Integrating the Life Sciences from Molecule to Organism

The Physiologist

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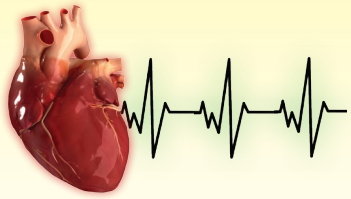
Program and Abstracts Issue

2012 APS Conference:
Autonomic Regulation of Cardiovascular Function in Health and Disease

July 2012 • Omaha, Nebraska



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Sponsored by: The American Physiological Society, the Canadian Society for Exercise Physiology, and the American College of Sports Medicine

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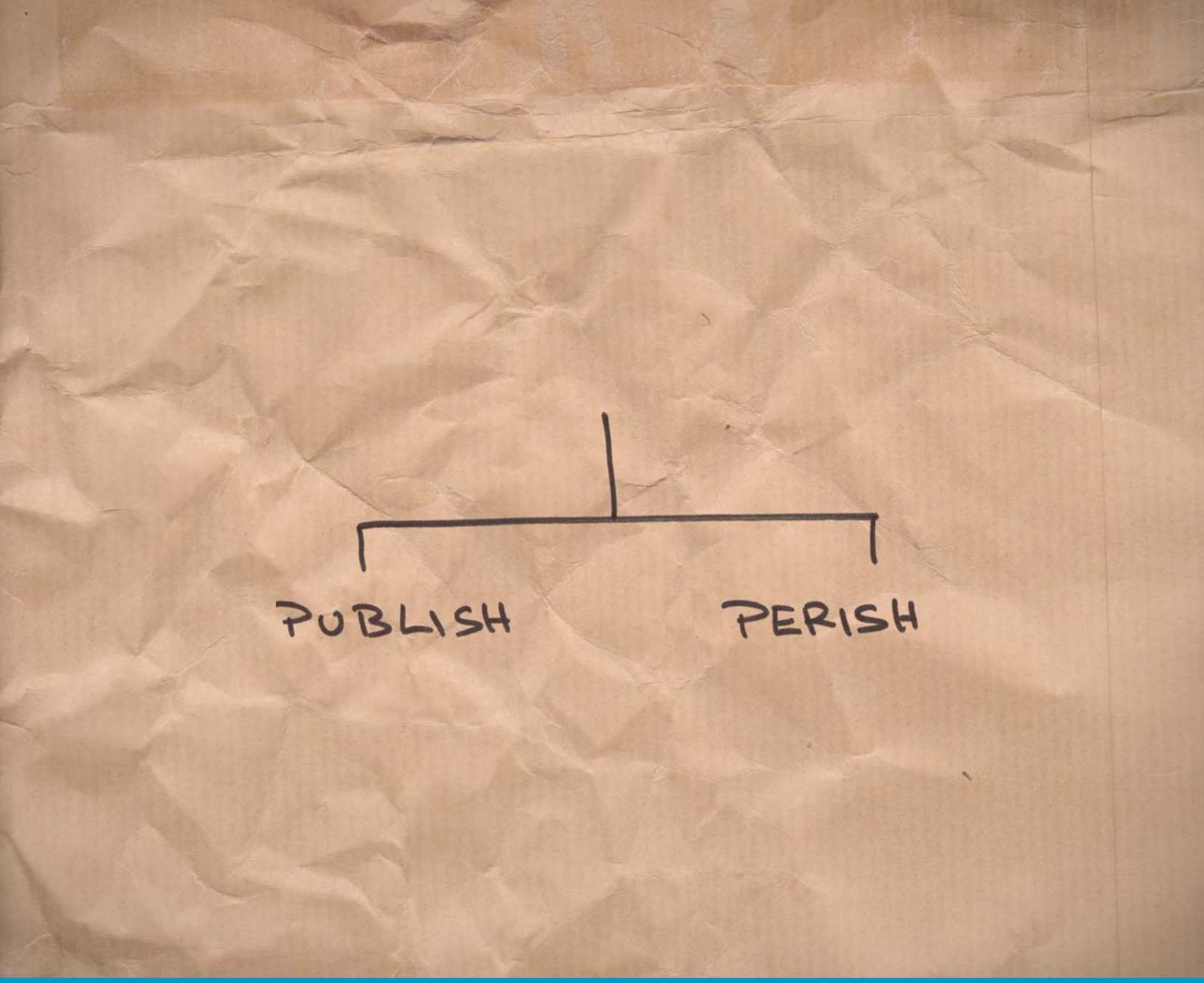

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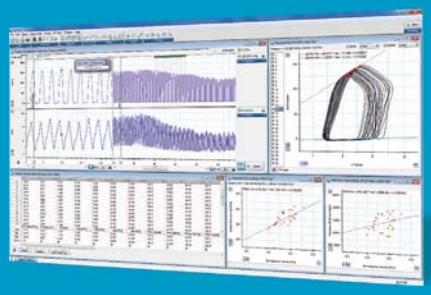

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INSIDE

"Enthusiasm is Everything[1]"

Kim Barrett, Univ. of California, San Diego
Bene Machado, Sociedade Brasileira de Fisiologia and
Sue Barman, Michigan State Univ.

APS President Susan M. Barman and President-Elect Kim E. Barrett visited Brazil at the invitation of Dr. Aldo B. Lucion, the President of the Sociedade Brasileira de Fisiologia (SBFis; Brazilian Physiological Society) and Dr. Benedito H. Machado, President-Elect of SBFis. Barman and Barrett participated in the XLVII Congress Annual Scientific Meeting of SBFis held in the city of Gramado on September 2-5, 2012. Following the Congress, Barman and Barrett traveled to Ribeirão Preto to meet with faculty and trainees at the Department of Physiology, School of Medicine of Ribeirão Preto, University of São Paulo, campus of Ribeirão Preto (USP-RP).

This visit by APS Leadership to Brazil importantly extends the collaboration between the American and Brazilian Physiological Societies that was initiated at the 2009 IUPS Congress in Kyoto, Japan with discussions among Machado, Gary Sieck (then APS President) and Martin Frank (APS Executive Director). In the summer of 2010, Sieck, Frank, and Peter Wagner (then APS President) visited three institutions in Brazil to explore ways in which the two Societies could work collaboratively to increase mutually beneficial scientific engagement. APS is certainly looking forward to the opportunity to partner with SBFis and six other physiological societies to organize the inaugural Pan-American Physiological Congress, Physiology without Borders, to be held in Iguassu Falls, Brazil on August 2-6, 2014 http://panam2014.com/. In addition, Brazil will host the 38th IUPS meeting in Rio de Janeiro in 2017 with the theme The Rhythms of Life; APS will doubtless participate in programming for that meeting as well.

The XLLVII Congress of SBFis was the first time since 2006 that the Society held its annual meeting separate from the multi-society meeting of FeSBE (Federação de Sociedades de Biologia Experimental), comparable to our Experimental Biology meeting. The independent meeting this year was intended to spotlight the discipline of physiology, and especially integrative physiology, which has long been a tradition in Brazilian research laboratories. In addition to speakers from many Brazilian institutions, there was representation by physiologists from Chile, Germany, Portugal, Greece, the UK, as well as the USA on the scientific and educational program. Barman and Barrett were amazed to learn that 75% of the approximately 1,000 meeting attendees were trainees [graduate students (50%) and undergraduate students (25%)]. These young and enthusiastic physiologists were eager to describe the results of their latest research projects at the poster ses-

(continued on page 219)

[1]*From a quote from Pele (b.1940, Minas Gerais, Brazil), probably the most famous ever Brazilian footballer (also an actor and politician). The full quote is "Enthusiasm is everything. It must be taut and vibrating like a guitar string."*

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Kim Barrett, Bene Machado, and Sue Barman outside of the Department of Physiology at USP-RB.

sions. And while some posters were in Portuguese, the trainees all had an excellent command of English and discussed their findings with considerable flair.

Barman briefly spoke on behalf of APS during the opening session of the Congress, and Barman and Barrett were co-presenters at an interactive session entitled "Getting your work published in the journals of the American Physiological Society and avoiding ethical problems along the way." They were very pleased by the active participation by the many trainees and faculty members who attended the session. Barman also spoke at a session entitled "Perspectives for the Physiological Sciences on the next decade" which was sponsored by the APS and The Physiological Society. The other speakers were Michael Spyer (President of The Physiological Society) and Rodrigo Iturriaga (President of the Latin-American Association of Physiological Sciences). Machado was the organizer of the session and he asked the speakers to discuss emerging research approaches and the challenges we face in using these methods to effect conceptual advancements. Barman shared her knowledge of the central neural control of the cardiovascular system, with an emphasis on recent insights into the role played by increased sympathetic nerve activity in the pathogenesis of hypertension and heart failure.

During their visit to the Department of Physiology at USP-RP, Barman and Barrett were able to meet with several faculty, researchers, and trainees to discuss some of APS's initiatives that could benefit students and faculty in Brazil. The assembled group talked about the many travel award programs and professional opportunity awards available to graduate students, the undergraduate summer research program, David Bruce undergraduate poster award program, the Latin American Initiative, educational tools available through the Archive of Teaching Resources, and the many Professional Skills Training (PST) Workshops offered by APS both online and face-to-face.

The meeting at USP-RP also provided Barman and Barrett with an opportunity to learn about graduate education in Brazil. All graduate students are supported by Fellowships provided by state and federal agencies. Most students initially enter a masters degree program; upon satisfactory completion, they may be eligible for admission to doctoral programs. Thus, students are awarded Fellowships that cover, on average, six years of training in physiology as well as in numerous other disciplines. CAPES, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, is the Brazilian Federal Agency that supports and evaluates graduate education on a regular basis. The Physiology graduate program at USP-RP has consistently received the highest ranking possible from CAPES, based, in part, on assessing program publications that include student authors.

Since publications are a key measure in evaluating success of their graduate programs, several of the faculty expressed an interest in having a live version of the APS PST Course on Writing and Reviewing for Scientific Journals at USP-RP. One possibility would be to run the course in conjunction with their Fifth "Symposium Covian," a meeting held in honor of their founding Chair, Miguel Covian. It is expected that many students will be eager to participate, including those from other institutions and those enrolled in a novel multi-institutional physiology graduate program that is sponsored by SBFis. As for other APS PST courses on writing and reviewing, students will need to have completed a draft manuscript before the course begins. Machado and Wamberto Varanda, chair of Department of Physiology at USP-RP, will submit an application to the APS International Committee to request funds for this program through the Latin American Initiative. If the course goes forward, it will be an excellent opportunity for the APS members who act as instructors to contribute to the development of the next generation of physiologists in Brazil, as well as establishing new international contacts.

In summary, this was a very productive visit. Barman and Barrett were impressed by the strong support provided by the Brazilian government for training young physiologists, commenting that perhaps this would be something that the US government might emulate. They also greatly appreciated the wonderful hospitality of their hosts, Bene Machado and Lusiane M. Bendhack, who opened their home so they could enjoy typical Brazilian lunches. Barman and Barrett hope to promote continued collaborations between APS and SBFis, including helping to bring an APS PST course to Brazil and the prospect of excellent science at the Pan-American Physiological Congress in 2014. ❖

Opening Session at the XLVII Congress Annual Scientific Meeting of SBFis in Gramado Brazil. Ilma Brum (at the podium), Director of SBFis; Tadeu Rantim, former president of SBFis; Maria Marques, former president of SBFis; Sue Barman, President of APS; Maria José Campaganole-Santos, Coordinator of the Multicenter Graduated Program in Physiology by SBFis; Aldo B. Lucion, President of SBFis; Mike Spyer, President of Physiological Society; Eduardo M. Krieger, former president of SBFis; and José Antuens Rodrigues, former president of SBFis.

John F. Perkins, Jr. Memorial Awardee Reports on Research Experiences

Andras Garami

The John F. Perkins, Jr. Memorial Award for International Physiologists promotes cultural exchange and scientific collaborations by providing supplementary aid to families of foreign scientists working for a minimum of three months in the US. Andras Garami was the recipient of the spring 2012 Perkins Award. Garami spent three months working in the lab of APS member Andrej A. Romanovsky, at St. Joseph's Hospital and Medical Center, AZ. Romanovsky is also a past Perkins Award recipient. Below is Garami's report on how he and his wife used the award.

"I am very grateful to the Perkins Award Committee for granting me the John F. Perkins, Jr. Memorial Award for International Physiologists. This award made it possible for me to bring my wife, Eszter, to the United States with me and to enrich our cultural experiences. My host, Dr. Romanovsky, was very kind and hospitable. He lent us a car for the duration of our stay and took us to several local attractions, such as the Musical Instrument Museum, the Desert Botanical Garden, and the Frank Lloyd Wright's Taliesin West. We hiked the San Francisco Peaks in northern Arizona together, where he taught us about the region's diverse mountain flora. We also hunted mushrooms there. Thanks to the award, Eszter and I were able to spend a week in Yellowstone National Park, which is one of the greatest and most beautiful parks in the United States.

"The scientific part of my visit was also very productive. As indicated in the application, our primary goal was to process data from our earlier experiments on the roles of prostaglandin D2 in the regulation of body temperature. We met this goal. Furthermore, I was able to run additional—critical—experiments, which allowed us to strengthen the conclusions of our study. I also performed the necessary statistical analyses and prepared final figures for publication. By the end of my stay, I had drafted a manuscript about the complex effects of prostaglandin D2 on thermoregulation.

"Dr. Romanovsky, who was both my host and a former recipient of the Perkins Award, asked me to indicate in my report that he is grateful to the American Physiological Society for awarding me this prestigious fellowship. He felt very satisfied that my wife, Eszter, and I were able to travel during our visit, and that we had the opportunity to experience the culture and natural beauty of America. He believes that the Perkins Award is unique in that it places high priority on a scientist's family life and cultural experiences; most other fellowships and awards either ignore these aspects of life or treat them as obstacles on the way to scientific achievements. Dr. Romanovsky appreciates this humane side of the Perkins Award." ❖

Eszter, Andras and Dr. Romanovsky under the unique logo of Frank Lloyd Wright Taliesin West, Scottsdale, AZ.

Andras and his wife Eszter at the entrance of Yellowstone National Park.

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Report on the African Association of Physiological Sciences Congress and Teaching Workshop
Ismailia, Egypt, Sept. 2-5, 2012

Penny Hansen
Memorial Univ. of Newfoundland, Canada

Although English was the language of the Sixth congress of the African Association of Physiological Sciences (AAPS), you could hear Arabic, Afrikaans, Igbo, and Swahili being spoken as colleagues chatted with new and old friends during lunch and coffee breaks. This cultural diversity was enhanced by the appearance of the female attendees who were dressed in everything from niqab to colorful abaya and hijab to western-style business suits. The Congress was held at the Forsan Island Mercure Hotel in the beautiful town of Ismailia alongside the Suez Canal. The organizer, Professor Yasser El-Wazir and his team from the Suez Canal Univ. had thought of everything so that registration and other arrangements went smoothly and efficiently. Ninety-six physiologists from 13 countries attended. Looking around I saw approximately equal numbers of men and women of all ages, well-distributed from students up to the most senior African physiologists, such as Professors Olusoga Sofola from Nigeria and Amal Saeed from Sudan. The inclusion of graduate students and young faculty members with older speakers in the symposia ensured that one of the key objectives of the Congress was fulfilled: to update knowledge and improve communication and presentation skills of junior African physiologists.

Fifty-three of the attendees arrived a day early on Sept. 2 to participate in a day-long workshop sponsored by APS and IUPS: Trends and Challenges in Physiology Education: Africa and the World. The day started with a provocative talk by Olusoga Sofola who spoke on teaching practical physiology with limited equipment. The morning continued with brief talks on how to use stories and narratives to enhance teaching and learning, followed by participants working in small groups to create stories to use in their own teaching. After lunch, each person selected a topic to

AAPS Teaching Workshop small group discussion: Sally Mohamed, Samar Hussein, Doaa Attia El-Said, Menna Allah El-Meniawy, and Roux Saartjie.

AAPS Board: Magda Ibrahim, Roux Saartjie, Anthony Ebeigbe, Prem Gathiram, Olusoga Sofola, Amal M Saeed, Yasser El-Wazir, Frank Mojiminiyi, and M. Faadiel Essop.

AAPS Teaching Workshop attendees and presenters: Tony Macknight, Gary Sieck, Frank Mojiminiyi, Penny Hansen, Mohamed Khaled, Sally Mohamed, and Moamen Rabiee.

discuss in a small group facilitated by an expert in the area. These included such diverse topics as using the internet to promote active learning, creating learning objectives, and active learning in large lectures. Summaries of the small group discussions from morning and afternoon were recorded on posters for all to view and discuss over lunch and at the closing plenary session.

The Congress continued during Sept. 3-5 with a full program of nine invited plenary lectures, two symposia comprising eight invited speakers, and 15 oral presentations and 24 posters from accepted abstracts. The topics ranged from molecular to whole animal research, from analysis of the state of research in Africa to studies of the physiological effects of natural plant extracts. There was an appropriate focus on the pathophysiology of illnesses and medical conditions common in Africa.

Another important aspect of the Congress was the meeting of the AAPS General Assembly at which officers and board members were elected (photo 3). Other key results of the meeting were launching of an AAPS newsletter and scientific journal. The Newsletter will be edited by Professor Yasser El-Wazir (Egypt) and the journal by Professor Anthony B. Ebeigbe (Nigeria). The first issue of the journal will be devoted to the proceedings of this Congress. Five African Physiological Societies participated in the Congress, those of Egypt, Morocco, Nigeria, South Africa, and Sudan. All agreed that the Congress resulted in strengthening of AAPS as a scientific society with regular activities and dues-paying individual members and societies. Formal feedback from attendees of the Teaching Workshop and Congress was universally positive, indicating that the meeting had met its objectives and that AAPS could look forward to a bright future. ❖

Chapter News

Indiana Physiological Society
2nd Annual Meeting

On February 11, 2012, 121 students, fellows, faculty, and industry scientists, came together at the Alumni Center of Ball State Univ. in Muncie, IN for the second annual meeting of the Indiana Physiological Society. The participants came from multiple institutions: Ball State Univ., Indiana Univ. School of Medicine-Muncie, Indiana Univ. School of Medicine, Indianapolis, Indiana Univ. Purdue Univ. Indianapolis, Indiana State Univ., Indiana Univ. Purdue Univ. Fort Wayne, Depauw Univ., and Univ. of Southern Indiana.

The meeting included featured guest speakers, as well as research presentations from graduate students, an afternoon poster session, and an education breakout session. The meeting began with an introduction from the president, Dr. Bonnie Blazer-Yost, in which the theme of the meeting was introduced as "Peak Performance: Mice to Men." She noted the importance of physiology to both classroom teaching and as a research discipline. Following the introduction, the first keynote speaker, Dr. Michael Joyner, Professor of Anesthesiology at the College of Medicine, Mayo Clinic spoke about "Physiology versus Reductionism." His speech beautifully followed the introduction in reminding the audience of the importance of physiology as a science, and set the tone for the meeting. He provided literature examples of what can happen in scientific disciplines when a reductionist approach does not consider the physiology. The keynote speaker was then followed by five student speakers, who presented their research in ten-minute intervals with five minutes of questions. The student speakers were followed by a lively poster session, in which a total of 41 posters were displayed for presentation in the main area of Ball State Univ. Alumni Center.

During the poster session there was an education breakout session led by Dr. Patricia Clark of the Department of Biology at IUPUI. There were three discussion items: pedagogy in physiology classes at the university level; INPhys outreach to K-12 classrooms, including promotion and active participation in PhUn week; and other opportunities for the promotion of physiology and sciences in general.

Opening remarks by President Bonnie Blazer-Yost at the Ball State Univ. Alumni Center.

Keynote Speaker Dr. Michael Joyner (center) with President-elect Derron Bishop (left) and President Bonnie Blazer-Yost (right).

INPhys members examine posters in the Atrium of Ball State University's Alumni Center.

Professors Norma Adragna (left) and Peter Lauf (right) from Wright State Univ. present Julia Hum with the Peter Lauf and Norma Adragna Travel Award.

Following the poster and breakout session, the group reconvened for the second keynote speaker R. Dustan Sarazan, the vice president and chief scientific officer for Data Sciences International. The title of his talk was "In vivo cardiovascular research using chronically instrumented animal models." In his talk he began by enthusiastically discussing his adventures working with whole animal models in research. He mentioned how he traveled and adjusted procedures to different animals, such as giraffes in Africa or bears in Alaska. He then discussed the historical development of devices to study whole animal models from externally mounted equipment to the current status of implanted devices.

After the keynote speaker, the meeting continued with four more student speakers. The day concluded with presentations of awards and the closing statements that included the introduction of the new President-elect, Allan Albig, from Indiana State Univ. and a new councilor, Randall Roper, from Indiana Univ., Purdue Univ. Indi-anapolis. Guest attendees, Professors Peter Lauf and Norma Adragna from Wright State Univ., generously donated money for a travel award to be used for attendance at an APS meeting. Julia Hum won the travel award for her research entitled, "Live imaging of Src activation in osteocytes in response to mechantransduction." Other awards were presented to both undergraduate and graduate students for their research. At this point all

Tanmoy D. Lala, Undergraduate Student Researcher from Depauw Univ. Department of Biology.

Aric King, Undergraduate Student Researcher from Indiana State Univ. Department of Biology.

Meredith Kohr, Graduate Student, Indiana Univ. School of Medicine, Department of Cellular and Integrative Physiology.

Stephanie Flaig, Graduate Student Indiana Univ. Purdue Univ. –Indianapolis Department of Biology.

Ahmed Malik, Graduate Student, Indiana Univ. Purdue Univ., Indianapolis; accepting on behalf of Jeffrey Solzak.

Peter Corridon, Graduate Student, Indiana Univ. School of Medicine Department of Biomolecular Imaging and Biophysics.

the attendees where thanked for being part of such a successful meeting and reminded of how much hard work went into the planning and organizing of the meeting from the officers, council, and the 2012 organizing committee.

It is important to mention that the meeting was made possible by the support from Ball State Univ., which hosted the meeting, and Indiana Univ. School of Medicine-Muncie Campus, as well as sponsors including Data Sciences International, Kent Scientific, JEOL, Carl Zeiss Inc., iWorx, and the American Physiological Society. The generous support provided for two excellent keynote speakers, as well as for food served throughout the meeting and monetary awards for outstanding student projects.

New elected INPhys officers: from left to right Randall Roper (Councilor), Michael Sturek (Past-president), Bonnie Blazer-Yost (President), Derron Bishop (President-elect), and Allan Albig (new President-elect).

