evaluated: (1) high-resistance concentric-eccentric training (H) 3 d/wk (HHH); (2) H training 2 d/wk (HH); (3) 3 d/wk mixed model consisting of H training 2 d/wk separated by 1 bout of low-resistance, high-velocity, concentric only (L) training (HLH); and (4) 2 d/wk mixed model consisting of H training 1 d/wk and L training 1 d/wk (HL). We hypothesized the prescriptions involving 2 d/wk H training (HH, HLH) would yield greater muscle regrowth than HHH (insufficient recovery/

inflammatory burden) and HL (insufficient H frequency) and further, the HLH prescription would yield overall superior gains in muscle function and mobility indices due to the insertion of 1 d/wk L training. **Results.** The HLH prescription maximized gains in thigh muscle mass and total body lean mass. HLH also showed the greatest gains in knee extension maximum isometric strength, and reduced cardiorespiratory demand during steady-state walking. HHH was the only prescription that led to increased muscle expression of pro-inflammatory cytokine receptors and this was associated with a lesser gain in TMM and total body lean mass compared to HLH. **Conclusions.** Considering the results in total, it appears the HLH prescription offers some distinct advantages over the other doses, while the HL program is subpar for many of the outcomes studied here. We can conclude from this randomized dose-response trial that older adults benefit greatly from 2 d/wk high-intensity RT, and may further benefit from inserting an additional weekly bout of low-load, explosive RT. **Funding Sources:** P2CHD086851 (Bamman), T32HD071866-04 (BR).

39.10

ADVERSE ULTRASTRUCTURAL REMODELING AND MITOCHONDRIA DYSFUNCTION OF SKELETAL MUSCLE IN HEART FAILURE

Michael Rogowski[1], Pamela Powell[2], Lianwu Fu[3], Jim Collawn[3], Marcas Bamman[4], and Louis Dell'Italia[1,2].

[1]Sch. of Med., Cardiovascular Dis., Univ. of Alabama Birmingham, Birmingham AL, [2]Dept. of Vet. Affairs Hosp., Birmingham AL, [3]Sch. of Med., Cell Development and Integrative Biology, Univ. of Alabama Birmingham, Birmingham AL, [4]Sch. of Medicine, Ctr. for Exercise Med., Univ. of Alabama Birmingham, Birmingham AL.

Though a secondary feature of chronic heart failure (HF), significant muscle loss is a profound morbidity that directly results in decreased capacity to complete activities of daily living, contributing to loss of independence and decreased quality of life. Despite its frequency as a clinical feature of HF, the pathological process and underlying mechanisms of skeletal muscle (SM) wasting in this disease remain elusive. To this end, we sought to examine the specific pathology at the ultrastructure level in order to better characterize the degradation of SM in HF. Using an *in vivo* rat model, we induced volume overload HF through the creation of an aorto-caval fistula. The descending aorta is punctured through the vena-cava, allowing arterial flow into the vena-cava resulting in dramatic increase in venous return to the heart, causing volume overload and subsequent HF over 12 weeks. Surgical shams that omit the aorto-caval puncture serve as controls. Upon sacrifice, gastrocs were extracted and fixed appropriately for immunohistochemical or transmission electron microscopy analysis, as well as flash frozen for mitochondria analysis. Electron microscopy of SM with HF revealed extensive disruption of sarcomere morphology, increased glycogen deposition, and aberrant mitochondria organization and morphology. SM fiber cross sectional area was significantly decreased (18 %) in HF. Decreased protein expression levels of Drp1, Hsp60, and LC3II suggest diminished mitophagy in SM due to HF, contributing to mitochondria dysfunction. Mitochondria function was assessed for Complex I, Complex IV, and citrate synthase activity in skeletal muscle that trended towards significant decrease in Complex IV ($p=.10$) in total homogenate fraction in HF. Cardiomyocyte degeneration in volume overload HF is induced by excess chronic mechanical stretch, yet we observe similar morphological degeneration in skeletal myocytes as well. This suggests that the physiologic environment induced by the failing heart condition results in an overlapping pathological degradation in the skeletal muscle. In addition to atrophy, this adverse cytoskeletal remodeling also appears to negatively impact mitophagy and mitochondrial function in skeletal muscle. Further study is needed to resolve the mechanisms by which cellular processes initiate ultrastructure degradation skeletal muscle during HF. Funding by NIH 1T32HD071866 and P01 HL051952.

39.11

MITOCHONDRIAL PROTEIN CONTENT IS ENHANCED BY LIFELONG PHYSICAL ACTIVITY

Joanisse S.[1], Pollock R.[2], O'Brien K.[2], Lazarus N. R.[2], Smith K.[3], Wilkinson D. J.[3], Phillips B. E.[3] Harridge S. D. R[2*], Atherton P. J.[3*], Philp A.[1*]

[1]Sch. of Sport, Exercise and Rehabilitation Sci., Univ. of Birmingham. [2]Ctr. of Human and Aerospace Physiological Sci., Kings Coll. London. [3]Div. of Med. Sci. and Graduate Entry Med., Univ.of Nottingham.* Joint corresponding authors.