Fifteenth Annual Meeting of the Nebraska Physiological Society

The annual meeting of the Nebraska Physiological Society (NPS) was held on Saturday, October 6 at the Frey Conference Suite on the campus of Wayne State College in Wayne, NE. The meeting became the 15th annual meeting of the NPS. The meeting was financially supported by the American Physiological Society (APS), Wayne State College, Kent Science Corporation, Transonic Systems Inc., AD Instruments, World Precision Instruments, Data Sciences International, Novus Biologicals, Molecular Devices, Vernier and the Univ. of Nebraska Medical Center.

Over 90 individuals participated in the scientific/educational conference. The attendees included 27 faculty members, 12 postdoctoral fellows, 17 graduate students, and nine undergraduate students. In addition, 21 teaching professionals also attended. Overall, institutions from Nebraska, South Dakota, Wisconsin and Washington were represented.

The scientific/educational sessions began with welcome from Wayne State College President Curt Frye and opening remarks from Barbara Engebretsen, President of the NPS from Wayne State College.

Following Engebretsen's introductory remarks, the APS-sponsored keynote research address was made by Jerome Dempsey, Medicine, Physiology, Kinesiology and Veterinary Science at the Univ. of Wisconsin-Madison. His presentation was entitled "Humans in Hypoxia: The Good, the Bad and the Ugly." Dempsey's presentation was followed by a break in which attendees were able to visit exhibitor booths and view posters. Barbara Goodman then gave the Vernier-sponsored educational address from Physiology at Sanford School of Univ. of South Dakota. Her talk was entitled, "Use of Inquiry to Enhance Student Learning."

Following Goodman's presentation, NPS oral presentations were made—one oral presentation selected from undergraduate, graduate and postdoctoral categories based on merit. The first presenter was Murali Ganesan, Department of Internal Medicine/DEM at the Univ. of Nebraska Medical Center. His talk was entitled "Thromboxane—Prostanoid Receptor Deficiency Reduces Adipose Tissue

Noah Marcus, winner of the Lee Zucker Award with President Dr. Engebretsen.

Graduate Student Poster Awardee, Cassandra Hays with President Dr. Engebretsen.

Undergraduate Student Poster Awardee, Trent Ahlers with President Elect, Dr. Fassbinder-Orth.

Dr. Engebretsen recognizing teacher participation at the NPS meeting.

Macrophage Accumulation and Systemic Insulin Resistance in Obesity." This was followed by a talk by Tamra Llewellyn, a graduate student from Department of Cellular and Integrative Physiology at the Univ. of Nebraska Medical Center. Her presentation was entitled "Exercise Training Normalizes SFO-Mediated Sympathoexcitation." The third speaker was Carrie Brown, an undergraduate student from Wayne State College. Her presentation was "Activity and Frequency of the ITPA P32T Variant Among Colorectal Patients."

After the student and postdoctoral presentations, two concurrent breakout sessions took place. Ed and Lee Brogie from Wayne Middle School, Joe Myer from Norfolk, NE, and Jim Rynearson from Vernier, coordinated a teaching workshop about "Teaching Physiology Concepts with Vernier Data Acquisition System for Outreach and Education". The workshop was conducted by Engebretsen, Harold Schultz, Univ. of Nebraska Medical Center, Karla Haack, Univ. of Nebraska Medical Center, Tammy Evetovich, Goodman and Jim Rynearson from Vernier.

The second workshop was organized for undergraduate student, graduate student and postdoctoral research associate and was entitled "What's Next? Career and Professional Development for Trainees." The panelists included: Tamra Llewellyn and Erin Rosenbaugh (graduate students, Univ. of Nebraska Medical Center), Kelly Pitts, (Corgenix Medical Corporation; current Chair of the APS Physiologists in Industry Committee), Matthew Zimmerman, (Associate Professor of Physiology, Univ. of Nebraska Medical Center), Shawn Pearcy, (Professor of Biology, Wayne State College), Noah Marcus, (Postdoctoral Research Associate in Department of Cellular and Integrative Physiology at the Univ. of Nebraska Medical Center). This workshop was very well attended and produced a great deal of discussion and interest.

Lunch immediately followed the workshops. During the lunch period, attendees also joined the Table Talks with some of the speakers: Dempsey, Goodman, Swenson, Viswanathan, Zimmerman and graduate student Alicia Schiller.

The afternoon sessions commenced with the NPS keynote research address by Erik Swenson, from the Department of Medicine and Physiology and Biophysics at the Univ. of Washington. Swenson's talk was entitled "Acetazolamide and High Altitude Illness: New Appreciation for an Old Hand." This was followed by a two-hour period devoted to poster viewing and judging. During the poster viewing, teachers attended additional sessions. ADinstruments had a representative to demonstrate online LabTutor.

Following the poster session, Saraswanthi Viswanathan, from the Departments of Internal Medicine & Physiology at the Univ. of Nebraska Medical Center gave the NPS local scientist research address. Her talk was entitled "Inflamed Fat: Does Oxidative Stress Start with Fire?"

The afternoon session concluded with poster awards and recognitions. The winner of the undergraduate division received a $500 travel award to present his/her poster at the 2013 Experimental Biology meeting in Boston, MA. The undergraduate winner was Trent Ahlers from Life Science Department at Wayne State College for his poster entitled "Activation of the Glucocorticoid Receptor by Dexam-ethasone Enhances BHV-1 Productive Infection."

The winner of the graduate division received a $250 travel award to present his/her poster at the 2013 Experimental Biology meeting in Boston, MA. The graduate winner was Cassandra Hays from the Departments of Ophthalmology and Visual Sciences & Cellular and Integrative Physiology at the Univ. of Nebraska Medical Center for her poster entitled "Outflow Facility Effects of Two Novel Glaucoma Drainage Devices in Human Ocular Anterior Segments."

The winner of the postdoctoral division received a $250 Lee Zucker Award. The postdoctoral winner was Noah Marcus from the Department of Cellular and Integrative Physiology at the Univ. of Nebraska Medical Center for his poster entitled "Carotid Body Denervation Attenuates Increased Sympathetic Nerve Activity in Congestive Heart Failure." In addition, the speakers received a certificate and the students received a gift for their participation in this year's meeting.

Cindy Norton, Executive Director of NPS from the Univ. of Nebraska Medical Center, received a gift from Engebretsen and Lambert for acknowledgement of her service to the NPS.

Graduate Students participating at the Nebraska Physiological Society Meeting.

At the conclusion of the meeting, the NPS business meeting was called to order and chaired by NPS President, Engebretsen. Karla Haack gave a presentation on outreach activities over the past year. This was followed by an update on the APS Chapter Advisory Committee activities and the chapter grant program reporting by Engebretsen for Harold Schultz. NPS Secretary/Treasurer Hong Zheng from the Univ. of Nebraska Medical Center then gave the treasurer's report and this was followed by Science Policy Liaison report by graduate student Alicia Schiller from the Univ. of Nebraska Medical Center. Engebretsen presented the Past-President Award to Patrick Lambert from Creighton Univ. for his service to the NPS.

The NPS council members for 2012-2013 were then announced. President: Keshore Bidasee, Univ. of Nebraska Medical Center; Past-President: Engebretsen; President-Elect: Carol Fassbinder-Orth, Creighton Univ.; Councilors: Yifan Li, Univ. of South Dakota; Matthew Zimmerman, Univ. of Nebraska Medical Center; Babu Padanilam, Univ. of Nebraska Medical Center; and Student Councilor: Alicia Schiller.

Final remarks were then made by Engebretsen and the meeting was adjourned. ❖

Fourth Annual Meeting of the Tennessee Physiological Society

The Tennessee Physiological Society (TPS) held its 4th annual meeting on October 19, 2012 at the Millennium Maxwell House Hotel in Nashville, TN. The meeting was hosted by the Department of Physiology at Meharry Medical College. Attendees included 25 faculty and 75 students/postdoctoral fellows from Belmont Univ., East Tennessee State Univ., Meharry Medical College, the Univ. of Tennessee Health Science Center at Memphis, and Vanderbilt Medical School.

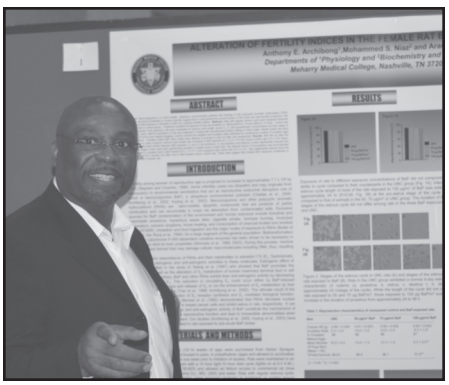
The meeting began with opening remarks by Dr. Zhongmao Guo, president of TPS in 2012, and Dr. Hubert Rucker, Chairman of the Department of Physiology at Meharry Medical College. The morning sessions featured three faculty lectures and three graduate student oral presentations. The titles of the three faculty lectures were: "The Central Melanocortin System: Roles in Energy Homeostasis, Obesity, Growth and Vertebrate Evolution;" "Regulation of Cerebral Blood Flow by Endogenous Hydrogen Sulfide;" and "Estrogen Regulates Astrocytic Glutamate Transporters: Mechanism for Estrogen-induced Neuroprotection." These lectures were given respectively by Roger Cone, Professor and Chairman of the Department of Molecular Physiology at Vanderbilt Univ.; Charles Leffler, a Distinguished Professor of Departments of Physiology and Pediatrics at the Univ. of Tennessee Health Sciences Center; and Eunsook Lee, Assistant Professor of Department of Physiology at Meharry Medical College.

The three student oral presentations included: "Stabilizing rescued δf508 CFTR at the plasma membrane by potentiation of its interaction with Na+/H+ exchanger regulatory factor 1," presented by Kavisha Arora, Univ. of Tennessee Health Sciences Center; "Dysfunction in mTORC2/Akt signaling disrupts brain D2R signaling and DA homeostasis," presented by Olga Dadalko, Vanderbilt Univ.; and "Restoration of function to CXT-damaged mouse ovary using NPBC," presented by Letitia Lyons, Meharry Medical College.

The symposium continued in the afternoon with a poster session. A total of 32 posters were displayed and discussed. Following this poster session, attendees reconvened for the APS-sponsored Keynote Lecture delivered by Adebayo Oyekan, Professor and Director of the Center for Cardiovascular Disease at the College of Pharmacy and Health Sciences Texas Southern Univ. His lecture was entitled "PPARα and hypoxia as regulators of renal function and blood pressure". In his talk, Oyekan addressed the molecular mechanisms underlying the protective role of PPARα on salt-sensitive hypertension and consequent renal injury. Specifically, activation of PPARα up-regulates the expression of nitric oxide synthase and heme oxygenase 1, which elevate the generation of nitric oxide, bilirubin and carbon monoxide. These molecules reduce vascular tone, increase renal blood flow and glomerular filtration rate and increases sodium excretion, and therefore relieving hypertension and renal injuries induced by high salt loading and hypoxia.

A brief business meeting followed the keynote lecture. Belmont University was voted to hold the 5th TPS meeting in 2013. Thereafter, three student awards were announced. During the meeting, the student oral and poster presentations were evaluated by four judges who selected two graduate students for TPS travel awards to be used for the EB2013 meeting, and one high school student for the best undergraduate/high school student presentation award. The P.K. Lauf and N.C. Adragna Travel fellowship award went to Olga Dadalko. The American Physiological Society Travel Fellowship Award went to Laura Buckman who presented a poster entitled: Obesity is associated with elevated plasma s100b which is

The audience is listening to Dr. Charles Leffler's lecture.



Dr. Anthony E. Archibong (Associate Professor, Meharry Medical College) presents his research.

Ms. Olga Dadalko (graduate student, Vanderbilt University) presents her research.

reduced following weight-loss associated with roux-en-y gastric bypass surgery. Finally, the Best Undergraduate/High School Student Presentation Award went to Cole Pickney. His poster was entitled: Assessing the role of the MC3R in fat deposition post ovariectomy.

The 2012 TPS meeting was made possible by financial support from the Department of Physiology at Meharry Medical College. We are grateful to the Department of Physiology office staff, especially Ms. Ella Hamilton and Ms. Linda Nelson, who managed local arrangements including scheduling conference rooms, poster session space, and food and beverages served throughout the meeting (reception, breakfast, lunch, coffee breaks, etc.), and printing the meeting program. Corporate sponsorships were received from Southern Scientific and Mid-West Scientific (MidSci) for the best undergraduate/high school student award. The American Physiological Society provided funding to support the keynote speaker and student travel awards. ❖

Student award recipients and past and current TPS officers: Dr. Donald B. Thomason (TPS2010 president), Dr. Kate Ellacott (TPS Treasurer), Dr. Eric Delpire (TPS2009 president), Mr. Cole Pickney (the Best Undergraduate/High School Student Presentation Award winner), Ms. Laura Buckman (American Physiological Society Travel Fellowship Award winner), Dr. Tom Ecay (TPS2011 president), and Dr. Zhongmao Guo (TPS2012 president).

Publications

New Editorial Board of *Physiology*

The new Editorial Board of the journal *Physiology*, under the leadership of Editor in Chief, Gary Sieck had its first meeting October 8-9, 2012 in Bethesda, MD. Gary Sieck assumed the leadership of the journal as of July 1, 2012. The Editorial Board meets annually to propose and discuss topics and authors suited for publication in *Physiology*. Authors of topics deemed by the Board to be timely and meritorious are invited to submit papers on the specific topic. Changes afoot include short, snappy article titles and bimonthly publication schedule changing to the release of issues in January, March, etc. ❖

Caption: Gary Sieck, EIC *Physiology*, and Editorial Board in Bethesda, MD. Back: Benedito Machado; April Larson (editorial assistant); Siqi Liu; Carlos Mantilla; Jane Reckelhoff; Ole Petersen; Pam Lucchesi; Gary Sieck; Rolf Hubmayr; Michael Spyer; Asrar Malik. Front: Virginia Miller; Shirley Kingsley-Berg (editorial assistant); Nanduri Prabhakar; Joey Granger; Hannah Carey Merryn Tawhai; Hsaio Chang Chan; Tobias Wang. *Not pictured:* David Allen; Roger Enoka; Jeffrey Fredberg; Gabby Haddad; Amira Klip; Heini Murer; Rita Scheman (APS Director of Publications).

New Regular Members

***transferred from student membership**

Melissa W. Acosta
Acosta Patent & Consulting, TX
Todd Alexander
Univ. of Alberta, Canada
Fahaid Hassan Al-Hashem
King Khalid Univ., Saudi Arabia
Lise Wogensen Bach
Aarhus Univ., Denmark
Manuj Kr. Bharali
Rajiv Gandhi Univ., India
Andrea Bonetto
Thomas Jefferson Univ., PA
Trevor N. Brown
Helmholtz Ctr. Environ.Res., Germany
Adam J. Case
Univ. of Nebraska
Yoshihiko Chiba
Hoshi Univ., Tokyo, Japan
Havovi Chichger
Brown Univ., Providence, RI
Robert H. Chow
Univ. of Southern Calif., Los Angeles
Gin C. Chuang
Louisiana State Univ., New Orleans
Wellington Da Silva Cortes
Fed. Rural Univ., Rio De Janeiro, Brazil
Antonio Crisafulli
Univ. of Cagliari, Italy
Tracy Criswell
Wake Forest Univ., NC
Stuart F. Cruickshank
Robert Gordon Univ., Aberdeen, UK
Mei-Zhen Cui
Univ. of Tennessee, Knoxville
Lisa M. Curtis
Univ. of Alabama, Birmingham
AL Zachary J. Domire
East Carolina Univ., Greenville, NC
Jakob Kisbye Dreyer
Univ. of Copenhagen, Denmark
Joseph Wayne Duke
Univ. of Oregon
Darin James Falk
Univ. of Florida, Gainesville
Timothy J. Fort
Valdosta State Univ., GA
Michael A. Freed
Univ. of Pennsylvania
Philip Michael Gallagher
Univ. of Kansas, Lawrence
Kathleen Gavin
Univ. of Colorado
Debebe Gebremedhin
Medical College of Wisconsin
Junhong Gui
Yale Univ., New Haven, CT
Sachin A. Gupte
Univ. of South Alabama, Mobile
Peter Hajdu
Univ. of Cincinnati, OH
Guichun Han
Texas A&M Univ.
Samantha Paige Harris
Univ. of California, Davis
Jeffrey Robb Holt
Boston Children's Hosp., MA
Pamela J.Hornby
Janssen Pharmaceutical J&J, PA
Devin Horton
Univ. of Utah, Salt Lake City
Xin Huang
Univ. of Wisconsin, Madison
Nicholas Michael Hurren
Univ. of Texas Med. Branch, Galveston
Robert Hyldahl*
Brigham Young Univ., UT
Joseph Michael Hyser
Baylor College of Med., TX
Patrick Y. Jay
Washington Univ., St. Louis, MO
Quan Jiang
Univ. of Hong Kong
David Eric Kling
Boston College, MA
Mary Kotlarczyk
Univ. of Pittsburgh, PA
Gabriel Kreiman
Boston Children's Hosp., MA
Renee Labiris
McMaster Univ., Canada
Michael S. Landy
New York Univ., NY
Jen-Wei Lin
Boston Univ., MA
Hesheng Liu
Massachusetts Gen. Hosp., Charlestown
Ruijie Liu
Cincinnati Children's Hosp., OH
Isao Matsui
Osaka Univ., Japan
Takashi Matsui
Univ. of Hawaii, Honolulu
Takaaki Matsumoto
Chukyo Univ., Toyota, Japan
Christopher Mazzochi
Active Life Scientific, CA
Hiroshi Mihara
Univ. of Toyama, Japan
Catherine R. Mikus*
Duke Univ., NC
Sabyasachi Moulik
Univ. of Prince Edward Isl., Canada
Robyn Maree Murphy
La Trobe Univ., Australia
Michael Muskulus
Norwegian Univ. of Sci. and Tech.
Toru Nabika
Shimane Univ., Izumo, Japan
Tetsuji Nakamoto
Kyushu Dental College, Japan
Genevieve Nguyen
Center for Interdisciplinary Res. in Bio., Paris, France
Syotaro Obi
Univ. of Tokyo, Japan
Jeb Orr
Vanderbilt Univ., TN
Alejandro Ortiz-Acevedo
Univ. of Puerto Rico, Mayaguez
Christina Pabelick
Mayo Clinic, Rochester, MN
Dinesh Pal
Univ. of Michigan
Frank Palermo
Univ. of Colorado, Boulder
Melissa Pangelinan
Rotman Res. Inst., Toronto, Canada
Anthony M. Payne
Quinnipiac Univ., Hamden, CT
Claire M. Peppiatt-Wildman
Univ. of Kent, UK
Brenda J. Peters
St. Ambrose Univ., Davenport, IA
Paolo Pianosi
Mayo Clinic, Rochester, MN
David Anthony Power
Austin Health, Heidelberg, Australia
Chris Royer
Lovelace Respiratory Res. Inst., NM
Byungkyu Ryu
Korea Univ., Gyeonggi-Do, Republic of Korea
Grazyna Barbara Sadowska
Woman & Infants' Hospital, RI
Adeel Safdar
Harvard Med. School, Boston, MA
Enrico Schulz
TU München, München, Germany
Stephanie Schulz
Stanford Univ., CA
Jessica Scott
NASA Johnson Space Center, TX
Madhulika Sharma
Univ. of Kansas
Brian J. Siroky
Cincinnati Childrens' Hosp., OH
David Anthony Stoltz
Univ. of Iowa
Sun-Sang Joseph Sung
Univ. of Virginia
Masakazu Suzuki
Shizuoka Univ., Japan
Xiaoyue Tan
Nankai Univ., China
Jordan Taylor
Princeton Univ., NJ
Jennifer A. Teske
Univ. of Arizona
Binu Tharakan
Texas A&M Univ., HSC

American Physiological Society
Professional Skills Training
2013 Course Calendar

January
Writing and Reviewing for Scientific Journals
4-Day Live Course

February
Presenting a Scientific Poster
7-Day Online Course

March
Networking at a Scientific Meeting
7-Day Online Course

April
Experimental Biology

May
Interviewing for an Academic Position
10-Day Online Course

June
Writing and Reviewing for Scientific Journals
6-Week Online Course

July
Writing and Reviewing for Scientific Journals
6-Week Online Course

August
Writing and Reviewing for Scientific Journals
6-Week Online Course

September
Interviewing for an Industry Position
10-Day Online Course

October
Abstract Writing for Scientific Meetings
7-Day Online Course

November
Creating a Poster for a Scientific Meeting
7-Day Online Course

December
Find PST on Facebook:
facebook.com/APS.PST
Watch for the 2014 Calendar

Course availability dependent on enrollment.

Visit our Website for More Information and Deadlines:
http://www.the-aps.org/PST

Join APS at Experimental Biology 2013!

APS Annual Meeting
April 20-24, 2013

Abstract Deadline: Thursday, November 8, 2012
Early Registration Deadline: Friday, February 22, 2013
Housing Deadline: Friday, March 22, 2013

www.experimentalbiology.org

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EB2013 BOSTON

Experimental Biology

Sponsors:

- American Association of Anatomists (AAA) CELEBRATING 125 YEARS!
- The American Physiological Society (APS)
- American Society for Biochemistry and Molecular Biology (ASBMB)
- American Society for Investigative Pathology (ASIP) CELEBRATING 100 YEARS!
- American Society for Nutrition (ASN)
- American Society for Pharmacology and Experimental Therapeutics (ASPET)

April 20-24, 2013

Boston Convention & Exposition Center

9-11-12

Emily Tomayko
Inst. of Medicine, Washington, DC
Gary P. Van Guilder
South Dakota State Univ.
David Alan Vesey
Princess Alexandra Hosp., Australia
Saraswathi Viswanathan
Univ. of Nebraska Med. Ctr.
Kimberly Vogt
Marian Univ., IN
Yuping Wang
Louisiana State Univ., Shreveport
Gang Wang
Weill Cornell Med. College, NY
Amanda K. Welch
Univ. of Florida, Gainesville
Peter Williamson
Univ. of Sydney, Australia
Gunter B. Wolf
Univ. Hospital, Jena, Germany

New Graduate Student Members

Al-Shaimaa Ahmed
Univ. of Calgary, Canada
Puneet Arora
New York Chiropractic College
Brittni Baynes
Lousiana State Univ., HSC
Austin Basil Bigley
Univ. of Houston, TX
Lance Bollinger
East Carolina Univ., NC
Sarika Chaudhari
Univ. of North Texas, HSC
Jennifer Marie Colon
Univ. of Puerto Rico School of Med.
Elisabeth Cook
California State Univ., San Bernardino
Emily J. Cox
Washington State Univ.
Jennifer Dolan
State Univ. of New York, Buffalo
Andrea Michelle Du Bois
California State Univ., Fullerton
Anthony Adam Duplanty
Univ. of North Texas
Lucien Daniel Durosier
Ctr. De Research Hospital Sainte, Justine, Canada
Rui Feng
Univ. of Cincinnati, OH
Justin Fletcher
Univ. of Missouri
Daniel Gamu
Univ. of Waterloo, Canada
Zachary Aaron Graham
Univ. of Kansas
Jonathan Gumucio
Univ. of Michigan
Jamie Hibbert
East Carolina Univ., NC
Brenna Renee Hill
Penn State Univ.
Miara Akiel Jeffress
Howard Univ., Washington, DC
Lawrence Cody Johnson
Univ. of Colorado, Boulder
Danielle Jin-Kwang Kim
Penn State Univ.
Aimee M. Layton
Columbia Univ., NY
Alessandro Da Costa Machado
Univ. Federal Fluminense, Brazil
Neysha Martinez-Orengo
Ponce Sch. of Med. & Health Scis., Puerto Rico
David Maurer
Penn State Univ.
Niranjana Natarajan
Johns Hopkins Univ., MD
Pia O'Neill
Columbia Univ., NY
Girija Regmi
Oklahoma State Univ.
Chance William Reinhart
Univ. of Alberta, Canada
Megan Kathleen Rhoads
Univ. of Kentucky
Ruben Rodriguez
Univ. of California, Merced
Michael Schumacher
Univ. of Cincinnati, OH
Muhammad Asadullah Siddiqui
Queen Margaret Univ., UK
Alexander C. Sutton
Albany Medical College, NY
Lykke Sylow
Univ. of Copenhagen, Denmark
Marc Tuazon
Rutgers Univ., NJ
Benjamin Yaden
Eli Lilly and Company, IN
Johnny Yang
California State Univ., San Bernardino
Thomas Yarbrough
Univ. of South Alabama

New Undergraduate Student Members

Carissa Chamney
Drake Univ., IA
Vinh Dang
Michigan State Univ.

New Affiliate Members

Rachel Marie Firkins
Des Moines Univ., IA
Christopher Matthew Trimby
New Jersey Inst. of Tech.

Recently Deceased Members

Leon Cudkowicz
Highland, OH
Joe M. Dabney
Gaithersburg, MD
George D. Davis
New Orleans, LA
Bjorn Folkow
Goteborg, Sweden
Arthur B. French
Ann Arbor, MI
Robert W. Hamilton
Tarrytown, NY
Francis M. Knapp
Rancho Santa Fe, CA
John B. Stokes, III
Iowa City, IA

2012 APS Conference

Autonomic Regulation of Cardiovascular Function in Health and Disease
Omaha, NE, July 7-10, 2012

The 2012 APS Conference Autonomic Regulation of Cardiovascular Function in Health and Disease was held in Omaha, NE. The conference took place over three days at the downtown Hilton Omaha hotel. The Organizing Committee included Irving H. Zucker, Chair; Kaushik P. Patel, Co-Chair; and Harold D. Schultz all from the Univ. of Nebraska Medical Center, as well as Michael J. Joyner from The Mayo Clinic. The committee organized a program that included symposia, three plenary lectures, oral presentations for students and postdoctoral fellows, interactive poster sessions, a career session, and social networking opportunities that made the conference a valuable experience for those who attended.

The conference was attended by 111 total registrants: of whom 30% of registrants were represented by young scientists, including 11 postdoctoral and 22 students. Thirty-one (28%) attendees identified themselves as APS members, and 17 (15%) registered as non-members; invited chairs and speakers made up the remaining 30 (27%) attendees. Table 1 (below) shows the breakdown of the different registration types. This conference also attracted registrants from outside the United States. Out of the 111 registrants, 11 (19%) represented countries from Australia, Brazil, Canada, China, Japan, Norway, Taiwan and the United Kingdom.

The conference program consisted of three plenary lectures and eight symposia on a wide variety of topics related to autonomic regulation in cardiovascular related to physiology, including a novel session called the Gladiator Session, which included a hot discussion on the various aspects of autonomic science. The audience was encouraged to share their ideas and thoughts with the speakers at the end of their talks. During the symposia there were oral presentation opportunities for the postdoctoral fellows and students attending the conference. During the conference, Conference Organizer Irving Zucker and APS Executive Director Martin Frank chaired a workshop on writing scientific papers. The conference also had several social activities including a Welcome and Opening Reception, which was designed to give attendees a chance to meet with long time colleagues, create new friendships, and enjoy some hot and cold hor d' oeuves and beverages. There were three afternoon poster sessions where scientists presented their work and discussed their findings with other attendees.

A total of 75 abstracts were submitted for the conference. Sixty of these abstracts were programmed as poster presentations. The remaining 15 abstracts were submitted by invited speakers. Of the abstracts submitted for the conference, 18 (24%) were submitted by a female first author; 22 (29%) were submitted from institutions outside of the United States, including six abstracts from China, four from Brazil, three from Taiwan, two each from Canada and the United Kingdom and one each from Hungary, Nigeria, Norway, Russia, and Thailand.

Conference Organizer Irving Zucker prepares for battle during the Gladiator Session.

On Tuesday evening, Zucker hosted the Banquet and Awards Presentation Dinner. Attendees gathered at the Joslyn Art Museum located in downtown Omaha for dinner, wine and conversation. During the event, five postdoctoral fellows and students were recognized as the recipients of the Research Recognition Award for Outstanding Abstract by a Graduate Student or Postdoctoral Fellow. The following individuals were presented with a certificate and cash prize: Stephen

Table 1. Registration Statistics

Registration Type	Number of Attendees (%)
APS Member	31 (28%)
Nonmember	17 (15%)
Postdoctoral	11 (10%)
Student	22 (20%)
Invited Chairs/ Speakers	30 (27%)
Total	**111 (100%)**

Attendees discuss their scientific findings during a poster session.

Travel awardees Tamra Llewelyn (left) and Amy Abbott (second from right) pose with the NIDDK award winners Ronee Harvey (center) and Vanitra Richardson (right) and Conference Organizer, Irving Zucker at the Joslyn Art Museum.

Abbott, Univ. of Virginia; Amy Arnold, Vanderbilt Univ.; Daniel Credeur, Univ. of Missouri, Columbia; Shekhar Deo, Univ. of Missouri, Columbia; and Tamra Llewelyn, Univ. of Nebraska Medical Center.

In addition Ronee Harvey, the Mayo Clinic, and Vanitra Richardson, Univ. of Arizona, were the recipients of the Porter Physiology Development Committee's Minority Travel Fellowship Award, which is provided to encourage participation of under-represented minority students in the physiological sciences. With support from the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), the fellowship provides reimbursement of all expenses associated with travel and participation in the conference. The recipients of the award were matched with APS members: Thomas Lohmeier, Univ. of Mississippi Medical Center, and John Horn, Univ. of Pittsburgh who attended the conference, offered guidance and made introductions to other scientists.

The American Physiological Society and the Organizing Committee gratefully acknowledge the financial support provided though a private donation from Richard Holland and generous educational grants from the Univ. of Nebraska Medical Center, Medtronics Cardiac and Vascular Group, the American Autonomic Society, ADInstruments, Quartzy, NIH, National Institutes of Diabetes and Digestive and Kidney Diseases, Data Science International, and Biocontrol Medical. ❖

2012 APS Intersociety Meeting

The Integrative Biology of Exercise-VI
October 10-13, 2012, Westminster, CO

The 2012 APS Intersociety Meeting, The Integrative Biology of Exercise-VI, was held in the vibrant town of Westminster, CO. Intersociety Meetings are held every four years and offer concurrent symposia and exhibits. This meeting was organized by P. Darrell Neufer (Chair), East Carolina Univ.; Keith Baar, Univ. of California, Davis; Frank Booth, Univ. of Missouri, Columbia; David Brown, East Carolina Univ.; Paige Geiger, Kansas Univ. Medical Center; Mark Hargreaves, Univ. of Melbourne, Australia; Judy Muller-Delp, Univ. of Florida; Michael Joyner, The Mayo Clinic; William Kraus, Duke Univ.; Deborah Muoio, Duke Univ.; Henriette Pilegaard, Univ. of Copenhagen, Denmark; Espen Spangenburg, Univ. of Maryland; and Scott Trappe, Ball State Univ. The program for this 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 45% of the total registrants. APS members made up 21% of the attendees, closely followed by non-members (14%) and sponsoring societies (5%) attendees respectively. Invited speakers and chairs represented the remaining 15% of attendees. This meeting also had a large international presence with some participants coming for the first time to the United States and their first meeting. Out of the 350 registrants, 9% of registrants came from Canada, 10% of registrants represented countries from Europe and 14% from countries such as Australia, Brazil, Japan, India, South Korea, and Thailand. Table 1 shows the breakdown of the different registration types.

The meeting opened with an informal Opening Reception, which gave participants the opportunity to network and catch-up with colleagues while enjoying some delicious hors d'oeuvres. The meeting program allowed for two concurrent symposia each morning and afternoon, with a total of 12 symposia at which many interesting and exciting issues were presented. There was also active participation from the audience, who were encouraged to ask questions or make comments. In addition to the symposia sessions there were also two plenary lectures.

The three day meeting also included three separate poster sessions. During these sessions, established scientists and student attendees presented their abstract work to their colleagues and peers. There were a total of 216 programmed abstracts for the meeting. Out of the abstracts that were submitted, 25% had a female first author; 14% of the submitted abstracts came from countries in Europe, closely followed by Canada with 10% and Japan with 9%. Furthermore, 8% of abstracts also came

Table 1. Registration Statistics

Registration Type	Number of Attendees (%)
APS Member	74 (21%)
Nonmember	49 (14%)
Postdoctoral	33 (10%)
Student	123 (35%)
Invited Speaker	52 (15%)
Sponsoring Societies	19 (5%)
Total	**350 (100%)**

Meeting attendees during one of the poster sessions.

The NIDDK Awardees are presented with a certificate at the closing banquet: APS Executive Director, Martin Frank, Zachary Graham, Nicholas Aguirre, Ana Valencia, and Meeting Organizer, P. Darrell Neufer.

Meeting Organizer, P. Darrell Neufer (left) and APS Executive Director, Martin Frank (far right) congratulate the travel award winners. Travel Award winners L-R are: Katsuhiko Funai, Erin Giles, Michael Stec, Kelsey Fisher-Wellman, Robert Jacobs, and Dara Slopack.

from institutions in Australia, Brazil, and Thailand.

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 a certificate and cash prize. The Postdoctoral winners of the award were: Katsuhiko Funai, Washington Univ. School of Medicine, and Erin Giles, Univ. of Colorado, Denver. The student award winners were: Kelsey Fisher-Wellman, East Carolina Univ., Robert Jacobs, Univ. of Zurich, Switzerland, Dara Slopack, York Univ., Canada, and Michael Stec, Univ. of Alabama, Birmingham.

In addition, the following were the recipients of the Porter Physiology Development Committee's Minority Travel Fellowship Award, provided to encourage participation of under represented minority students: Nicholas Aguirre, Univ. of California, Davis; Olubusayo Awe, Morehouse Univ.; Zachary Graham, Univ. of Kansas; and Ana Valencia, Univ. of Maryland. With support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the fellowship provides reimbursement of all expenses associated with travel and participation in the conference. The recipient is matched with an APS member attending the conference that offers guidance and makes introductions to the other scientists.

The American Physiological Society and the Organizing Committee gratefully acknowledges the financial support provided through generous educational grants from: NIAMSD, NIDDK, Stealth Peptides, GlaxoSmithKline, and Seahorse Bioscience. The American Physiological Society also wishes to thank the co-sponsors, the American College of Sports Medicine and the Canadian Society for Exercise Physiology for their support of this meeting. ❖

Calls for Papers

Current Calls for Papers

Physiological Genomics

Mitochondrial Metabolism

NextGen Sequencing Technology-Based Dissection of Physiological Systems

Technology Development for Physiological Genomics

Journal of Applied Physiology

The Role of Inflammation in Skeletal Muscle, Connective Tissue, and Exertional Injuries: To Block or Not to Block?
(*January 1, 2013*)

Eccentric Exercise
(*February 1, 2013*)

Advances in Physiology Education

Teaching and Learning of Professional Ethics

AJP-Cell Physiology

Cellular Circadian Rhythms
(*December 31, 2012*)

Stem Cell Physiology and Pathophysiology
(*December 31, 2012*)

Proteomic and Metabolomic Approaches to Cell Physiology and Pathophysiology
(*December 31, 2012*)

AJP-Gastrointestinal and Liver Physiology

Physiology and GI Cancer

Intestinal Stem Cells in GI Physiology and Disease

Innovative and Emerging Technologies in GI Physiology and Disease

AJP-Heart and Circulatory Physiology

Mitochondria in Cardiovascular Physiology and Disease
(*December 31, 2012*)

Pathophysiology of Hypertension (*March 31, 2013*)

AJP-Lung Cellular and Molecular Physiology

Bioenginering the Lung: Molecules, Materials, Matrix, Morphology, and Mechanics

Translational Research in Acute Lung Injury and Pulmonary Fibrosis (*July 1, 2013*)

AJP-Regulatory, Integrative, and Comparative Physiology

Fetal and Neonatal Programming: Epigenetic Modification of Phenotype
(*June 30, 2013*)

Integrative and Translational Physiology: Inflammation and Immunity in Organ System Physiolgy
(*June 30, 2013*)

Integrative and Translational Physiology: Integrative Aspects of Energy Homeostasis and Metabolic Diseases
(*June 30, 2013*)

AJP-Renal Physiology

Renal Solute Co-Transporters and Exchangers
(*July 1, 2013*)

Chronic Kidney Disease and Fibrosis
(*July 1, 2013*)

Renal Acid-Base Physiology
(*July 1, 2013*)

Pathophysiology of Acute Kidney Injury
(*July 1, 2013*)

American Journal of Physiology—Endocrinology and Metabolism

Islet Biology
(*June 30, 2013*)

Novel Aspects of Adipocyte Biology
(*June 30, 2013*)

CNS Control of Metabolism
(*June 30, 2013*)

For a complete list of current Calls for Papers, visit *The Physiologist* website.

PHYSIOLOGY IN PERSPECTIVE: THE WALTER B. CANNON AWARD LECTURE (SUPPORTED BY THE GRASS FOUNDATION)

Michael J. Joyner
Mayo Clinic

"Is Physiology Redundant?"

SATURDAY, APRIL 20, 5:30 PM

HENRY PICKERING BOWDITCH AWARD LECTURE

Johnathan Tune
Indiana Univ. Sch. of Med.

"Translational Insights Into the Regulation of Coronary Blood Flow

SUNDAY, APRIL 21, 5:45 PM

CLAUDE BERNARD DISTINGUISHED LECTURESHIP OF THE APS TEACHING OF PHYSIOLOGY SECTION

Eric Mazur
Harvard School of Engineering and Applied Sci.

"Confessions of a Converted Lecturer"

SUNDAY, APRIL 21, 10:30 AM

HUGH DAVSON DISTINGUISHED LECTURESHIP OF THE APS CELL AND MOLECULAR PHYSIOLOGY SECTION

Amira Klip
The Hospital for Sick Children

"Insulin Signal Transduction Meets Vesicle Traffic via Rab GTPases and Unconventional Myosins"

SUNDAY, APRIL 21, 2:00 PM

ERNEST H. STARLING DISTINGUISHED LECTURESHIP OF THE APS WATER AND ELECTROLYTE HOMEOSTASIS SECTION

Donald E. Kohan
Univ. of Utah Health Sci. Ctr.

"Collecting Duct Endothelium: The Last Word in Sodium and Water Excretion and Blood Pressure Regulation"

SUNDAY, APRIL 21, 3:15 PM

CARL LUDWIG DISTINGUISHED LECTURESHIP OF THE APS NEURAL CONTROL AND AUTONOMIC REGULATION SECTION

Roger A. Dampney
Univ. of Sydney

"Central Mechanisms Regulating Co-ordinated Cardiovascular and Respiratory Function in Stress and Arousal"

MONDAY, APRIL 22, 8:00 AM

SOLOMON A. BERSON DISTINGUISHED LECTURESHIP OF THE APS ENDOCRINOLOGY AND METABOLISM SECTION

Ellis R. Levin
Univ. of California, Irvine

"Extra-nuclear Estrogen Receptors: Functions for Physiology and Patho-Physiology"

MONDAY, APRIL 22, 10:30 AM

EDWARD F. ADOLPH DISTINGUISHED LECTURESHIP OF THE APS ENVIRONMENTAL AND EXERCISE PHYSIOLOGY SECTION

Douglas R. Seals
Univ. of Colorado

"The Remarkable Anti-aging Effects of Aerobic Exercise on Arteries"

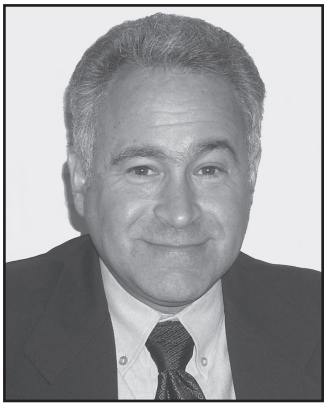
MONDAY, APRIL 22, 2:00 PM

Joseph Erlanger Distinguished Lectureship of the APS Central Nervous System Section

Charles W. Bourque
McGill Univ. and Montreal Gen. Hosp.

"Verney's Osmoreceptor: An Integrated Unit Comprising Ion Channels, Glial Cells and Mechanosensitive Neurons"

Monday, April 22, 3:15 pm



Carl W. Gottschalk Distinguished Lectureship of the APS Renal Section

Jeff Sands
Emory Univ. Sch. of Med.

"Regulation of Renal Urea Transport"

Monday, April 22, 3:15 pm

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

Aron Fisher
Univ. of Pennsylvania Sch. of Med.

"The Serpentine Path to a Novel Mechanism Based Inhibitor of Acute Inflammatory Lung Injury"

Tuesday, April 23, 10:30 am

Robert M. Berne Distinguished Lectureship of the APS Cardiovascular Section

David J. Lefer
Emory Univ. Sch. of Med.

"A Long and Winding Road: The Story of Nitric Oxide in the Heart"

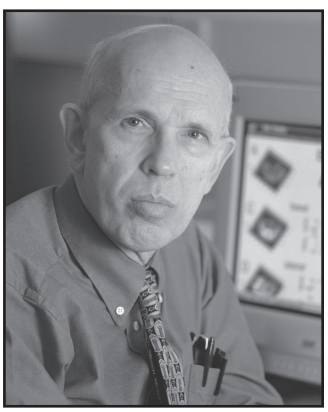
Tuesday, April 23, 2:00 pm

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

Stan Lindstedt
Northern Arizona Univ.

"From Tusko to Titin: Giant Insights from Comparative Physiology"

Tuesday, April 23, 3:15 pm



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

Ole H. Petersen
Cardiff Univ.

"Calcium Signal Mechanisms in Epithelial Cells: Roles in Physiology and Pathology"

Tuesday, April 23, 3:15 pm

APS President's Symposia
Nobel Prize in Physiology or Medicine Lecture

Linda Buck
Fred Hutchinson Cancer Res. Ctr.

"Unraveling Smell"

Wednesday, April 24, 4:45 pm

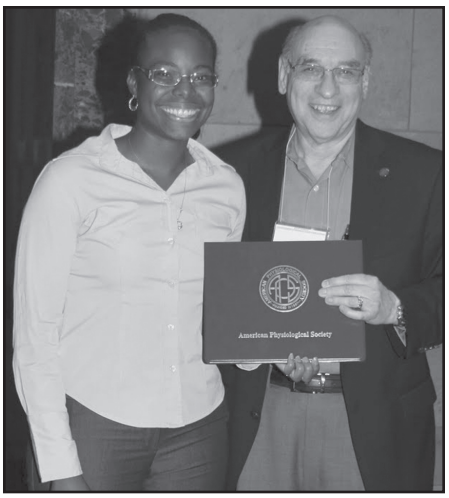
APS/NIDDK Minority Travel Fellows Attend the 2012 APS Conferences

The APS regularly awards Travel Fellowships for underrepresented minority students to attend the APS scientific meetings with funds provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). In the final year of support, these Fellowships provided up to $1,800 in expense reimbursement for meeting registration, transportation, meals, and lodging.

The application reviews were led by Porter Physiology Development and Minority Affairs Committee Members, Maggie Curras-Collazo and Nikki Jernigan. Two applications were funded to attend the "Autonomic Regulation of Cardiovascular Function in Health and Disease" from July 7-10, 2012 at the downtown Hilton Omaha in Omaha, NE (Table 1). Four applicants received funding to attend the "Integrative Biology of Exercise" conference from October 10-13, 2011 at the Westin Westminster Hotel in Westminster, CO (Table 2).

The travel awards are open to graduate students, postdoctoral students, and advanced undergraduate students from minority groups underrepresented in science (i.e., African Americans, Hispanics, Native Americans, and Pacific Islanders). The specific intent of this award is to increase participation of pre- and postdoctoral minority students in the physiological sciences.

Fellows in the APS/NIDDK Minority Travel Fellowship program not only received financial support to attend these meetings, but were also provided professional guidance through pairings with APS members who served as mentors to the Fellows for the duration of the meeting. Thanks to the time and expertise offered by mentor volunteers, Fellows were able to maximize their time and more fully experience the many aspects of this meeting.



Vanitra Richardson, Travel Fellow, and Irving Zucker at the AUTO Conference.

Table 1: Fellows and Meeting Mentors at the 2012 "Autonomic Regulation of Cardiovascular Function in Health and Disease" Conference.

Travel Fellow	Meeting Mentor
Ronee Harvey Mayo Clinic	Thomas Lohmeier Univ. of Mississippi Med. Ctr.
Vanitra Richardson Univ. of Arizona	John Horn Univ. of Pittsburgh

Table 2: Fellows and Meeting Mentors at the 2012 APS Intersociety Meeting, "Integrative Biology of Exercise"

Fellow	Meeting Mentor
Nicholas Aguirre Univ. of California, Davis	Troy Hornberger Univ. of Wisconsin, Madison
Olubusayo Awe Morehouse College	Greg Cartee Univ. of Michigan
Zachary Graham Univ. of Kansas	Keith Baar Univ. of California, Davis
Ana Valencia Univ. of Maryland	Bill Schrage Univ. of Wisconsin

Martin Frank, APS Executive Director, Zachary Graham, Nicholas Aguirre, Ana Valencia, and P. Darrell Neufer, Conference Organizer.