Sedentary ageing is associated with progressive declines in muscle mass, strength and oxidative capacity. Whilst the age-associated reduction in muscle mass is well characterised, less is known regarding the mechanisms responsible for the decline in oxidative capacity. The purpose of the current study was therefore to (1) investigate the effect of ageing on mitochondrial protein content, and (2) examine whether life-long physical activity in the older adult (i.e. masters athletes) results in enhanced mitochondrial protein content compared to age-matched old sedentary and young active adults. Muscle biopsies were obtained from the vastus lateralis of 8 young (YG: 22 ± 3 years, 24 ± 3 kg/m^2) and 8 old (SED: 67 ± 2 years, 27 ± 3 kg/m^2) adults not previously engaged in a formal exercise training programme and 8 master athlete (MST: 65 ± 5 years, 26 ± 2 kg/m^2) male adults. Immunoblotting was used to assess mitochondrial and mitochondrial-related protein abundance in skeletal muscle. Comparison between YG and SED did not reveal any age-associated declines in mitochondrial protein content. In contrast, the protein content of electron transport chain (ETC) complexes I, II and IV were significantly greater in MST compared to both YG and SED ($p<.001$). In parallel, protein content of PGC-1α, a purported mediator of a mitochondrial biogenesis was 3- and 5-fold greater in MST compared to YG and SED respectively ($p<.001$). Further, the abundance of proteins related to fat and carbohydrate metabolism were greater in MST. VLCAD protein content was greater in MST compared to SED ($p<.05$), whilst PDH was increased in MST compared to both YG and SED ($p<.05$). Based on our results, we conclude that ageing is not associated with a decline in protein content of ETC I, II, IV and PGC-1α. Further, we show that mitochondrial related protein content was substantially increased in master athletes, suggesting that exercise can maintain mitochondrial content into later life.

39.12

EFFECTS OF HEIGHTENED INFLAMMATION ON ARGININE TRANSPORTERS AND METABOLIC ENZYME EXPRESSION IN DIFFERENTIATED PRIMARY HUMAN PROGENITOR CELLS

Thalacker-Mercer A., Blum J., Roman H., Riddle E., Gupta D.
Cornell Univ., Div. of Nutritional Sci., Ithaca, NY.

Background: The underlying etiology of skeletal muscle atrophy with aging (i.e. sarcopenia) is multifactorial and appropriate therapies are ambiguous. Recently, our lab identified *Arginine and Proline Metabolism* as the metabolic pathway most strongly associated with skeletal muscle index (SMI) among older adults; seven circulating metabolites were positively correlated with SMI in both untrained and resistance exercise trained older adults. Arginine attenuates skeletal muscle wasting induced by diseases with heightened inflammation. However, the relationship between arginine and proline metabolism and skeletal muscle health is largely unknown. Recognizing that older muscle is susceptible to heightened inflammation that induces skeletal muscle deterioration and pathological remodeling, we hypothesized that inflammation disrupts arginine metabolism in skeletal muscle. Objective: Determine the effects of inflammation on arginine transporter and metabolic enzyme gene expression in differentiated primary human progenitor cells. Methods: Skeletal muscle biopsies were collected from younger men and women after an overnight fast. Primary human skeletal muscle progenitor cells harvested from the biopsies were cultured in growth media for 7 days, switched to differentiation media (DM) for 3 days, and then incubated for 2 days in DM in the presence or absence of 10 ng/mL of the proinflammatory cytokine TNFα. Gene expression of the arginine transporters (*CAT1* and *CAT2*) and metabolic enzymes was measured using quantitative PCR and a PCR array, respectively, on RNA collected from the cultured cells. Results: Incubation with TNFα increased the expression of *NFKB*, *IL6*, and *CAT2* ($p<0.05$), suggesting increased arginine uptake with inflammation. Additionally, inflammation decreased the expression of five metabolic genes (ornithine decarboxylase-1, pyrroline-5-carboxylate reductase-1, spermine synthase, creatine kinase, and ornithine aminotransferase) and increased the expression of prolyl-4-hydroxylase subunit alpha-1. Reduced expression of metabolic enzymes with inflammation (*in vitro*) was consistent with lower circulating levels of the related metabolites among older adults (*in vivo*) that we previously observed. Conclusions: Overall these results suggest that elevated TNFα, such as that observed in older adults, alters skeletal muscle arginine transport and metabolism and may be associated with skeletal muscle deterioration and pathological remodeling. Funding: Cornell University, Affinito-Stewart Grant.

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SKELETAL MUSCLE PHENOTYPES IN MKX-NULL MICE

Takayuki Akimoto[1,2], Yutaka Kano[3], Kazutaka Nakamura[2], Shigeru Miyaki[4], Hiroshi Asahara[5], Takashi Ushida[2]
[1]Lab. of Muscle Biology, Waseda Univ., [2]Univ. of Tokyo, Grad. Sch. of Med., [3]Univ. of Electro-Communications, [4]Hiroshima Univ. Hosp., [5]Tokyo Med. and Dental Univ.

Tendons are fibrous connective tissues attaching muscles to bones. Tendons serve to move the bones or structures through muscles. Recently, we have found a homeotic gene, Mohawk homeobox (Mkx) as a regulator for development and/or homeostasis of tendons (Ito et al., PNAS, 2010). The Mkx gene also expressed in skeletal muscle, suggesting the Mkx plays some roles in skeletal muscle. The purpose of this study was to determine muscle phenotypes in Mkx-null mice. As a result, the Mkx-null mice showed an increase in muscle mass compared with WT mice. We also found an increase of MyHCIIa fibers in the null-mice. There was no difference in muscle strength between WT mice and the null-mice, while the null-mice showed higher muscle fatigue resistance. These results suggest that Mkx gene serves as a regulator of skeletal muscle function.

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