Ronee Harvey, Travel Fellow, and Irving Zucker at the AUTO Conference.

APS UNDERGRADUATE SUMMER RESEARCH FELLOWSHIPS

the-aps.org

Below is a listing of undergraduate summer research fellowships offered by the American Physiological Society. Note that fellowships that specifically target underrepresented students are marked with an asterisk (*). All APS fellowships encourage applications from women and minority trainees.

***Persons underrepresented in biomedical research include:**

- Individuals from underrepresented ethnic/racial groups: American Indians or Alaska Natives, Blacks or African Americans, Hispanics or Latinos, Native Hawaiians or Other Pacific Islanders
- Individuals with disabilities
- Individuals from disadvantaged backgrounds

Undergraduate Summer Research Fellowships

Available to: Undergraduate students

These fellowships support full-time 1st- through 3rd-year undergraduate students with minimal research experience to work 10 weeks in the laboratory of an established APS investigator and to attend the following year's Experimental Biology meeting. The program is open to any undergraduate worldwide. Fellows receive $4,000 stipend and up to $1,300 in reimbursement for EB travel; hosts receives $300 unrestricted grant.

Application deadline: February 2

the-aps.org/ugsrf

STEP-UP Summer Research Symposium

NEW!

Undergraduate Research Excellence Fellowships

Available to: Undergraduate students

These fellowships support full-time 2nd- through 4th-year undergraduate students with significant research experience to work for 10 weeks in the laboratory of an established APS investigator and to attend the following year's Experimental Biology meeting. The program is open to any undergraduate worldwide. Fellows receive $4,000 stipend and up to $1,300 in reimbursement for EB travel; hosts receives $300 unrestricted grant.

Application deadline: February 2

the-aps.org/ugref

APS STEP-UP Fellowships for Underrepresented Undergraduate Students*

Available to: Undergraduate students

These fellowships support full-time undergraduate U.S. students from groups traditionally underrepresented in biomedicine (e.g., from disadvantaged backgrounds and certain racial and ethnic groups and individuals with disabilities) to work for 8-12 weeks in the laboratory of an established APS investigator working in an National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) related area. Students will also attend a STEP-UP symposium at the end of the summer with other STEP-UP fellows from across the U.S. Fellows receive $3,500 stipend and reimbursement for travel to the STEP-UP meeting.

Application deadline: February 22

the-aps.org/stepup

STEP-UP Summer Research Symposium

NEW!

APS STRIDE Fellowships for Underrepresented Undergraduate Students*

Available to: Undergraduate students

The APS STRIDE fellowship provides hands-on summer research experience for underrepresented undergraduate students interested in exploring biomedical research careers. The program provides exposure to the core National Heart, Lung, and Blood Institute (NHLBI) mission areas of cardiovascular, pulmonary, hematologic, and sleep disorders research. Fellows receive $4,000 stipend and up to $1,200 in reimbursement for EB travel; hosts receive $500 unrestricted grant. Accommodations are available for students with disabilities.

Application deadline: February 2

the-aps.org/stride

NEW!

APS IOSP Fellowships for Underrepresented Undergraduate Students*

Available to: Undergraduate students

The APS Integrative Organismal Systems Physiology (IOSP) fellowship provides hands-on summer research experience for undergraduate underrepresented students interested in exploring comparative and evolutionary biology research careers. The program provides exposure to IOS mission areas of comparative and evolutionary research. Fellows receive $4,000 stipend, $1,050 subsistence, and up to $750 in reimbursement for EB travel; hosts receive $500 unrestricted grant. Accommodations are available for students with disabilities.

Application deadline: February 2

the-aps.org/iosp

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How to Believe in Others (and Other Musings on Mentoring)

Kim E. Barrett
Univ. of California, San Diego, School of Medicine, La Jolla, CA 92093

In April 2012, I received the Bodil M. Schmidt Nielsen Distinguished Mentor and Scientist Award from the APS, one of the most gratifying honors I have been blessed with in my career to date. It was truly humbling that colleagues, trainees from my lab, and others I have mentored in less formal settings, were willing to take the time to write letters on my behalf, and thrilling that the Women in Physiology Committee selected me on the basis of these letters among what I am sure was a group of at least equally deserving colleagues. While I can personally take pride in the scientific contributions that my group has made over the years, I know that none of these would have been possible without the dedicated efforts of our entire team, from undergraduates to visiting professors. Further, these research contributions, in my view, are not nearly as important as the fact that I have been able to contribute to the career development of the next generation of scientists.

As for most people, my approach to and passion for mentoring have been immensely shaped by my own positive experiences with a series of talented mentors. I was a very shy child and teenager, but my teachers—and especially Valerie Tickner, Elsa Cameron, Ann Parkin and Gill Ellis—had great confidence in me and supported my development as a fledgling scientist. They provided me with the confidence to consider university, which was a path for only a small minority in 1970's England and an unknown world to my parents, neither of whom even finished high school in wartime London. In particular, my high school chemistry teachers, Ann and Gill, alerted me to opportunities to explore different colleges such as a two day introductory course at the one I finally selected, Univ. College London. It was at this event that I met my next influential mentor, Fred Pearce, at that time a young faculty member in the Department of Chemistry. My group was assigned to work with him on a lab exercise and I was very impressed (and a little star-struck) by his ability to ask the sorts of questions about our results that allowed us to build our own understanding. I was horrified, therefore, at

Kim E. Barrett

the last social gathering of the course, to spill an entire cup of steaming tea down his front. I was truly mortified, and even more so when I arrived for an interview for a place at UCL about a year later and realized to my utmost dismay that Fred would be my interviewer. However, he betrayed no evidence that he remembered the tea debacle, and set about putting me at ease and recruiting me to the school. He later became my PhD supervisor, and remains to this day a trusted advisor, all-round supporter, and friend.

Of the many things Fred taught me, one was probably most important for the next stage of my life and career. He encouraged me to seek postdoctoral training in the US with the admonition that I would need to "put myself about a bit," a soccer phrase encouraging players to chase the ball that also implies the need to personally make sure that people register your existence and contributions. Initially, this did not come easily, but my other key mentors through my postdoctoral fellowship and early faculty years in San Diego—Dean Metcalfe, Kiertisin Dharmsathaphorn, Steve Wasserman and Jon Isenberg—ensured that I would not be allowed to retreat into my shell. There is a substantial literature showing that women (and underrepresented minorities) in academia are particularly susceptible to the "imposter syndrome" and my shyness certainly ensured that I was not immune to this. However, each of my mentors proactively identified opportunities for me to contribute that further bolstered my confidence. It is notable, moreover, that none of my formal mentors after leaving school have been women. In part, this reflects the paucity of women, at least initially, in my

Dr. Kim Barrett, a native of the United Kingdom, obtained her B.Sc. and Ph.D. degrees from the Department of Chemistry at University College London. Following a post-doctoral fellowship at the National Institutes of Health, she joined the faculty of UCSD School of Medicine in 1985, and rose to her current rank of Professor of Medicine in 1996. Her research interests center on the normal and abnormal biology of the intestinal epithelium and their relevance to a variety of digestive diseases including inflammatory bowel diseases, infectious diarrheal diseases, and peptic ulcer disease. She has received a number of honors for her research, including the Bowditch and Davenport Lectureships of the American Physiological Society, the McKenna Lectureship of the Canadian Association of Gastroenterology, and the degree of Doctor of Medical Science, honoris causa, from Queens University Belfast. She is the author or editor of several books and monographs, including Gastrointestinal Physiology *(McGraw-Hill, 2006) and more than 200 peer-reviewed journal articles, book chapters and reviews. She has also been highly active in professional societies and in scholarly editing. She is President-Elect of the American Physiological Society and will begin a one-year term as President in 2013. She was Chair of the APS Publications Committee for six years, which involved oversight of the Society's 14 journals and adjudication of all ethical issues arising in the journals. She is also the past Editor-in-Chief of* American Journal of Physiology-Cell Physiology *and the current Deputy Editor-in-Chief for the* Americas of Journal of Physiology, *among other editorial assignments.*

chosen field. However, it is important to remember that your mentor does not need necessarily to have shared your life experiences to be effective—they just have to display a willingness to understand them. I have also received great sustenance from a group of women peers--we all supported each other as we navigated the early hurdles of grants, tenure, papers and the inevitable rejections together.

Another important influence in my professional life has been my involvement with societies--not only the APS, but also the American Gastroenterological Association. The APS and AGA were, and remain, critical in my development not only as a scientist, but also as a confident contributor to my discipline overall. After I had some reviewing under my belt, Kiertisin Dharmsathaphorn suggested that I volunteer myself to serve as an editorial board member on at least one journal where we sought to publish our work. This was how I met Dale Benos, who to my amazement not only added me to the editorial board of *AJP-Cell Physiology*, but a few years later also suggested that I apply to be Editor-in-Chief as his term was ending. I followed Dale into this and many of the roles he served in our society, and learned a huge amount about service, dedication and generosity. We lost this talented and caring individual, himself the mentor to a huge number of trainees and colleagues, way too soon. Sadly, Kiertesin and Jon too are gone after untimely deaths—a reminder that we should take every opportunity to thank people we are grateful to while they are still around to hear it.

This description of my own career development, and especially the talented individuals who showed me the ropes at many pivotal career stages, therefore leads me to the answer to the question posed in the title of this piece. To believe in others, first you have to believe in yourself. Thanks to people who took the time to probe my interests and motivations, and who encouraged me out of my shell, I learned to believe in myself and so have had the privilege of mentoring others in turn. I think the essential attributes called for from a mentor can be summed up as the "triple A," accessibility, adaptability, and appreciation. In the remainder of this article, I will touch on each of these.

First, accessibility. Certainly, this changes over time, but you cannot be effective as a mentor if you can never make time for people. As a junior faculty member, my door was always open. Being just across the hall from the lab, I could often recognize the change in tone that signaled an impending problem by simply listening with half an ear as I worked on proposals and manuscripts at my desk. Now, however, having moved into a full-time administrative position as Dean of Graduate Studies, the majority of my daylight time is spent in an entirely separate building from my lab. But it is still just as critical to ensure undivided attention and focus even if members of my group can no longer just stick their heads around the door and ask to talk. I have learned to schedule meetings with trainees at the beginning or end of the day when I am less likely to be disturbed or distracted, and to make time for both one-on-one meetings and those with the wider group. Electronic communication can help, but it is no substitute for meeting face-to-face. Indeed, from time to time I have had "reluctant mentees" who have used my schedule as an excuse to avoid meeting, often a sign that experiments are not panning out as hoped. I have dealt with these situations by insisting on a series of regular standing meetings. My fantastic assistant also knows that it is critical to make room for the occasional "emergency" contact, which can equally be negative or positive, news about a grant received or a manuscript accepted is most exciting for the teller and for me while still fresh!

In the area of adaptability, like my own career and my own need for mentors, the needs of my trainees have clearly evolved over time, and certainly differ between individuals. Certainly, it is exciting to move from discussing the nuts and bolts of a scientific career to the unwritten rules of the game and future plans. It is also important to judge when it is time to step back and allow your mentee to fly solo, and when to nudge a reluctant fledgling out of the nest. My own mentors were so effective because they gently forced me to do things that I thought I could not, ask questions at meetings, contact prospective collaborators, put myself about a bit…..eventually, even I forgot that I was only pretending not to be shy. The mentor role also implies being open to a trainee's possible changes in career direction. Indeed, one of the saddest things I hear as a Graduate Dean is that many doctoral students are afraid to talk to their advisor if they are contemplating a career that involves anything other than turning into his or her clone. We all have an obligation, in my view, to help students explore the full range of opportunities available to them with the benefit of a doctoral education—and to use our networks to connect our mentees with individuals who can serve as resources in other areas, such as pharma, biotech, or teaching in a small undergraduate college. The APS is also a great starting point for these explorations, with a wealth of on-line resources and programs offered at EB. And while I believe that mentoring can profitably extend for life, sometimes a relationship simply runs its natural course. In these cases, it's fine to end things amicably with a "no-fault divorce" and to pass your mentee along to a colleague who can better serve their needs.

Finally, appreciation. In the early stages, the work you devote to mentoring usually accrues direct benefits to you in the form of data, publications and grants. It costs nothing to make sure that you assign appropriate credit as you get the invitations to speak while your students and post-docs stay behind working hard in the lab. But as your own career evolves and/or the talents of your trainees emerge, the time comes to step back. In my opinion, the mark of a truly effective mentor is to be able to take genuine pleasure in the accomplishments of others (indeed, this is excellent preparation too for the life of an administrator!). I have tried to continue to be generous with my time and advice even when there is no direct benefit to me or, even more importantly, when it may actually cost me something. This does not imply that you need to be a doormat, but it does open an even wider universe of viable mentees, such as junior faculty at my own institution and beyond and, in my current role, staff members. It is just important to remember that while you can play a key role as an impartial outsider with a different vantage point, you are usually a supplement rather than a substitute in the mentoring relationship. However, when I have gotten the balance right, this has certainly been a most satisfying way to give back to the discipline, as well as a really pleasant way to broaden my own personal network.

In closing, therefore, physiology is fundamentally an enterprise of people.

It has been a wonderful opportunity throughout my career to have played some small role in the development of those people, in itself a very substantial reward. I am indeed humbled and grateful to have been recognized publicly for these efforts, particularly with an award that celebrates Bodil Schmidt-Nielsen, the first woman President of the APS and herself without peer as a mentor. As I contemplate my own upcoming tenure as APS President, the fifth woman in this role, I will remind myself of my mentors' advice and hope that I can live up to Bodil's example.

Acknowledgements

In addition to my valued mentors (both those named in this article and those who remain nameless), I am especially grateful to my former mentee and current colleague, Declan McCole, who did the very hard job of pulling the nomination packet together with his characteristic humor and grace. I also am indebted to the colleagues and mentees who wrote on my behalf: Mark Donowitz, Mike Reid, Barbara Jung, Stephen Keely, Fermin Sanchez de Medina Lopez Huerta, Alfred Chappell, Jimmy Chow, Michael Scharl, Melissa Kahn, Pradipta Ghosh, Hui Dong, and Jorge Uribe. I thank the Women in Physiology Committee for selecting me for the award and the APS for sponsoring it, and my assistant, Glenda Wheeler, for generally keeping my work life on track so I have the dedicated time to mentor others. I would also like to acknowledge the colleagues in addition to those listed above for whom I have served as a mentor since my days as a post-doc, including (in approximate chronological order) Tracy Tashof, Eva Szucs, Shalini Shah, Renee Glover, Cindy Bailey, Gianluigi Rossi, An Yen, Richard Quist, Udom Kachintorn, Piapong Vongkovit, Mana Vajanaphanich, Kenley Chin, Taweesuk Buranawuti, Cornelia Gelbmann, Jurgen Stein, Jurgen Ries, Christopher Myers, Jane Smitham, Sean Calandrella, Nelson Chang, Silvia Resta-Lenert, Lone Bertelsen, Zachary Sellers, Biguang Tuo, Alfred Chappell, Raschid Hoda, Wolfgang Tillinger, Michael Scharl, Gisela Paul, Cheryl Stork, Michael Bunz, Ronald Marchelletta, Anouk Van Berkel, Roos Visser, Elise Roel, Rachel Klinkenburg, Harrison Penrose, Taylaur Smith, Nilay Shah, and Melanie Gareau as well as countless other medical students and undergraduates who have helped in our work. Finally, nothing I do would be possible without the support and supreme patience of my loving husband, Peter Pierce.

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To comment on this article, go to http://www.the-aps.org/forum-musings. ❖

Science Policy

Stand Up for Animal Research with the Science Action Network

A new campaign organized by the UK-based Understanding Animal Research (UAR) and the pro-research blog Speaking of Research makes it easy for scientists to voice support for animal research. Dubbed the Science Action Network (SAN), this project collates instances of animal research discussions across the internet and lets participants know where they can make a difference—whether it be by offering kudos to informative discussions or setting straight the misinformation spread by animal rights activists.

Animal rights activists have long mobilized their followers to swamp online discussions with misinformation and spurious accusations. SAN offers a way for the pro-research community to likewise make its presence felt and combat the distortions prevalent on the web. As UAR Interim Chief Executive Tony Causey told The Physiological Society: "We want to make sure that those speaking for research are those who understand the research."

SAN is focused particularly on areas where quick actions can make a difference, asking supporters to take "just five minutes every week" to defend animal research. Most common action requests are for simple steps such as voting in an online poll, signing a petition (like this one: http://tinyurl.com/researchpetition), retweeting information, or adding to an article's comment thread. More involved supporters might delve deeper to email the editors of sites that run misinformation or pen a guest post to explain the scientific value of research and the steps taken to ensure humane care for animals.

There are several ways to become a part of SAN. One is to follow Understanding Animal Research or Speaking of Research on Facebook. This option provides brief updates throughout the week and weekly round-ups of successes and opportunities. Those who are on Twitter can follow the SAN handle @ARnonsenseRT or follow and use the hashtag #ARnonsense—short for "animal rights nonsense." Even without a Twitter account, you can follow #ARnonsense tweets by bookmarking the URL http://tinyurl.com/ARnonsense. ❖

APS Congratulates Society's Newest Nobel Laureate Robert J. Lefkowitz

Robert J. Lefkowitz

The American Physiological Society (APS) congratulates its member Robert J. Lefkowitz, who has been awarded the 2012 Nobel Prize in Chemistry. He will share the award with Brian Kobilka of Stanford University. The researchers were recognized for their groundbreaking work involving G-protein-coupled receptors which has provided an important framework for drug development.

Lefkowitz has been a member of the APS for more than a decade. The physician-scientist is an investigator at the Howard Hughes Medical Institute and is the James B. Duke Professor of Medicine and Biochemistry at the Duke University Medical Center. Kobilka was a postdoctoral fellow in the Lefkowitz laboratory during the 1980s.

In 2001 Lefkowitz was selected to deliver the APS' Perspectives in Physiology: Walter B. Cannon Memorial Lecture, the Society's preeminent award lecture and recognizes an outstanding scientist for their contributions to the field.

The Nobel Prize in Chemistry is awarded by the Royal Swedish Academy of Sciences, Stockholm, Sweden.

APS Members Elected to the Institute of Medicine

The IOM announced the names of 70 new members and 10 foreign associates during its 42nd annual meeting. Three APS members were included in the list of new members: Nancy M. Bonini, investigator, Howard Hughes Medical Institute; and Florence R.C. Murray Professor of Biology, department of biology, Univ. of Pennsylvania, Philadelphia; Donald E. Ingber, Judah Folkman Professor of Vascular Biology, departments of pathology and surgery, Harvard Medical School and Children's Hospital Boston; professor of bioengineering, Harvard School of Engineering and Applied Sciences; and founding director, Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston; and Lloyd B. Minor, dean designate, Stanford Univ. School of Medicine, Stanford, CA. Election to the IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service. The newly elected members raise IOM's total active membership to 1,732 and the number of foreign associates to 112. With an additional 84 members holding emeritus status, IOM's total membership is 1,928.

Charles M. Tipton, Emeritus Professor of Physiology at the Univ. of Arizona, a former APS Councillor and Chair of the EEP Section, received the Clark W. Hetherington Award from the American Academy of Kinesiology, their highest honor, for mentorship of future leaders and for a commitment to scholarship.

Sudip Bajpeyi is now Assistant Professor in the Department of Kinesiology at the Univ. of Texas, El Paso. Prior to this move, Bajpeyi was an Instructor in the Department of Endocrinology at Pennington Biomedical Research Center, Baton Rouge, LA.

Anna Thalacker-Mercer has taken the position of Assistant Professor in the Division of Nutritional Sciences at Cornell Univ., Ithaca, NY. Prior to this move Dr. Thalacker-Mercer was in the Department of Physiology and Biophysics at the Univ. of Alabama, Birmingham, AL. ❖

Positions Available

Physiologist Position

Vertebrate Physiologist: Georgia Southern University's Department of Biology Vertebrate Physiology Position Search #67064 invites applications for a vertebrate physiologist position. The full text advertisement, including information about the department, faculty, and the complete position announcement with all qualifications and application instructions, is available at www.bio.georgiasouthern.edu. The position requires teaching, service, and research responsibilities as well as a terminal degree. We seek a vertebrate physiologist with broad training in physiology and anatomy. The successful candidate's research will address questions in organismal physiology using approaches that integrate multiple levels of organization. The successful applicant will teach undergraduate and graduate courses, including Comparative Animal Physiology. Ability to teach Comparative Vertebrate Anatomy is preferred. Required qualifications: PhD by December 31, 2012; demonstrated excellence in research; potential to attract extramural funding; expertise to teach Comparative Animal Physiology. Preferred *Qualifications:* postdoctoral experience; expertise to teach Comparative Vertebrate Anatomy. Screening of applications begins November 5, 2012 and continues until the position is filled. The preferred position starting date is August 1, 2013. A complete application consists of a cover letter addressing the qualifications cited above; a curriculum vitae; statements of research interests and teaching interests/philosophy; three letters of reference. Applications must be sent electronically as a single PDF attachment (include applicant name in file name); letters of recommendation in PDF format may be sent separately via email. Other documentation may be requested. Only complete and electronically submitted applications will be considered. Finalists will be required to submit to a background investigation. Georgia is an open records state. Georgia Southern is an AA/EO institution. Individuals who need reasonable accommodations under the ADA to participate in the search process should

contact the Associate Provost. Applications and nominations should be sent to Dr. C. Ray Chandler, Search Chair, Search #67064; Email: chandler@georgiasouthern.

Faculty Positions

Department Chair, Pharmacological and Physiological Science: Saint Louis University, a Catholic Jesuit institution dedicated to education, research, service and health care, has started a national search for the next William Beaumont Professor and Chair of the Department of Pharmacological and Physiological Science (http://medschool.slu.edu/pharmphys). The department encompasses multidisciplinary research in the cardiovascular, endocrine and neuroscience areas and has an outstanding record in graduate education supported in part by an NIH-T32 training grant currently in its 22nd year. The department seeks an individual with the vision and leadership to build and maintain robust basic and translational research programs, and continue the strong commitment to graduate and medical education. The successful applicant will have a PhD and/or MD degree, a strong record of academic achievement, a solid level of extramural research funding and experience in both graduate student and medical student education. Interested candidates should submit a cover letter, curriculum vitae and a description of their leadership vision to http://jobs.slu.edu (Req. ID# 20120062). Letters of nomination may be sent by email to Enrico Di Cera, Chair of the Search Committee (enrico@slu.edu). Saint Louis University is an Affirmative Action, Equal Opportunity Employer, and encourages nominations and applications of women and minorities.

Kinesiology Tenure Track Faculty Positions (2); Assistant/Associate Professor Biomechanics; Assistant/Associate Professor Integrative Physiology: For full position details visit the following website: http://www.admin.mtu.edu/hro/facpers/facvac.htm. 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. The university is also in its sixth year of a strategic faculty hiring initiative (see http://ww.mtu.edu/sfhi). We also have a Dual Career Program which assists departments with partner orientation to the university and community and identification of possible positions for partners (see www.dual.mtu.edu). Michigan Technological Univ. is an Equal Opportunity Educational Institution/Equal Opportunity Employer. Michigan Tech is one of four major research universities in the state and is located in the heart of Upper Michigan's scenic Keweenaw Peninsula in Houghton, MI. This rural community is known for its abundant snowfall, beautiful summers, and outstanding four-season recreational opportunities. The university maintains its own downhill ski facility, a nationally recognized cross-country ski trail system, and an 18-hole golf course. The Department of Kinesiology and Integrative Physiology is home to over 130 students. For more information about the department, visit www.mtu.edu/kip. Review of applications will begin Nov 15, 2012 for the Biomechanics position and December 15th 2012 for the Physiology position and will continue until the positions are filled. ❖

Distinguished Physiologists

Letters to Terry Dwyer

Craig Hassler writes: "Sorry for the tremendous delay in my response.

"As with most young people, I headed off for college without any idea what I was going to do with my working life. I started off to be an engineer as was the tradition in my family. However this was not to be and I ended up as a physiologist.

"Following a marvelous stay in the laboratories of Walter Randall (at Loyola-Chicago), for my doctoral work, it was time to find a job. I was recruited by the Battelle Memorial Institute (a large non-profit contract research laboratory. Battelle had won several large government projects relevant the development of an artificial heart. They needed a cardiovascular physiologist and I needed a job which has now extended for 42 years.

"Cardiovascular physiology has been the common thread throughout my career. And physiologic measures have become more integral part of the drug discovery and safety evaluation processes, an area in which Battelle is extensively involved. In addition, I have enjoyed being involved in a wide range of projects not directly related to cardiovascular physiology.

"I have had the pleasure to see cardiovascular physiology grow from smoke kymographs with manual calculation of parameters to the common usage of sophisticated instrumentation such as implantable telemetric devices, automated data collection systems and imaging."

David A. Prince writes: "Thank for your letter of August 13th inquiring about my current activities. I am still an active investigator with support from the NIH. There are four postdoctoral fellows in my lab at the moment and we have continued to do work related to the pathophysiology of epilepsy in animal models. My lab and office are at Stanford Medical Center and we have had a number of interesting recent publications related to mechanisms of cortical synaptic and other activities following traumatic brain injury in a rat model.

"All in all, my academic career in neuroscience has been a gratifying one, particularly in relation to the outstanding group of trainees who have come to the laboratory. This is, after all, the most important thing that a faculty member can do. We recently had a reunion at Asilomar, CA attended by 60 neuroscientists, most of whom received training in our laboratories. Many of these individuals have made major contributions to their fields. It was a most gratifying experience for me as it was also a celebration of my 80th birthday." ❖

Wine Wizard

Hi all:

Between travel and work, opportunities for tasting have become less and less, so I cannot offer you a report of the usual quality you have come to expect. For this I apologize. While I expect to compensate in November when Harrieth and I will be taking a couple of weeks "off" in Barossa and McLaren Vale (South Australia), I am not sure I can provide a useful column in November since the wines we will see in Oz are likely not available in the USA, plus with the equality between USA and AUS dollars, they will have outgrown my budget anyway. But I will try. Just don't hold your breath. Not worth it.

Peter Wagner

White/Rose wines

2010 Villa Maria Sauvignon Blanc "private bin", Marlborough, New Zealand $10. Villa Maria is very dependable. Despite the moniker "private bin" this is their lowest tier effort. Nonetheless, it is great stuff. Typical NZSB with all the ripe gooseberry/lime/citrus flavors, very clean palate, acidity softer than most NZSB but quite enough, viscosity and length we have come to expect from Marlborough. You can pay more, but you probably won't get more.

2011 Chateau Routas Rose, France $10. Not sure from just where this hails but that does not matter. You look at this and are not encouraged – just a shimmer of pink, there cannot be much to this wine. The nose has rose petal and some caramel and is stronger than the wine's pallor predicted. So too the fruit intensity on the palate is surprisingly good with clean citrusy red cherry and raspberry. It is dry, balanced and has good length.

Red wines

2010 Seghesio Zinfandel, Sonoma county, CA $19. While their "lowest tier" zin, it is just as good this year as in past years, and a bit better than the 2009 which I recommended October 2011. It has a young, fresh and forward grapey/raspberry nose, with a touch of oak char. It has excellent red cherry and raspberry fruit, with soft tannin and good acidity. There is no sweetness, but a nice touch of dry herbs. It is very clean, balanced and has good length. It is not an over-extracted wine at all, and has elegance. This is a wine to serve your boss, assuming you like her.

2009 Bitch Grenache, Spain. $9. Truly, that is the name. Don't shoot the messenger. It has a forward floral red raspberry nose with some black pepper. The same features on the palate, and the mouthfeel is very ripe and almost sweet, with intense fruit. Acidity and tannin are balanced, length is reasonable. This is a wine to serve your boss, assuming you do not like her.

2009 Bogle Petite Sirah, CA $8.50. Great value for the price, no question. The nose has blueberries and dark cherries. The palate has very rich, ripe dark fruit flavors which easily cope with the medium high tannins. This is a big, solid, extracted wine. Interesting element of sage and honey can be identified. There is a freshness to the wine. Needs good red meat, to be sure. Note: I said the preceding in the October 2011 column. The 2009 is still on the shelves, I tried it again last week, and the description has not changed, nor has the price. Go for it.

2010 Van Ruitan Zinfandel, Lodi "old vine" $7. 14.8% alcohol, so drive carefully. This is a steal. Floral red berry nose with a touch of oak char; light oak and good red berry fruit on the palate. It not extracted, tannic, overdone or sweet. Just nice and tasty.

2010 Wine Guerrilla Zinfandel, Sonoma County $12. 14.5% alcohol. There is a nice red berry nose followed by a medium weight wine on the palate, with juicy red berries that are ripe and very slightly sweet. It is not tannic or extracted, has very good acidity to balance the ripeness, making it bright and lively.

2009 Point Concepcion Pinot Noir, "Salsipuedes," Santa Barbara, CA $16. This is a big wine, 14.7% alcohol, with a nose of cherry, vanilla and anise. The palate is very forward and rich with dark cherry and plum, spice, modest oak, good acid, light tannin, and a bit of heat at the finish.

Enjoy! It may all you get from me until December. ❖

2013

March 7-10
The 6th International Conference on Ocular Infections (ICOI), Santa Monica, CA. *Information:* Shirley Dinenson, Conference Secretary, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland. Tel.: +41 22 5330 948; Fax: +41 22 5802 953; Email: sdinenson@paragon-conventions.com; Internet: http://www.ocularinfections.com/.

March 10-13
The Jeruslem International Conference on Neuroplasticity and Cognitive Modifiability, Jeruslem, Israel. *Information:* Internet: http://www.brainconference.com/en/.

April 22-23
The 60th International Conference of the Israel Heart Society, Jerusalem, Israel. *Information:* Michal Keinan, 60 Medinat Hayehudim St., Herzliya 46766. Tel.: 972-3-5767738; Email: secretariat@icimeeting.com; Internet: http://www.israelheart.com.

May 17-22
2013 American Thoracic Society International Conference, Philadelphia, PA. *Information:* ATS International Conference Department. Tel.: 212-315-8652; Email: conference@thoracic.org; Internet: http://conference.thoracic.org/2013/.

June 22-25
6th International Conference on Children's Bone Heath, Rotterdam, Netherlands. *Information:* Janet Crompton. Tel.: +44 (0)1453 549929; Fax: +44 (0) 1453 548919; Email: iccbh@ectsoc.org; Internet: http://www.iccbh.org.

June 23-28, 2013
The 34th Annual Meeting of International Society for Gravitational Physiology: Gravita-tional Effects from Micro to Macro Biology, Toyohashi, Aichi, Japan. *Information:* ISGP34@sozo.ac.jp; Internet: http://www2.sozo.ac.jp/~ISGP34/.

June 30 to July 3, 2013
24th International Symposium on Pharmaceutical and Biomedical Analysis (PBA 2013), Bologna, Italy. *Information:* http://www.pba2013.org.

July 15-19
10th World Congress on Neurohypophysial Hormones, Bristol, England. *Information:* Internet: http://www.vasopressin.org/#/wcnh-x/4014208.

July 21-26
37th Congress of the International Union of Physiological Sciences (IUPS 2013), Birming-ham, United Kingdom. *Information:* Internet: http://www.iups2013.org/.

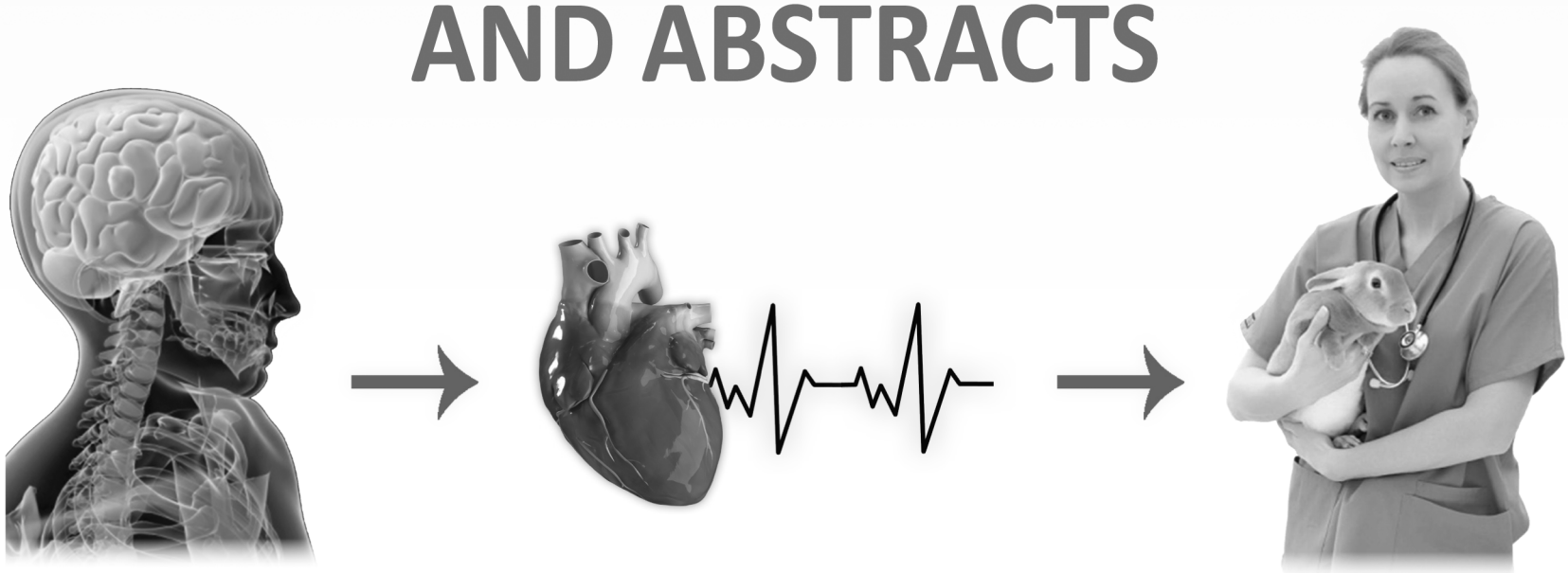
September 6-9
45th European Brain and Behaviour Society Meeting, Munich, Germany. *Information:* Internet: http://ebbs2013.com/.

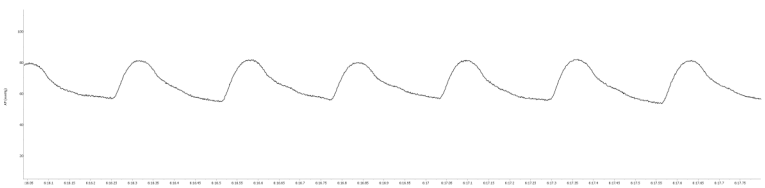
2012 American Physiological Society Conference

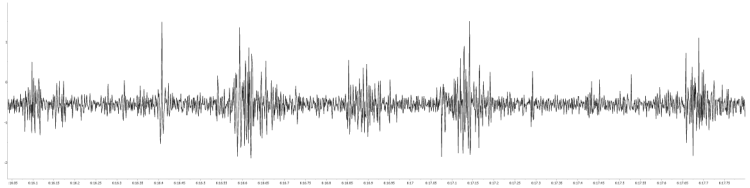
Autonomic Regulation of Cardiovascular Function in Health and Disease

Omaha, Nebraska • July 7-10, 2012

MEETING PROGRAM AND ABSTRACTS







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2012 APS Conference
Autonomic Regulation of Cardiovascular Function in Health and Disease

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Acknowledgements

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2012 APS Conference:
Autonomic Regulation of Cardiovascular Function in Health and Disease
July 7—10, 2012
Omaha, Nebraska

Saturday July 7, 2012	Sunday July, 8, 2012	Monday July 9, 2012	Tuesday July 10, 2012
3:00 PM **Registration Opens** 7:00—10:00 PM **Opening and Welcome Reception**	7:00—9:00 AM **Breakfast** 9:00—10:00 AM Plenary Lecture I: **Advances in the Central Renin-angiotensin System** **C. Sigmund**, Univ. of Iowa 10:00 AM—12:00 Noon Symposia I: **Angiotensin Converting Enzyme 2 and ANG (1-7): Roles in Central Hypertension** Participants: **I. Zucker,** (Chair), Univ. of Nebraska Med. Ctr. **L. Gao,** (Chair), Univ. of Nebraska Med. Ctr. **D. Diz,** Wake Forest Univ. **E. Lazartigues**, Louisiana State Univ. Hlth. Sci. Ctr. 12:00 Noon—2:00 PM **Lunch and Poster Presentations** 2:00—4:00 PM Symposia II: **Oxidative Stress and Sympathetic Regulation** Participants: **K. Haack,** (Chair), Univ. of Nebraska Med. Ctr. **E. Rosenbaugh,** (Chair), Univ. of Nebraska Med. Ctr. **J. Chan**, Chang Gung Mem. Hosp., Taiwan **M. Zimmerman**, Univ. of Nebraska Med. Ctr. 4:00—4:15 PM **Coffee Break** 4:15—6:00 PM Symposia III: **Mechanisms of Baro and Chemoreceptor Sensory Transduction: A Link to Sympatho-excitation in Disease** Participants: **R. Del Rio,** (Chair), Univ. of Nebraska Med. Ctr. **N. Marcus,** (Chair), Univ. of Nebraska Med. Ctr. **F. Abboud,** Univ. of Iowa **N. Prabhakar,** Univ. of Chicago	7:00—9:00 AM **Breakfast** 9:00—10:00 AM Plenary Lecture II: **Neuromodulatory Pathways and Central Control of Sympathetic Activity in Hypertension and Heart Failure** **F. Leenen**, Univ. of Ottawa, Canada 10:00 AM—12:00 Noon Symposia IV: **Sympatho-excitatory Mechanisms in Cardiovascular Disease** Participants: **N. Sharma** (Chair), Univ. of Nebraska Med. Ctr. **H. Zheng,** (Chair), Univ. of Nebraska Med. Ctr. **M. Esler,** Univ. of Melbourne, Australia **J. Francis,** Louisiana State Univ. Coll. of Vet. Med. 12:00 Noon—2:30 PM **Lunch and Poster Presentations** 2:30—4:30 PM Symposia V: **Sympathetic Mechanisms in Human Hypertension** Participants: **S. Chan,** (Chair), Chang Gung Mem. Hosp., Taiwan **I. Zucker,** (Chair), Univ. of Nebraska Med. Ctr. **I. Biaggioni,** Vanderbilt Univ. **J. Stewart,** New York Med. Coll. 4:30—4:45 PM **Coffee Break** Symposia VI: 4:45—6:00 PM **The Gladiator Session** Participants: **I. Zucker,** (Chair), **M. Chapleau,** (Chair), Univ. of Iowa Coll. of Med.	7:00—9:00 AM **Breakfast** 9:00—10:00 AM Plenary Lecture III: **Muscle Sympathetic Reflexes in Humans** **L. Sinoway**, Pennsylvania State Univ. 10:00 AM—12:00 Noon Symposia VII: **Nitric Oxide and Sympatho-vagal Regulation** Participants: **Y-L. Li** (Chair), Univ. of Nebraska Med. Ctr. **M. Chapleau,** (Chair), Univ. of Iowa Coll. of Med. **D. Paterson,** Oxford Univ., UK **J. Paton,** Univ. of Bristol, UK 12:00 Noon—2:30 PM **Lunch and Poster Presentations** 2:30—4:30 PM Symposia VIII: **Device Therapy for Hypertension and Heart Failure** Participants: **I. Biaggioni,** (Chair), Vanderbilt Univ. **J. Stewart,** (Chair), New York Med. Coll. **T. Lohmeier,** Univ. of Mississippi Med. Ctr. **M. Dunlap,** Case Western Reserve Univ. **P. Sobotka,** Medtronics 4:45—5:45 PM Career Session: **The *Ins* and *Outs* of Authorship** Presented by: **I. Zucker,** Univ. of Nebraska Med. Ctr. **M. Frank,** American Physiological Society 7:00—10:00 PM **Dinner and Awards Presentation**

GENERAL INFORMATION

Location:

The 2012 APS Conference: Autonomic Regulation of Cardiovascular Function in Health and Disease will be held July 7—10, 2012 at the Hilton Omaha hotel located at: 1001 Cass Street, Omaha, NE 68102, telephone (402) 998-3400, FAX: (402) 998-4242.

Onsite Registration Hours:

Saturday, July 7……. ……3:00—8:30 PM
Sunday, July 8…….7:00 AM—6:00 PM
Monday, July 9……7:00 AM—6:00 PM
Tuesday, July 10……..7:00 AM—5:00 PM

On-Site Registration Fees:

APS Member..... $600
Retired Member $400
Nonmember..... $700
Postdoctoral..... $450
Student $400

The registration fee includes entry into all scientific sessions, opening reception and lunches.

Payment Information:

Registrants may pay by institutional or personal check, traveler's check, MasterCard, VISA or American Express. 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.**

Press:

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.

Ancillary Session:

Career Workshop: This special session entitled: "The *Ins* and *Outs* of Authorship" will be presented by Irving Zucker, University of Nebraska Medical Center and Martin Frank, American Physiological Society. Discuss the criteria for authorship and various roles authors can play during the research process and preparation and publication of a manuscript. Through case studies, explore real-life scenarios and how best to deal with the various issues that can arise with authorship.

Dinner and Awards Event:

Join your colleagues for an evening of dining at the Joslyn Art Museum. Tickets are $50 each and are available on a first-come, first-served basis at the APS Registration desk. Only a limited number of tickets will be available.

Program Objective:

The purpose of this conference is to provide a scientific forum for the exchange of ideas and the presentation of the most recent data on the regulation of sympathetic nerve activity in health and disease. Sympathetic activation, while considered a physiologically relevant and important regulator of arterial pressure, blood flow and vascular resistance, is thought to contribute to pathology, if overactive. This is especially true in those conditions that require a high level of sympathetic tone to compensate for an abnormal cardiac output or where sympathetic nervous activity sustains arterial pressure in a range that is clearly detrimental to organ function. It is critical that a comprehensive understanding of the integrative mechanisms that take part in abnormal sympathetic function take place so that more rational therapy for these disorders can be developed. In this conference we will specifically focus on disorders that have been characterized as involving abnormalities in sympathetic regulation. Furthermore, there will also be an integrative approach to understanding sympathetic regulation and will incorporate genetic, molecular, cellular and whole animal approaches to the topics covered.

Target Audience:

The intended audience for this conference includes all levels of researchers working in the field of autonomic regulation.

SUNDAY, JULY 8, 2012

Plenary Lecture

1.0 PLENARY LECTURE I

Sun., 9:00 - 10:00 AM, Blackstone B.

Chair: **Irving Zucker,** *Univ. of Nebraska Med. Ctr.*

9:00 AM **1.1** Advances in the Central Renin-angiotensin System. **Curt Sigmund.** *Univ. of Iowa.*

Symposia I

2.0 ANGIOTENSIN CONVERTING ENZYME 2 AND ANG (1-7): ROLES IN CENTRAL HYPERTENSION

Sun., 10:00 AM - 12:00 Noon, Blackstone B.

Chairs: **Irving Zucker,** *Univ. of Nebraska Med. Ctr.* **Lie Gao,** *Univ. of Nebraska Med. Ctr.*

10:00 AM **2.1** Brain Angiotensin Peptides and Control of Blood Pressure. **Debra Diz.** *Wake Forest Sch. of Med.*

10:30 AM **2.2** ACE2 Regulation in Hypertension. **Eric Lazartigues.** *Louisiana State Univ. Hlth. Sci. Ctr.*

11:00 AM **2.3** Regulation of Thermogenic Capacity by the Brain Renin-Angiotensin System: Role of Adipose AT2 Receptors. **Justin Grobe.** *Univ. of Iowa.* **(3.14).**

11:15 AM **2.4** Angiotensin II Enhances Synaptic Amplification in Sympathetic Ganglia–Implications for Baro-reflex Gain and Blood Pressure Control. **Mitchell Springer.** *Univ. of Pittsburgh.* **(3.15).**

11:30 AM **2.5** MAS Receptor in the RVLM Mediates Cardiac Sympatho-inhibitory Effects of ACE2 Over-expression in Mice with Chronic Heart Failure. **Liang Xiao.** *Univ. of Nebraska Med. Ctr.* **(3.16).**

11:45 AM **2.6** Deletion of the Proton Receptor GPR4 is Associated with Lower Blood Pressure and Lower AT1 Receptors in Brain Regions Involved with Neural Control of Arterial Pressure. **Snezana Petrovic.** *Wake Forest Sch. of Med.* **(3.4).**

Poster Session

3.0 POSTER SESSION I

Sun., 12:00 Noon - 2:00 PM, Blackstone A.

Board #

1 **3.1** Angiotensin Type 2 Receptors in the Inter-mediolateral Cell Column of the Spinal Cord: Negative Regulation of Sympathetic Nerve Activity and Blood Pressure. **L. Gao, J. Chao, J. Gao, and K-J. Parbhu.** *Univ. of Nebraska Med. Ctr.*

2 **3.2** Caudal Ventrolateral Medulla Activation by Acute Hypoxia is Independent of Changes in Arterial Blood Pressure. **L. King, C. Heesch, S. Friskey, B. Ruyle, D. Kline, and E. Hasser.** *Univ. of Missouri.*

3 **3.3** Angiotensin II Inhibits Protein Phosphatase 2A and Activates Calcium/Calmodulin Kinase II in Central Neurons. **U. Basu, S. Alikunju, and M. Zimmerman.** *Univ. of Nebraska Med. Ctr.*

4 **3.4** Deletion of the Proton Receptor GPR4 is Associated with Lower Blood Pressure and Lower AT1 Receptors in Brain Regions Involved with Neural Control of Arterial Pressure. **X. Sun, E. Tomassi, R. Sah, D. Diz, and S. Petrovic.** *Wake Forest Sch. of Med. and Univ. of Cincinnati.*

5 **3.5** Angiotensin II Intra-neuronal Signaling Involves Increased Levels of Protein Kinase C β and δ. **S. Alikunju, and M. Zimmerman.** *Univ. of Nebraska Med. Ctr.*

6 **3.6** Hydrogen Peroxide Modulates Membrane Properties in Second-order Nucleus Tractus Solitarii Neurons. **T. Ostrowski, E. Hasser, C. Heesch, and D. Kline.** *Dalton Cardiovascular Res. Ctr, Univ. of Missouri.*

7 **3.7** Inhibition of Soluble Epoxide Hydrolase Prevents Kidney Fibrosis and Inflammation Induced by Unilateral Ureteral Obstruction. **J. Kim, K. Long, and B. Padanilam.** *Univ. of Nebraska Med. Ctr.*

8 **3.8** miR-210 has an Anti-apoptotic Effect in Pulmonary Artery Smooth Muscle Cells During Hypoxia. **D. Gou, R. Ramchandran, J. Sarkar, K. Kang, Z. Wang, and U. Raj.** *Shenzhen Univ., Shenzhen, People's Rep. of China, and Univ. of Illinois at Chicago.*

9 **3.9** Selective Carotid Body Chemosensory Denervation Improves Breathing Instability and Autonomic Dysfunction in Heart Failure Rats. **R. Del Rio, N. Marcus, and H. Schultz.** *Univ. of Nebraska Med. Ctr.*

10 **3.10** Nonclassical G Protein Coupled Receptor Kinase 5 Regulation of Angiotensin II Type 1 Receptor in CATH.a Neurons. **K. Haack, C. Engler, and I. Zucker.** *Univ. of Nebraska Med. Ctr.*

11 **3.11** Ganglionic Doubling of Sympathetic Baroreflex Gain. **J. Horn, P. Kullmann, and M. Springer.** *Univ. of Pittsburgh.*

12 **3.12** Activation of Nuclear Factor-kappa B Lowers Protein Expression of Voltage-gated Sodium Channels in Nodose Neurons from Heart Failure Rats. **H. Tu, J.**

Board #

Liu, and Y-L. Li. *Univ. of Nebraska Med. Ctr.*

13 **3.13** Integrated Circulation and Respiration in Physiology and Medicine I: Why we Changed our Circulatory Structure and Function after Birth. **X-G. Sun.** *Fuwai Hosp., Natl. Ctr. for Cardiovascular Diseases, Chinese Academy of Med. Sci., Beijing, People's Rep. of China.*

14 **3.14** Regulation of Thermogenic Capacity by the Brain Renin-Angiotensin System: Role of Adipose AT2 Receptors. **J. Grobe, S. Park, X. Liu, and C. Sigmund.** *Univ. of Iowa.*

15 **3.15** Angiotensin II Enhances Synaptic Amplification in Sympathetic Ganglia–Implications for Baroreflex Gain and Blood Pressure Control. **M. Springer, and J. Horn.** *Univ. of Pittsburgh.*

16 **3.16** MAS Receptor in the RVLM Mediates Cardiac Sympatho-inhibitory Effects of ACE2 Over-expression in Mice with Chronic Heart Failure. **L. Xiao, and I. Zucker.** *Univ. of Nebraska Med. Ctr.*

17 **3.17** Nuclear Factor-kB Gene Silencing in the Rostral Ventrolateral Medulla Attenuates Angiotensin II Induced Hypertension. **A. Mitra, and I. Zucker.** *Univ. of Nebraska Med. Ctr.*

18 **3.18** ER Stress in RVLM Mediates Neurogenic Hypertension through Activation of PI3K/Akt Pathway. **Y. Chao, and J. Y. H. Chan.** *Natl. Cheng Kung Univ., Tainan, Taiwan, and Chang Gung Mem. Hosp., Kaohsiung, Taiwan.*

19 **3.19** Severe Hypertension is Unmasked in Methionine Sulfoxide Reductase-A Deficient Mice by Controlling for Differences in Locomotor Activity. **R. Sabharwal, F. M. Abboud, and M. W. Chapleau.** *Univ. of Iowa.*

20 **3.20** Expression of ROS Catabolic Enzymes in the Medial Nucleus Tractus Solitarii of Rats and Up-regulation During Acute Hypoxia. **T. Ostrowski, S. Barr, H. Dantzler, E. Hasser, D. Kline, and C. Heesch.** *Univ. of Missouri.*

21 **3.21** Withdrawn.

22 **3.22** CAT Cardiovascular Responses to Hypoxemia with Both, One, Neither Arterial Chemo-receptor(s). **R. Fitzgerald, A. Dehghani, and S. Kiihl.** *Johns Hopkins Univ., and Shiraz Univ. Sch. of Med., Iran.*

23 **3.23** Progression of Carotid Body Chemosensory Potentiation and Cardio-

Board #

respiratory Alterations During Intermittent Hypoxia: The Chemoreflex Link to Autonomic Dysfunction. **R. Del Rio, E. Moya, and R. Iturriaga.** *Univ. of Nebraska Med. Ctr., and Pontificia Univ. Catolica de Chile, Santiago, Chile.*

24 **3.24** Obstructive Sleep Apnea is Associated with Increased Chemoreflex Sensitivity in Patients with Metabolic Syndrome. **I. Trombetta, C. Maki-Nunes, E. Toschi-Dias, M. J. N. N. Alves, M. U. P. B. Rondon, F. X. Cepeda, L. F. Drager, A. M. F. W. Braga, G. Lorenzi-Filho, and C. E. Negrão.** *Heart Inst. at Univ. of São Paulo, Brazil.*

25 **3.25** C1 and RTN Neuron Stimulation Produces Cortical Arousal in Sleeping Rats. **S. Abbott, M. Coates, R. Stornetta, and P. Guyenet.** *Univ. of Virginia.*

Symposia II

4.0 OXIDATIVE STRESS AND SYMPATHETIC REGULATION

Sun., 2:00 - 4:00 PM, Blackstone B.

Chairs: **Karla Haack,** *Univ. of Nebraska Med. Ctr.*
Erin Rosenbaugh, *Univ. of Nebraska Med. Ctr.*

2:00 PM **4.1** Oxidative Stress-associated Signals in Regulation of Sympathetic Activity and Blood Pressure. **Julie Y. H. Chan.** *Chang Gung Mem. Hosp., Kaohsiung, Taiwan.*

2:30 PM **4.2** Nanoformulated Antioxidants: Delivery to Central Neurons and Modulation of Angiotensin II Intra-neuronal Signaling. **Matthew Zimmerman.** *Univ. of Nebraska Med. Ctr.*

3:00 PM **4.3** ER Stress in RVLM Mediates Neurogenic Hypertension through Activation of PI3K/Akt Pathway. **Yung-Mei Chao.** *Natl. Cheng Kung Univ., Tainan, Taiwan.* **(3.18).**

3:15 PM **4.4** Severe Hypertension is Unmasked in Methionine Sulfoxide Reductase-A Deficient Mice by Controlling for Differences in Locomotor Activity. **Rasna Sabharwal.** *Univ. of Iowa.* **(3.19).**

3:30 PM **4.5** Expression of ROS Catabolic Enzymes in the Medial Nucleus Tractus Solitarii of Rats and Up-regulation During Acute Hypoxia. **Tim Ostrowski.** *Univ. of Missouri.* **(3.20).**

Symposia III

5.0 MECHANISMS OF BARO AND CHEMORECEPTORS SENSORY TRANSDUCTION: A

LINK TO SYMPATHO-EXCITATION IN DISEASE

Sun., 4:15 - 6:15 PM, Blackstone B.

Chair: **Rodrigo Del Rio,** *Univ. of Nebraska Med. Ctr.*
Noah Marcus, *Univ. of Nebraska Med. Ctr.*

4:15 PM **5.1** Sensory Neuronal Signals are Powerful Regulators of the Hypertensive State. **François M. Abboud.** *Univ. of Iowa.*

4:45 PM **5.2** Gaseous Messengers in Oxygen Sensing by the Carotid Body. **Nanduri Prabhakar.** *Univ. of Chicago.*

5:15 PM **5.3** CAT Cardiovascular Responses to Hypoxemia with Both, One, Neither Arterial Chemoreceptor(s). **Robert Fitzgerald.** *Johns Hopkins Univ.* **(3.22).**

5:30 PM **5.4** Progression of Carotid Body Chemosensory Potentiation and Cardio-respiratory Alterations During Intermittent Hypoxia: The Chemoreflex Link to Autonomic Dysfunction. **Rodrigo Del Rio** *Univ. of Nebraska Med. Ctr.* **(3.23).**

5:45 PM **5.5** Obstructive Sleep Apnea is Associated with Increased Chemoreflex Sensitivity in Patients with Meta-bolic Syndrome. **Ivani Trombetta.** *Heart Inst., Univ. of São Paulo, Brazil.* **(3.24).**

6:00 PM **5.6** C1 and RTN Neuron Stimulation Produces Cortical Arousal in Sleeping Rats. **Stephen Abbott.** *Univ. of Virginia.* **(3.25).**

MONDAY, JULY 9, 2012

Plenary Lecture

6.0 PLENARY LECTURE II

Mon., 9:00 - 10:00 AM, Blackstone B.

Chair: **Kaushik Patel,** *Univ. of Nebraska Med. Ctr.*

9:00 AM **6.1** Neuromodulatory Pathways and Central Control of Sympathetic Activity in Hypertension and Heart Failure. **Frans Leenen.** *Univ. of Ottawa, Canada.*

Symposia IV

7.0 SYMPATHO-EXCITATORY MECHANISMS IN CARDIOVASCULAR DISEASE

Mon., 10:00 AM - 12:00 Noon, Blackstone B.

Chair: **Neeru Sharma,** *Univ. of Nebraska Med. Ctr.*
Hong Zheng, *Univ. of Nebraska Med. Ctr.*

10:00 AM **7.1** Psychogenic Cardiovascular Disease-Neural Mechanisms. **Murray Esler.** *Baker IDI Heart & Diabetes Inst., Melbourne, Australia.*

10:30 AM **7.2** Role of Inflammatory Cells in the Progression of Cardiovascular Disease. **Joseph Francis.** *Louisiana State Univ., Coll. of Med.*

11:00 AM **7.3** Klotho and Central Regulation of Sympathetic Nerve Discharge. **MJ Kenney.** *Kansas State Univ.* **(8.1).**

11:15 AM **7.4** α2C-Adrenoceptor Stimulation Restores α2A-Adrenoceptor Malfunction in Hypertensive Rats. **Torill Berg.** *Univ. of Oslo, Norway.* **(8.2).**

11:30 AM **7.5** Paraventricular Nucleus and Renal Sympathetic Nerve Activity in Hyper-adipose Rats: Possible Mechanisms for O-besity Induced Hypertension. **Marli Martins-Pinge.** *State Univ. of Londrina, Brazil.* **(8.3).**

11:45 AM **7.6** The Subfornical Organ is Activated During Chronic Heart Failure and Exhibits Enhanced Sympathoexcitation in Response to Angiotensin II. **Tamra Llewellyn.** *Univ. of Nebraska Med. Ctr.* **(8.4).**

Poster Session II

8.0 POSTER SESSION II

Mon., 12:00 Noon - 2:30 PM, Blackstone A.

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26 **8.1** Klotho and Central Regulation of Sympathetic Nerve Discharge. **MJ Kenney, M. J. Mosher, and Y. M. Sang.** *Kansas State Univ.*

27 **8.2** α2C-Adrenoceptor Stimulation Restores α2A-Adrenoceptor Malfunction in Hypertensive Rats. **T. Berg, S. I. Walaas, B. Roberg, T. T. Huynh, and J. Jensen.** *Univ. of Oslo, and Norwegian Sch. Sport Scs., Oslo, Norway.*

28 **8.3** Paraventricular Nucleus and Renal Sympathetic Nerve Activity in Hyper-adipose Rats: Possible Mechanisms for O-besity Induced Hypertension. **M. Martins-Pinge, A. Mattos, and M. Fontes.** *State Univ. of Londrina, Fed. Univ. of Minas Gerais, Belo Horizonte, Brazil.*

29 **8.4** The Subfornical Organ is Activated During Chronic Heart Failure and Exhibits Enhanced Sympa-thoexcitation in Response to Angiotensin II. **T. Llewellyn, H. Zheng, N. Sharma, and K. Patel.** *Univ. of Nebraska Med. Ctr.*

30 **8.5** Paradoxic Elevations in Angiotensin II, Independent of Plasma Renin, Contribute to the Supine Hypertension of Primary Autonomic Failure. **A. Arnold, L. Okamoto, C. Shibao, A. Gamboa, S. Raj, D. Robertson, and I. Biaggioni.** *Vanderbilt Univ.*

31 **8.6** Norepinephrine Increases NADPH Oxidase-derived Superoxide Production in Peripheral Blood Mononuclear Cells from

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Healthy Humans. **S. Deo, N. Jenkins, J. Padilla, A. Parrish, and P. Fadel.** *Univ. of Missouri.*

32 **8.7** Exaggerated Pressor Response to Mental Stress in Men Compared to Women: Underlying Hemodynamic Mechanisms and Acute Effect of Exercise. **L. Vianna, B. Silva, and A. Nóbrega.** *Fluminense Fed. Univ., Rio de Janeiro, Brazil.*

33 **8.8** Relation of Cardiovagal Baroreflex Sensitivity to Impaired Carotid Artery Elastic Function in Patients with Tetralogy of Fallot. **A. Pintér, T. Horváth, A. Sárközi, D. Cseh, and M. Kollai.** *Semmelweis Univ., Budapest, Hungary.*

34 **8.9** Rho Kinase Inhibition Lowers Sympathetic Nerve Activity and Restores Baroreflex in Conscious Rabbits with Chronic Heart Failure. **K. Haack, L. Gao, P. Curry, and I. Zucker.** *Univ. of Nebraska Med. Ctr.*

35 **8.10** Blunted Adrenergic Vasoconstriction Impairs Blood Pressure Recovery Following Severe Hemorrhage in Obese Zucker Rats. **L. Xiang, S. Lu, and J. Clemer.** *Univ. of Mississippi Med.Ctr.*

36 **8.11** Withdrawn.

37 **8.12** C-Type Natriuretic Peptide in the PVN Mediates Renal Sympatho-inhibition. **B. Xu, H. Zheng, and K. Patel.** *Univ. of Nebraska Med. Ctr.*

38 **8.13** Neuroinflammation in Rostral Ventrolateral Medulla Contributes to Neurogenic Hypertension Following Chronic Systemic Inflammation. **K. Wu, S. H. H. Chan, and J. Y. H. Chan.** *Chang Gung Mem. Hosp., Kaohsiung, Taiwan.*

39 **8.14** Sympathoexcitation Induced by Ethanol in the Central Amygdala Involves Local Activation of NMDA Receptors in Anesthetized Rats. **Q. Chen, L. Gui, R. Larson, M. Gu, and J. Zhu.** *Michigan Tech. Univ., and Affiliated Hosp. Nantong Univ., People's Rep. of China.*

40 **8.15** Baroreflex Control of Leg Vascular Conductance During Simulated Carotid Hypertension in Young and Older Women. **D. Credeur, L. Vianna, and P. Fadel.** *Univ. of Missouri.*

41 **8.16** Nutritionally-induced Changes in Cardiovascular Parameters. **D. Dimitriev, and E. Saperova.** *Chuvash State Pedagogical Univ., Cheboksary, Russian Fed.*

42 **8.17** Nocturnal Hypoxemia Induced by Obstructive Sleep Apnea Determines

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Sympathetic Hyper-activation and Mood Disturbance in Patients with Metabolic Syndrome. **E. Toschi-Dias, I. C. Trombetta, L. F. Angelo, C. Maki-Nunes, F. X. Cepeda, M. J. N. N. Alves, L. F. Drager, G. Lorenzi-Filho, C. E. Negrão, and M. U. P. B. Rondon.** *Heart Inst. Univ. of São Paulo, Brazil.*

43 **8.18** Cardiovascular Responses of Nigerian Patients with Chronic Heart Failure to 6-minute Walk Test. **C. Anigbogu, O. Ajiboye, O. Olawale, and J. Ajuluchukwu.** *Coll. of Med., Lagos, Nigeria.*

44 **8.19** Withdrawn.

45 **8.20** Integrated Circulation and Respiration in Physiology and Medicine II: Why Variations of HR, SBP and Anatomic Tone Follow Respiratory Rhythm. **X-G. Sun.** *Fuwai Hosp., Natl. Ctr. for Cardiovascular Diseases, Chinese Academy of Med. Sci., Beijing, People's Rep. of China.*

46 **8.21** Integrated Circulation and Respiration in Physiology and Medicine III: Why HF Patients Appear Oscillatory Breathing During Sleep and Exercise. **X-G. Sun.** *Fuwai Hosp., Natl. Ctr. for Cardiovascular Diseases, Chinese Academy of Med. Sci., Beijing, People's Rep. of China.*

Symposia V

9.0 SYMPATHETIC MECHANISMS IN HUMAN HYPERTENSION

Mon., 2:30 - 4:30 PM, Blackstone B.

Chair: **Samuel Chan,** *Chang Gung Mem. Hosp., Kaohsiung, Taiwan.*
Irving Zucker, *Univ. of Nebraska Med. Ctr.*

2:30 PM **9.1** Impaired Autonomic Regulation of Blood Pressure and Hypertension. **Italo Biaggioni.** *Vanderbilt Univ.*

3:00 PM **9.2** Acute and Chronic Orthostatic Intolerance, Maladaptive Autonomic Regulation. **Julian Stewart.** *New York Med. Coll.*

3:30 PM **9.3** Paradoxic Elevations in Angiotensin II, Independent of Plasma Renin, Contribute to the Supine Hypertension of Primary Autonomic Failure. **Amy Arnold.** *Vanderbilt Univ.* **(8.5).**

3:45 PM **9.4** Norepinephrine Increases NADPH Oxidase-derived Superoxide Production in Peripheral Blood Mononuclear Cells from Healthy Humans. **Shekar Deo.** *Univ. of Missouri.* **(8.6).**

4:00 PM **9.5** Exaggerated Pressor Response to Mental Stress in Men Compared to Women: Underlying Hemodynamic Mechanisms and Acute Effect of Exercise. **Antonio Nobrega.**

Fluminense Fed. Univ., Rio de Janiero, Brazil. **(8.7).**

4:15 PM **9.6** Relation of Cardiovagal Baroreflex Sensitivity to Impaired Carotid Artery Elastic Function in Patients with Tetralogy of Fallot. **Alexandra Pinter** *Semmelweis Univ., Budapest, Hungary.* **(8.8).**

Symposia VI

10.0 THE GLADIATOR SESSION

Mon., 4:45 - 6:00 PM, Blackstone B.

Chairs: **Mark Chapleau,** *Univ. of Iowa Coll. of Med.*
Irving Zucker, *Univ. of Nebraska Med. Ctr.*

TUESDAY, JULY 10, 2012

Plenary Lecture

11.0 PLENARY LECTURE III

Tues., 9:00 - 10:00 AM, Blackstone B.

Chair: **Harold Schultz,** *Univ. of Nebraska Med. Ctr.*

9:00 AM **11.1** Muscle Sympathetic Reflexes in Humans. **Lawrence Sinoway.** *Pennsylvania State Univ.*

Symposia VII

12.0 NITRIC OXIDE AND SYMPATHO-VAGALREGULATION

Tues., 10:00 AM - 12:00 Noon., Blackstone B.

Chair: **Yu-Long Li,** *Univ. of Nebraska Med. Ctr.*
Mark Chapleau, *Univ. of Iowa Coll. of Med.*

10:00 AM **12.1** Targeting Cyclic Nucleotides to Rescue Cardiac Sympathovagal Phenotypes in Cardiovascular Disease. **David Paterson.** *Oxford Univ., UK.*

10:30 AM **12.2** The Blood Brain Barrier and Control of Arterial Pressure. **Julian Paton.** *Univ. of Bristol, UK.*

11:00 AM **12.3** Involvement of PIN in Angiotensin II De-pendent Regulation of Neuronal Nitric Oxide Synthase in the PVN of Rats with Chronic Heart Failure. **Neeru Sharma.** *Univ. of Nebraska Med. Ctr.* **(13.1).**

11:15 AM **12.4** Autonomic/hypoxemia-induced Ventricular Fibrillation in Epileptic Rats. **Isaac Naggar.** *SUNY Downstate Med. Ctr.* **(13.2).**

11:30 AM **12.5** Effect of Dietary Omega-3 Fatty Acids on the Heart Rate Variability Response to Physiological Challenges in a Canine Model of Sudden Cardiac Death. **George Billman.** *Ohio State Univ.* **(13.3).**

11:45 AM **12.6** Response of Intracardiac Ganglion Neurons to Nicotine in Type-2 Diabetic Rats. **Yu-Long Li.** *Univ. of Nebraska Med. Ctr.* **(13.6).**

Poster Session III

13.0 POSTER SESSION III

Tues., 12:00 Noon - 2:30 PM, Blackstone A.

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47 **13.1** Involvement of PIN in Angiotensin II Dependent Regulation of Neuronal Nitric Oxide Synthase in the PVN of Rats with Chronic Heart Failure. **N. Sharma, T. Llewellyn, H. Zheng, and K. Patel.** *Univ. of Nebraska Med. Ctr.*

48 **13.2** Autonomic/hypoxemia-induced Ventricular Fibrillation in Epileptic Rats. **I. Naggar, H. Kam-ran, J. Lazar, and M. Stewart.** *SUNY Downstate Med. Ctr.*

49 **13.3** Effect of Dietary Omega-3 Fatty Acids on the Heart Rate Variability Response to Physiological Challenges in a Canine Model of Sudden Cardiac Death. **G. Billman.** *Ohio State Univ.*

50 **13.4** Carotid Body Denervation Attenuates Increased Sympathetic Nerve Activity in Congestive Heart Failure. **N. Marcus, R. Del Rio, H. Levin, and H. Schultz.** *Univ. of Nebraska Med. Ctr., and Coridea, New York.*

51 **13.5** High Fidelity Autonomic Nerve Signals using Bipolar Nanoelectrode Arrays. **A.G. Akingba, A. Mahmood, M. Shen, J. Garlie, and P-S. Chen.** *Indiana Univ. Sch. of Med., and Purdue Univ.*

52 **13.6** Response of Intracardiac Ganglion Neurons to Nicotine in Type-2 Diabetic Rats. **J. Liu, H. Tu, and Y-L. Li.** *Univ. of Nebraska Med. Ctr.*

53 **13.7** Glutamatergic Receptors in Spinal Cord Mediates the Exaggerated Exercise Pressor Reflex in Rats with CHF. **H-J. Wang, K. Patel, I. Zucker, and W. Wang.** *Univ. of Nebraska Med. Ctr.*

54 **13.8** Sympathetic Nerve Recordings: A Glimpse of the Recent Past with an Eye on the Future. **M. J. Kenney, and L. J. Mosher.** *Kansas State Univ.*

55 **13.9** Unilateral Renal Denervation Enhances Baroreflex Function in Conscious Rabbits with Chronic Heart Failure. **A. Schiller, P. Curry, K. Haack, and I. Zucker.** *Univ. of Nebraska Med. Ctr.*

56 **13.10** Integrated Circulation and Respiration in Physiology and Medicine IV: Why and How Body Blood Flow Redistribution During Exercise? **X-G. Sun.** *Fuwai Hosp., Natl. Ctr. for Cardiovascular Diseases, Chinese Academy of Med. Sci., Beijing, People's Rep. of China.*

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57 **13.11** Integrated Circulation and Respiration in Physiology and Medicine V: Why and How to Increase the Cardiac Output During Exercise? **X-G. Sun.** *Fuwai Hosp., Natl. Ctr. for Cardiovascular Diseases, Chinese Academy of Med. Sci., Beijing, People's Rep. of China.*

58 **13.12** Autonomic Modulation: Emerging Paradigm for Cardiovascular Treatments? **K. J. Dormer, S. S. Po, and B. J. Scherlag.** *Univ. of Oklahoma Hlth. Sci. Ctr., and NanoMed Targeting Sys. Inc.*

59 **13.13** Cardiovascular Autonomic Control in the First Year After Spinal Cord Injury. **J. Inskip, M. McGrath, B. Kwon, and V. Clayton.** *Simon Fraser Univ., Burnaby, Canada.*

60 **13.14** Heart Rate Variability Responses to Exercise in Thai Brugada Syndrome Survivors. **R. Chanavirut, P. Makarawate, and N. Leelayuwat.** *Khon Kaen Univ., Thailand.*

Symposia VIII

14.0 DEVICE THERAPY FOR HYPERTENSION AND HEART FAILURE

Tues., 2:30 - 4:30 PM, Blackstone B.

Chairs: **Italo Biaggioni,** *Vanderbilt Univ.*
Julian Stewart, *New York Med. Coll.*

2:30 PM **14.1** Insight into Long-Term Neural Control of Arterial Pressure by Chronic Baroreflex Activation. **Thomas Lohmeier.** *Univ. of Mississippi Med. Ctr.*

3:00 PM **14.2** When the Levee Breaks: Sympathetic Control of Splanchnic Vessels Leading to Acute Heart Failure. **Mark Dunlap.** *Case Western Res. Univ.*

3:30 PM **14.3** Beyond BP Reduction, Clinical Implications of Renal Denervation. **Paul Sobotka.** *Medtronic, Inc.*

4:00 PM **14.4** Carotid Body Denervation Attenuates Increased Sympathetic Nerve Activity in Congestive Heart Failure. **Noah Marcus.** *Univ. of Nebraska Med. Ctr.* **(13.4).**

4:15 PM **14.5** High Fidelity Autonomic Nerve Signals using Bipolar Nanoelectrode Arrays. **A. George Akingba.** *Indiana Univ. Sch. of Med.* **(13.5).**

Career Session

15.0 THE INS AND OUTS OF AUTHORSHIP

Tues., 4:45 - 5:45 PM, Blackstone B.

Chairs: **Irving Zucker,** *Univ. of Nebraska Med. Ctr.*
Martin Frank, *American Physiological Society.*

4:45 PM **15.1** The *Ins* and *Outs* of Authorship. **Irving Zucker.** *Univ. of Nebraska Med. Ctr* and **Martin Frank,** *American Physiological Society.*

This meeting has been made possible by the generous support from:

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Autonomic Regulation of Cardiovascular Function in Health and Disease

Abstracts of Invited and Contributed Presentations

1.0: PLENARY LECTURE I

1.1
ADVANCES IN THE CENTRAL RENIN-ANGIOTENSIN SYSTEM

Curt Sigmund[1]
[1]Pharmacology, Univ. of Iowa, 2-454 BSB, Iowa City, IA, 52242.

The renin-angiotensin system (RAS) in the brain is well recognized as an important controller of cardiovascular (CV) function though its effects on blood pressure (BP), fluid intake, and sympathetic outflow, and has been implicated in hypertension. Growing evidence advancing the concept that the RAS, both in the brain and periphery, is also a controller of energy expenditure is gaining acceptance. We have obtained compelling data indicating that activation of the brain RAS, while simultaneously decreasing circulating RAS, results in increased energy expenditure. These data advance the novel concept that the central and peripheral RAS may differentially control energy balance. Moreover, our most recent data suggest a novel role for adipose AT_2R as a modulator of the actions of the brain RAS on adipose tissue and its resulting effect on energy expenditure. Activation of adipose AT_2R blunts energy expenditure induced in response to elevated brain RAS activity. Activation of the brain RAS also increases BP and fluid intake through efferent mechanisms distinct from those controlling energy expenditure. This plenary lecture will review the central pathways regulating ANGII synthesis, the role of renin in the brain, the contrasting mechanisms regulating cardiovascular and metabolic output of the brain RAS, and the interaction between the RAS in the brain and adipose tissue and its effects on energy balance. This work was funded by grants from the NIH, AHA, and the Roy J Carver Trust.

2.0: ANGIOTENSIN CONVERTING ENZYME 2 AND ANG (1-7): ROLES IN CENTRAL HYPERTENSION

2.1
BRAIN ANGIOTENSIN PEPTIDES AND CONTROL OF BLOOD PRESSURE

Debra Diz[1]
[1]Hypertension & Vascular Res. Ctr., Wake Forest Sch. of Med., 1 Medical Ctr. Blvd., Winston-Salem, NC, 27157-1032.

Alterations in autonomic outflow contribute to both cardiovascular and metabolic changes accompanying hypertension and aging. Investigation of our hypothesis that angiotensin (Ang) II and Ang-(1-7) in dorsal medullary nuclei favor activation of the sympathetic vs. parasympathetic systems, respectively, reveals divergent actions of the peptides on resting mean arterial pressure (MAP), baroreflex sensitivity for control of heart rate (BRS) and indices of metabolic function. Our studies further identify different anatomical, neurotransmitter and signaling pathways involved as potential mechanisms for the distinct actions of the peptides. Examples illustrating these concepts will be drawn from models of aging, as well as acute and chronic elevations of MAP in stress, fetal-programming and genetic hypertension. The influence of long-term alterations in medullary angiotensin peptides on cardiovascular responses to activation of nTS receptors for cardiometabolic hormones/transmitters such as leptin and CB1 endocannibinoids, and to differences in resting levels of local transmitters known to be involved in BRS, will be highlighted using data from transgenic animals. The functional interactions between the renin-angiotensin system (RAS) and the autonomic nervous system in brain and periphery illustrated in our studies continue to provide strong rationale for therapeutic interventions involving RAS blockade for cardiometabolic protection. The emerging new concept is that both reduced Ang II and elevated Ang-(1-7) may be required for optimal benefit over the long-term. (HL51952, HD474584).

2.2
ACE2 REGULATION IN HYPERTENSION

Eric Lazartigues
Dept. of Pharmacology & Experimental Therapeutics, Louisiana State Univ., New Orleans, LA 70112.

The last decade has seen the emergence of a compensatory arm of the Renin-Angiotensin System (RAS), comprising the Angiotensin Converting Enzyme type 2 (ACE2), the Angiotensin-(1-7) peptide and its receptor Mas. Importantly, this arm is thought to balance the over-activation of the classical ACE/Ang-II/AT1 receptor axis. Although several enzymes are involved in these modulatory effects, ACE2 appears to bethe main pivotal compensatory enzyme that can simultaneously reduce Ang-II and increase Ang-(1-7) levels. However, as high blood pressure develops,ACE2 expression and/or activity re being impaired. Evidence points to a negativeregulation that originates from the overactive arm of the RAS and affects the compensatory pathway. Various strategies have already been tested to restore ACE2 compensatory function, including gene therapy using virus delivery at the periphery or in the central nervous systemas well as injection of recombinant human ACE2. Another approach has been to use compounds identified as ACE2 “activators”. The exponential ACE2 literature suggests that several mechanisms are involved in the dysregulation of the carboxypeptidase, acting both at the gene, messenger RNA and protein level. Moreover, recent data from our group show that restoring ACE2 activity to normal levels is sufficient to significantly impact the development of hypertension. While all the above strategies have been shown to be beneficial at restoring ACE2 compensatory activity, they all have weaknesses. Therefore, new schemes are necessary that would ideally prevent both reduction of ACE2 expression and activity. Here, we will: 1) review the current state of knowledge regarding ACE2 dysregulation in hypertension, 2) highlight the advantages and inconveniences of the various strategies to restore ACE2 compensatory effects and 3) present some new data on novel approaches to restore a functioning compensatory ACE2/Ang-(1-7)/mas receptor axis.(NIH R01 HL093178, P20 GM103514 & AHA EIA8030004).Xu P., Sriramula S., Lazartigues E. 2011. Am J PhysiolRegulIntegr Comp Physiol. 300(4):R804-17.

3.0: POSTER SESSION I

3.1
ANGIOTENSIN TYPE 2 RECEPTORS IN THE INTERMEDIOLATERAL CELL COLUMN OF THE SPINAL CORD: NEGATIVE REGULATION OF SYMPATHETIC NERVE ACTIVITY AND BLOOD PRESSURE

Lie Gao[1], Jie Chao[1], Juan Gao[1], Karma-Jaya Parbhu[1]
[1]Cellular & Integrative Physiology, Univ. of Nebraska Med. Ctr., 985850 Nebraska Med. Ctr., Omaha, NE, 68198-5850.

Previously we demonstrated that AT2R in brainstem participated in the regulation of sympathetic outflow and cardiovascular function. In the present study, we evaluated the function of the AT2R in the intermediolateral cell column (IML) of the thoracic spinal cord in normal rats. We hypothesized that AT2R in the IML would exert a sympatho-inhibitory effect. We found that: (1) both AT1R and AT2R are expressed in the spinal cord, with higher levels in grey matter compared with white matter. (2) Microinjection of Ang II into the IML dose-dependently increased blood pressure (MAP) and sympathetic nerve activity (RSNA), which was completely abolished by Losartan, and attenuated by TEMPOL and apocynin; (3) activation of AT2R in the IML with CGP42112 evoked hypotension (□MAP: -21 ± 4 mmHg) and sympatho-inhibition (RSNA: 73 ± 3% of baseline), which were completely abolished by PD123319 and L-NAME; (4) blockade of AT2R in the IML with PD123319 significantly increased MAP (11 ± 1 mmHg) and sympathetic nerve activity (RSNA: 133 ± 13 % of baseline). Moreover, PD123319 significantly enhanced the AngII induced pressor response; (5) Employing whole-cell patch clamp, we further found that CGP42112 treatment augmented potassium current and decreased resting membrane potential in isolated IML neurons.In conclusion, these results suggest that, in the normal condition, AT2R in the IML tonically inhibit sympathetic activity by an NO/NOS dependent pathway inducing activation of potassium channel.

3.2
CAUDAL VENTROLATERAL MEDULLA (CVLM) ACTIVATION BY ACUTE HYPOXIA (AH) IS INDEPENDENT OF CHANGES IN ARTERIAL BLOOD PRESSURE (ABP)

Luise King[1], Cheryl Heesch[1], Sarah Friskey[1], Brian Ruyle[1], David Kline[1], Eileen Hasser[1]
[1]Veterinary Biomedical Sci., Uni. of Missouri, 134 Research Park Dr., Rm 352 Dalton Cardiovascular Res. Ctr., Columbia, MO, 65211.

Afferent baroreflex and chemoreflex signaling is integrated in the nucleus of the solitary tract and then sent to the CVLM. Hypoxia activates neurons in the CVLM, but also decreases ABP. To evaluate the influence of changes in ABP on CVLM neuronal activation due to AH, we stimulated the arterial chemoreflex while maintaining ABP constant. ABP was monitored in conscious rats (radiotelemetry) during 2 hrs of Normoxia (N: 21% O2, n=4), AH (10% O2, n=5) or AH and i.v. infusion of the vasoconstrictor phenylephrine (0.06-0.3mg/hr) to maintain ABP constant (AH+PE, n=4). Rats were perfused and brainstems processed for examination of Fos-immunoreactivity (IR) as an index of CVLM activation and tyrosine hydroxylase (TH)-IR to identify catecholaminergic neurons. AH led to a sustained decrease in ABP (-17±4 mmHg within 15 min). In AH+PE and N rats, ABP remained constant. Changes in breathing frequency and oxygen saturation during hypoxia were similar in AH and AH+PE rats. Compared to N (21±10 cells), hypoxia increased the number of Fos-IR CVLM neurons whether ABP decreased or was held constant (AH: 117±8; AH+PE: 128±18 cells). Furthermore, the number of activated catecholaminergic CVLM cells was similar in both AH groups (AH: 59+11 vs AH+PE: 59+13). Data suggest that decreased ABP during hypoxia does not contribute substantially to CVLM neuronal activation due to chemoreflex stimulation.

3.3
ANGIOTENSIN II (ANGII) INHIBITS PROTEIN PHOSPHATASE 2A AND ACTIVATES CALCIUM/CALMODULIN KINASE II IN CENTRAL NEURONS

Urmi Basu[1], Saleena Alikunju[1], Matthew Zimmerman[1]
[1]Cellular and Integrative Physiology, Univ. of Nebraska Med. Ctr., 985850 Nebraska Med. Ctr., Omaha, NE, 68198.

AngII signaling in the brain plays a critical role in regulating systemic cardiovascular function. AngII increases neuronal firing rate by elevating levels of reactive oxygen species (ROS), which, in turn, modulate ion channel activity. Ion channel activity can also be controlled by cellular kinases and phosphatases. However, the potential cross-talk between AngII, ROS, kinases, and phosphatases in modulating ion channel activity in central neurons remains unclear. Here, we tested the hypothesis that AngII stimulation of central neurons influences the levels

and activity of redox-sensitive proteins including calcium/calmodulin kinase II (CaMKII) and proteinphosphatase 2A (PP2A).Mouse CATH. aneurons were treated with AngII(100nM; 5 min – 24 hr) and activity of CaMKII was assessed by detecting its phosphorylated levels; while PP2A activity was determined using a ser/thr Malachite Green phosphatase activity assay. AngII significantly increased phosphorylated CaMKII levels from 2 to24 hr (3.17 and 3.19-foldincrease vs. vehicle,P<0.05) of stimulation. In contrast, AngII modestly decreasedPP2A protein levels from30 min to24 hr ofstimulation. PP2Aactivity decreased within 5 min of AngII stimulation to 1 hr (148 pM phosphate released at5 min and 134 pM at 1 hr vs.486 pM in vehicle-treated neurons). These data indicate that in neurons AngII inhibits PP2A activity while activating CaMKII. Future studies will investigate the role of ROS in mediating these AngII-induced changes in PP2A and CaMKII activity.

3.4
DELETION OF THE PROTON RECEPTOR GPR4 IS ASSOCIATED WITH LOWER BLOOD PRESSURE AND LOWER AT1 RECEPTORS IN BRAIN REGIONS INVOLVED WITH NEURAL CONTROL OF ARTERIAL PRESSURE

Xuming Sun[1], Ellen Tomassi[2], Renu Sah[3], Debra Diz[2], Snezana Petrovic[1]
[1]Physiology and Pharmacology, Wake Forest Sch. of Med., Winston-Salem, NC, 27157, [2]Surgery, Wake Forest Sch. of Med., Winston-Salem, NC, 27157, [3]Psychiatry, Univ. of Cincinnati, Coll. of Med., Cincinnati, OH, 45267.

The proton receptor GPR4, a G protein-coupled receptor that accepts protons as ligands, is activated in physiological pH range. GPR4 is relatively abundant in the brain, lung, and kidney. Here we examined GPR4 expression in the brain, using real-time RT-PCR on dissected brain regions and we found that GPR4 mRNA expression is ~5x higher in subfornical organ (SFO) than in other brain regions examined. GPR4/actin ratio (x10-2) of # of mRNA copies was: SFO 48; frontal cortex 12; medulla 11; hypothalamus 11; corpus callosum 10; pons 10; striatum 10; hippocampus 10; cerebellum 9; olfactory bulb 7. We confirmed the expression with immunohistochemistry. The SFO is involved in blood pressure (BP) and fluid balance regulation and has high angiotensin II AT1 receptor density. We therefore measured BP in GPR4-/- and +/+ mice and examined AT1 receptor expression with in vitro receptor autoradiography. GPR4-/- mice have fewer AT1 receptors in SFO (45 ± 29 (n=4) vs. 159 ± 38 fmol/mg protein in GPR4+/+ (n=3); p = 0.06) as well as paraventricular nucleus of the hypothalamus (53 ± 31 vs. 163 ± 8 fmol/mg protein in GPR4+/+; p = 0.03). The lower AT1 receptors were accompanied by lower BP, as measured by tail cuff (SBP in mm Hg: 93 ± 1 in GPR4-/- (n=7) vs. 108 ± 2 in GPR4+/+ (n=7); p=0.0002). Taken together these results posit the pH sensitive GPR4 as a potentially important regulator of BP via brain AT1-dependent mechanisms that may be sensitive to and regulated by systemic and/or local pH.

3.5
ANGIOTENSIN II INTRA-NEURONAL SIGNALING INVOLVES INCREASED LEVELS OF PROTEIN KINASE C (PKC) B AND Δ

Saleena Alikunju[1], Matthew C. Zimmerman[1]
[1]Cellular and Integrative Physiology, Univ. of Nebraska Med. Ctr., 42nd and Emile, Omaha, NE, 65850.

Aberrant angiotensin II (AngII) signaling in the central nervous system leads to cardiovascular dysfunction via, at least in part, over-activation of the sympathetic nervous system. We have previously reported that AngII enhances neuronal activation through the generation of reactive oxygen species (ROS) and subsequent regulation of Ca^{2+} and K^+channel activity. Additionally, previous studies have implicated various redox-sensitive kinases in the modulation of ion channel activity. We hypothesize that AngII increases expression of redox-sensitive PKC, which, in turn controls ion channel activity and neuronal firing. Using a neuronal cell culture model (CATH.a neurons) and Western blot analysis, we observed a significant increase in PKCβ protein levels following 2 hr of AngII stimulation (2.5 fold increase vs. vehicle, P<0.5). AngII also significantly elevated PKCδ protein levels within 1 hr (1.6 fold increase vs. vehicle, P<0.5) with a maximum increase after 24 hr (2.6 fold increase vs. vehicle, P<0.5) of stimulation. This AngII-induced increase in PKCβ/δ was confirmed with immunofluorescent confocal microscopy studies, which also showed an apparent translocation of PKC to the cell membrane. These data suggest that AngII intra-neuronal signaling involves up-regulation of both PKCβ and PKCδ. Future studies designed to investigate the role of AngII-induced ROS generation in mediating the increase in PKCβ/δ are currently underway.

3.6
HYDROGEN PEROXIDE (H_2O_2) MODULATES MEMBRANE PROPERTIES IN SECOND-ORDER NUCLEUS TRACTUS SOLITARII (NTS) NEURONS

Tim Ostrowski[1], Eileen Hasser[1], Cheryl Heesch[1], David Kline[1]
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H_2O_2, a stable reactive oxygen species, is a potent neuromodulator of cellular and synaptic activity. H_2O_2 is normally present in low concentrations, but rapidly increases during bouts of hypoxia-reoxygenation. Chemoafferent fibers terminate within the nTS, a center vital for cardiorespiratory responses to hypoxia. Thus, we determined the role of H_2O_2 on synaptic and membrane properties in the nTS using the patch clamp technique. Synaptic transmission was not altered by 10-500 μM H_2O_2, but membrane properties were modulated by 500 μM H_2O_2. Input resistance (IR) decreased with simultaneous hyperpolarization of membrane potential (MP) and action potential threshold (THR). Action potential discharge (APD) to depolarizing current was reduced with H_2O_2. Preventing the H_2O_2-induced hyperpolarization of MP (holding MP at -60 mV) resulted in augmented APD to current injection. During washout, MP returned to pre-H_2O_2 levels whereas THR remained hyperpolarized. This reduced the difference between MP and THR and increased APD excitability to depolarization compared to pre-H_2O_2. Catalase within the recording pipette ablated the effects of extracellular H_2O_2, indicating an intracellular site of modulation. Taken together, H_2O_2 reduces excitability of nTS neurons and upon removal results in hyperexcitability that may play a profound role in cardiorespiratory reflexes. Support: RO1 HL098602.

3.7
INHIBITION OF SOLUBLE EPOXIDE HYDROLASE PREVENTS KIDNEY FIBROSIS AND INFLAMMATION INDUCED BY UNILATERAL URETERAL OBSTRUCTION

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Epoxyeicosatrienoic acids (EETs), lipid metabolites produced from arachidonic acid by cytochrome P450 epoxygenases, have anti-inflammatory and pro-fibrinolytic functions in the cardiovascular system. Soluble epoxide hydrolase (sEH) is critical in the control of EET levels because of its ability to convert EETs to the less active dihydroxyeicosatrienoic acids (DHETs). Based on previous studies, we hypothesized that genetic deletion or pharmacological inhibition of sEH would attenuate tubulointerstitial fibrosis and inflammation in the unilateral ureteral obstruction (UUO) mouse model. UUO was performed by ligation of the left ureter near the kidney pelvis in sEH-knockout (Ephx2-KO) and wild-type (WT) male mice. In WT mice, the sEH inhibitor (tTUCB, 0.2 mg/day/mouse) or vehicle was administered by oral gavage. Tubulointerstitial fibrosis induced by UUO was abolished in Ephx2-KO and tTUCB-treated kidneys compared to that in WT and vehicle-treated kidneys respectively. Intriguingly, loss of Ephx2 gene or treatment with tTUCB also attenuated infiltration of neutrophil/macrophage and expression of pro-inflammatory proteins. These data demonstrate that blockage of sEH has anti-inflammatory and fibro-protective effects in UUO and, therefore, suggests the potential use of sEH inhibitors as a novel therapeutic agent for fibrotic disease.

3.8
MIR-210 HAS AN ANTIAPOPTOTIC EFFECT IN PULMONARY ARTERY SMOOTH MUSCLE CELLS DURING HYPOXIA

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MicroRNAs (miRNAs) were recently reported to play an important role in the pathogenesis of pulmonary arterial hypertension (PAH) but it is not clear which miRNAs are important or what pathways are involved in the process. Since hypoxia is an important stimulus for human pulmonary artery smooth muscle cell (HPASMC) proliferation and PAH, we performed miRNA microarray assays in hypoxia-treated and control HPASMC. We found that miR-210 is the predominant miRNA induced by hypoxia in HPASMC. Induction of miR-210 was also observed in whole lungs of mice with chronic hypoxia-induced PAH. We found that transcriptional induction of miR-210 in HPASMC is HIF-1 dependent. Inhibition of miR-210 in HPASMC caused a significant decrease in cell number due to increased apoptosis. We found that miR-210 appears to mediate its anti-apoptotic effects via the regulation of transcription factor E2F3, a direct target of miR-210. Our results have identified miR-210 as a hypoxia-inducible miRNA both in vitro and in vivo, which inhibits pulmonary vascular smooth muscle cell apoptosis in hypoxia by specifically repressing E2F3 expression.

3.9
SELECTIVE CAROTID BODY CHEMOSENSORY DENERVATION IMPROVES BREATHING INSTABILITY AND AUTONOMIC DYSFUNCTION IN HEART FAILURE RATS

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Sympathetic hyperactivity and breathing instability are major contributors to decompensation in chronic heart failure (CHF). Potentiation of the carotid body chemoreflex has been related to increased sympathetic outflow and generation of breathing abnormalities in CHF. We hypothesized that carotid body denervation (CBD) improves cardiovascular function and restores breathing stabilityin CHF.CBD was performed onmale rats after 16 weeks of coronary artery ligation. Ventilatory responses to acute hypoxia (FiO2 10%) and resting breathing were obtained by plethysmography.We assessed autonomic function by spectral analysis of heart rate (HRV) and systolic blood pressure variability (BPV) and by spontaneous baroreflex gain (BG). CHFrats exhibitedincreased breath-to-breath interval variability, enhancedhypoxic ventilatory responses, increasedlow-frequency HRV and BPV and decreasedBG compared to shams. CBD significantly reduced breathinginstability in CHF rats (SD1: 151.3±11.1 vs. 59.5±13.9 ms; SD2 129.9±10.3 vs. 67.8±11.4 ms, intact vs. CBD, $P< .05$,). Also,CBD decreased the

low-frequency HRV and BPV concomitant with a significant increase in the high-frequency HRV (32.7±2.3 vs. 51.2±13.1 au). Moreover, the reduced BGin CHF rats was partially reversed after CBD (P<.05). Our results show that CBD significantly improves breathing stability and autonomic function in CHF-rats. Supported by NIH PO1-HL62222.

3.10

NONCLASSICAL G PROTEIN COUPLED RECEPTOR KINASE 5 REGULATION OF ANGIOTENSIN II TYPE 1 RECEPTOR IN CATH.A NEURONS

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The Angiotensin II type 1 Receptor (AT1R) plays a pivotal role in the development of heart failure, and as such is upregulated in a number of tissues. AT1R and other G Protein Coupled Receptors are marked for internalization and recycling via G Protein Coupled Receptor Kinase (GRK) phosphorylation. GRK5, a regulator of AT1R, has been shown previously in aorta endothelial cells to stabilize IκBα, an inhibitory element of Nuclear Factor Kappa B (NFκB), a protein also involved in upregulation of AT1R. We hypothesized that in CATH.a neurons, GRK5 may regulate AT1R via interaction with the IκBα/NFκB dimer. Cells stimulated with 100 nM Angiotensin II (Ang II) for 4 hours led to a significant upregulation of AT1R, p65 NFκB and GRK5 proteins ($p<0.05$). Overexpression of GRK5 led to a normalization of AT1R and p65 NFκB following Ang II stimulation; conversely, silencing of GRK5 increased Ang II-mediated AT1R and p65 NFκB upregulation by 100%.Co-immunoprecipitation studies indicated that GRK5 and IκBα are physically associated and dissociate upon Ang II stimulation whereas GRK5 and NFκB do not associate. Examination of nuclear and cytosolic fractions of these neurons showed that GRK5 was present in both locations, and cytosolic GRK5 is increased following Ang II stimulation. Preliminary studies indicate that over-expression of a GRK5 nuclear export signal mutant increased AT1R expression. Taken together, these data suggest a nontraditional role of GRK5 as a regulator of AT1R.

3.11

GANGLIONIC DOUBLING OF SYMPATHETIC BAROREFLEX GAIN

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Convergent nicotinic synapses may generate amplification in sympathetic ganglia. However, an opposing view posits ganglia are simple relays. The issue is important because synaptic gain implies that ganglionic mechanisms control baroreflex gain. We hypothesized that cell damage explains the conflict. To test this, micro-electrode and patch electrode recordings were compared. With microelectrodes, 16 cells in the acutely isolated rat superior cervical ganglion (SCG) had Vrest=-57.0±1.8 mV, Rin=75.3±7.5 MÙ, a linear I-V relation and phasic firing. With patch electrodes, 16 dissociated SCG neurons (P15–20, 3–7 days in vitro) had Vrest=-70.0±1.3 mV, Rin=472.4±24.0 MÙ, a curved I-V relation, large h-currents, and 3 firing forms (tonic, phasic, intermediate). Whole cell data from intact ganglia were similar to data from dissociated cells and perforated patch data were similar to whole cell data. Thus, the results with whole cell recording were not artifacts of tissue culture or intracellular dialysis. We conclude microelectrodes introduce a ~10nS shunt. Adding 3–20nS shunts to dissociated cells with dynamic clamp linearized I-V relations and led to phasic firing. Impact upon synaptic gain was tested with bursts of virtual EPSPs (dynamic clamp) to mimic barosensitive vasomotor neurons. The results show that: ganglia can double preganglionic activity, periodic entrainment raises ganglionic gain, microelectrode damage masks gain in vivo, and they shed light on human microneurography.

3.12

ACTIVATION OF NUCLEAR FACTOR-KAPPA B LOWERS PROTEIN EXPRESSION OF VOLTAGE-GATED SODIUM CHANNELS IN NODOSE NEURONS FROM HEART FAILURE RATS

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Our previous study has shown that chronic heart failure (CHF) reduces protein expression of voltage-gated sodium ($Na_v1.7$) channels in rat nodose neurons. In the present study, we investigated the involvements of nuclear factor-kappa B (NF-kB) in CHF-decreased Na_v channel expression in rat nodose neurons. CHF was induced by left coronary arterial ligation. CHF reduced the protein expression of $Na_v1.7$ in the nodose neurons, and protein expression of NF-kB p65 and phosphorylated NF-kB p65 in the nodose neurons was higher in CHF rats than that in sham rats. Chromatin immunoprecipitation (ChIP) assays found that p65 NF-κB could interact with the promoter of Nav1.7, and CHF increased p65 binding to the promoter of $Na_v1.7$.Treatment with an NF-kB inhibitor (caffeic acid phenethyl ester, 10 μM, 24 h) significantly increased Na_v channel density in CHF nodose neurons, and partially reversed the reduced protein expression of Na_v channels in the CHF nodose neurons. These results indicate that activating NF-kB decreases the protein expression of $Na_v1.7$ channels in CHF nodose neurons.

3.13

INTEGRATED CIRCULATION AND RESPIRATION IN PHYSIOLOGY AND MEDICINE I: WHY WE CHANGED OUR CIRCULATORY STRUCTURE AND FUNCTION AFTER BIRTH

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INTRODUCTION: Since APS/EB2011&2012, ACCP2011 and APSR2011, we introduced theory system of integrated control and regulation of respiration-circulation, it appears to be clear for understanding of many questions in physiology and medicine. First, we try to explain mechanism of circulatory structural and functional changes after birth. QUESTION: Before birth, pulmonary blood flow is only ~9%, and >90% blood goes through foramen oval (FO) from right directly go to left atrium. After birth FO was closed normally. However, the mechanism of this closure is unclear. HYPOTHESIS: We try to use the sudden/abrupt change in alveolar PO2 (dominant) and PCO2 and blood “Trinity&#65533; of PO2 (dominant), PCO2 and [H+] after the first breath, to explain the mechanism for cardiovascular changes. EXPLANATIONS: The alveolar space without gases before birth, so it had a similar PO2, etc as all other tissues, i.e. < 20-40mmHg. After started the 1st breath, alveoli obtained room air and had similar PO2 to room air, i.e. ~140-150mmHg. Hyper-oxygen pulmonary vascular relaxation resulted that right heart had decreased afterward resistance due to over contracted pulmonary vascular structures and easily pumped all blood into pulmonary artery. Then its decreased blood volume in right atrium backward resulted in right atrium pressure lower than that in left atrium. Almost blood through lung came into left atrium increased its blood volume and pressure. The pressure difference between the right and left sides resulted closure of FO.

3.14

REGULATION OF THERMOGENIC CAPACITY BY THE BRAIN RENIN-ANGIOTENSIN SYSTEM: ROLE OF ADIPOSE AT2 RECEPTORS

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Manipulation of the renin-angiotensin system (RAS) has robust effects upon metabolism, and increasing evidence supports opposing roles for the local tissue versions of the RAS within the brain versus adipose in metabolic regulation. Previously we developed a mouse model of brain-specific RAS hyperactivity (the sRA model), with transgenic expression of human renin in neurons via the synapsin promoter, and human angiotensinogen via its own promoter. sRA mice are small and lean due to a robust elevation in resting metabolic rate, mediated through both increased adipose sympathetic drive and a suppression of the circulating RAS. Uncoupling protein-1 (UCP1) was specifically induced within inguinal adipose of sRA mice (25-fold, P=0.02). Treating differentiating 3T3L1 cells with 10 uM losartan had no effect on UCP1 mRNA, however 10 uM PD-123,319 specifically induced (2.4-fold), and CGP-42112a dose-dependently suppressed UCP1 both at baseline and with norepinephrine induction ($P<0.05$). Chronic infusion of CGP-42112a (50 ng/kg/min s.c., 8 weeks) into sRA mice resulted in normalization of resting metabolic rate (control 2.8±0.2, sRA 3.6±0.2, sRA+CGP 3.1±0.2 mL O2/100g/min) and inguinal UCP1 mRNA (sRA 24.6 vs. sRA+CGP 4.6-fold of control, P=0.02). These data support a role for adipose AT2 receptors in modulating the thermogenic capacity of adipose tissue. Ongoing studies are focused on elucidating the mechanisms of AT2-mediated morphological control within inguinal adipose.

3.15

ANGIOTENSIN II ENHANCES SYNAPTIC AMPLIFICATION IN SYMPATHETIC GANGLIA IMPLICATIONS FOR BAROREFLEX GAIN AND BLOOD PRESSURE CONTROL

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Angiotension II (ATII) increases blood pressure by acting on AT1 receptors in the kidney and brain. In addition, ATII excites sympathetic neurons by suppressing M-type K+ channels and possibly other effects. We hypothesized that these actions strengthen weak nicotinic synapses on sympathetic neurons and thereby increase the synaptic amplification that occurs when nicotinic EPSPs summate to drive postganglionic action potentials. To test this idea, dissociated rat sympathetic neurons (P13-P15) from the superior cervical ganglion were stimulated with physiologically realistic patterns of virtual nicotinic EPSPs using patch recording and dynamic clamp. Synaptic templates were constructed from a model consisting of 1 strong synapse and 8 weak synapses, each firing stochastically at an average rate of 1 Hz, in synchrony with a 5 Hz cardiac rhythm and assuming a 20% duty cycle. When weak synapses were adjusted to 60% of threshold synaptic conductance (gsyn), it produced a baseline gain of 1.75. Adding 50 nM ATII decreased threshold-gsyn by 30%, increased excitability as measured by spike responses to depolarizing current pulses, and increased synaptic gain to 2.6. In other words, ATII increased ganglionic gain and therefore baroreflex gain by 50%. With 6 weak synapses, ATII increased gain by 52.9 ± 14.4% (n=3). These data suggest

that AT1 receptor antagonists used clinically to control blood pressure act in part by decreasing synaptic gain in sympathetic ganglia.

3.16

MAS RECEPTOR IN THE RVLM MEDIATES CARDIAC SYMPATHO-INHIBITORY EFFECTS OF ACE2 OVER-EXPRESSION IN MICE WITH CHRONIC HEART FAILURE

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Elevated central angiotensin (Ang) II signaling contributes to the sustained increase of sympathetic outflow during chronic heart failure (CHF), which is associated with downregulation of ACE2 in the brain. We have previously shown that sympathetic outflow was attenuated in micewith neuron-selective ACE2 overexpression (SA) during CHF. However, it is not clear whether this putative sympatho-inhibitory effect is due to Ang-(1-7) and mas receptorsignaling in the pre-sympathetic neurons in those mice. We hypothesized that suppression of mas receptors in the RVLM increases cardiac sympathetic drive in SA mice during CHF. Five weeks after coronary artery ligation, baseline mean arterial pressure (MAP) and heart rate (HR) were recorded with telemetry for 3 days. Mas receptors were knocked down using lentiviral vectors encoding MAS1 shRNA (masKD) or scrambled control shRNA (scrb) were microinjected into the RVLM bilaterally. MAP and HR were recorded after one week of recovery. Autonomic tone was evaluated with ganglionic blockade using hexamethonium (Hex; 200 mg/kg ip).In SA mice, there was no change in HR after microinjection of scrb lentivirus (pre: 590±4 bpm vs. post: 588±6 bpm), however masKD increased HR (pre: 595±1 bpm vs. post 618±5 bpm, $p<0.05$). The differencein HR between scrb and masKD was normalized by Hex (scrb: 536 ±15 bpm vs. masKD 521 ±24 bpm). MAP in SA mice was decreasedsimilarlyin scrb and masKD mice. These data suggest that the cardiac sympatho-inhibitory effect of ACE2 overexpression in CHF is partially through mas signaling in RVLM.

3.17

NUCLEAR FACTOR-KB (NFKB) GENE SILENCING IN THE ROSTRAL VENTROLATERAL MEDULLA (RVLM) ATTENUATES ANGIOTENSIN II (ANGII) INDUCED HYPERTENSION

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AngII increases intracellular signaling in sympatho-excitatory centers in the brain such as the RVLM, causing upregulation of the Angiotensin-Type1-receptor (AT1R). We have previously shown in an in-vitro (CATH.a neuron) system upregulation of AT1R occurs via a transcription factor cascade mechanism involving NFkB, Ets-Like Protein-1 (Elk-1) and Activator Protein-1 (AP-1). To demonstrate the role of NFkB in-vivo, we hypothesized that silencing the NFkB gene in the RVLM, would attenuate AngII-induced hypertension. Male rats were implanted with telemetry for remote monitoring of blood pressure. After baseline recordings AngII was infused (350ng/kg/min) for 21 days and their MAP and heart rate were recorded for 1hour/day. The peak elevation of MAP occurred at day 7-10 post AngII infusion. The animals were then administered either a lentivirus-p65 shRNA or a lentivirus-scrambled shRNA, bilaterally into the RVLM. Within 3-4 days following injection of the p65-shRNA, MAP was reduced and was significant at 5-7 days post injection, as compared to the scrambled-shRNA group. Ten days after the lentiviral injections, the animals were euthanized and the brains removed for RVLM analysis. mRNA transcripts of p65, Elk-1 and AT1R showed significant reduction in the RVLM, compared to the scrambled-shRNA animals. Our results demonstrate the role of NFkB in activating downstream transcription factors leading to AT1R gene regulation in the RVLM.

3.18

ER STRESS IN RVLM MEDIATES NEUROGENIC HYPERTENSION THROUGH ACTIVATION OF PI3K/AKT PATHWAY

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Endoplasmic reticulum (ER) stress has been implicated in the pathology of neurodegenerative diseases. We have also shown that the ER stress in the rostral ventrolateral medulla (RVLM), where the sympathetic premotor neurons for maintenance of basal vasomotor tone are located, plays a contributing role in pathogenesis of neurogenic hypertension. The underlying mechanism is, however, unknown. In comparison to normotensive Wistar-Kyoto rats, expressions of GRP78 and the phosphorylated eukaryotic initiation factor 2α (eIF2α), two protein markers of ER stress, were significant greater in RVLM of the spontaneously hypertensive rats (SHR). Protecting the RVLM of SHR by microinjection bilaterally into the nucleus of an ER stress inhibitor, salubrinal, caused a significant decrease in systolic arterial pressure (SAP), alongside suppressions of the augmented GRP78 expression, eIF2α phosphorylation, reduction in phosphatidylinositol 3-kinase (PI3K) expression and dephosphorylation of Akt in the RVLM. Moreover, similar results in SAP were observed following microinjection bilaterally into RVLM of PI3K inhibitors, LY294002 or wortmannin. Collectively these results suggest that an exaggerated ER stress in SHR may contribute to neurogenic hypertension through activation of PI3K/Akt pathway in RVLM.

3.19

SEVERE HYPERTENSION IS UNMASKED IN METHIONINE SULFOXIDE REDUCTASE-A DEFICIENT MICE BY CONTROLLING FOR DIFFERENCES IN LOCOMOTOR ACTIVITY

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We recently demonstrated that mice deficient in the antioxidant enzyme methionine sulfoxide reductase-A (MsrA) exhibit mild hypertension (+10 mmHg, $P<0.05$) accompanied by decreases in locomotor activity and baroreflex sensitivity (BRS)*(Clin Auton Res, 2011; FASEB J, 2012)*. Because activity influences blood pressure (BP), we hypothesized that hypertensionin MsrA-/- mice would be more pronouncedif the comparison to control mice is made when activity is similar. BPand activity were recordedby telemetryfor 1 hourin young (11-18 wks) MsrA-/- (n=12) and control C57BL/6 (n=7) mice.Activity (units), mean BP (mmHg), systolic BP variability (BPV, SD, mmHg) and BRS (sequence technique, ms/mmHg) were measured. At similar low levels of activity,BP and BPV weremarkedly elevatedwhile BRS was decreasedin MsrA-/- *vs.* control mice (Table, *$P<0.05$).In contrast, whenBPwas increased during periods of high activity in control mice(Table, †$P<0.05$), BPV and BRS were relatively unaffected.We conclude:1) BP is positively correlated with increased activity; 2) When activity is similar, BP and BPV are markedly elevated in MsrA-/- *vs.* control mice; 3) Activity-level should be considered when assessing hypertension phenotypes; and 4)The increased BP and BPV and decreased BRSin MsrA-/- mice identify MsrA as a therapeutic target in hypertension. (HL14388, VA)

	MsrA-/- Low Act.	C57BL6 Low Act.	C57BL6 High Act.
Activity	3.3±0.8	3.5±1.1	15.0±3.8†
Mean BP	135±2*	103±2	126±3†
BPV	19.0±1.1*	2.5±0.5	3.7±0.7
BRS	0.86±.05*	2.37±.20	2.23±.10

3.20

EXPRESSION OF ROS CATABOLIC ENZYMES IN THE MEDIAL NUCLEUS TRACTUS SOLITARII (NTS) OF RATS AND UP-REGULATION DURING ACUTE HYPOXIA

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Reactive oxygen species (ROS) increase in the nTS following acute hypoxia and likely contribute to hypoxia-induced changes in cardiorespiratory function. H_2O_2 is a diffusible signaling molecule that is inactivated by catalase (CAT) and glutathione peroxidase (GPx). Immunohistochemistry in untreated rats identified CAT throughout the nTS. In NeuN-identified neurons, CAT was located perinuclear to a dense continuous network that extended into the cellular processes, presumably the endoplasmic reticulum. In microglia-like cells, CAT was identified in the cytosol and cell membrane. CAT was not localized to GFAP-identified astrocytes. GPx-1 staining was located perinuclear in nTS neurons, likely associated with the mitochondrial network. Astrocytes did not have GPx-1 staining. mRNA for the ROS inactivating enzymes superoxide dismutase (SOD) 1, SOD 2, CAT, Gpx1, and Gpx4 was expressed in tissue punches of the medial nTS of male rats exposed to 2 hr. of normoxia (21% O_2, n = 6) or hypoxia (10% O_2, n = 6). Only relative expression of Gpx1 was increased ($P< 0.02$) in the nTS of hypoxic (1.8 ± 0.3) versus normoxic rats (1.0 ± 0.1). Thus, enzymes responsible for catabolism of ROS are present in the nTS and upregulation of GPx-1 may be an early compensatory response to a hypoxic challenge. Support: NIH Multi-Investigator RO1 HL098602 (EMH, CMH, DDK).

3.21 Withdrawn.

3.22

CAT CARDIOVASCULAR RESPONSES TO HYPOXEMIA WITH BOTH, ONE, NEITHER ARTERIAL CHEMO-RECEPTOR(S)

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The purpose of this study was to determine the anesthetized, paralyzed, artificially ventilated cat's cardiovascular responses to hypoxemia with both carotid and aortic bodies connected to NTS, with *either* the carotid bodies *or* the aortic bodies connected to NTS, and with neither connected. Cats of either sex (2.5-4.0 kg) instrumented with an aortic flow probe, and cannulae (inferior vena cava, pulmonary artery, left auricle and ventricle, femoral artery) were first exposed to 8-10% O_2 in N_2 for 15min (hypoxic hypoxia, HHint; SaO2~45%), then to carbon monoxide (CO) hypoxia for 15min (COHint;SaO2~43%). While removing CO aortic depressor nerves were cut (aortic bodies resected;abr). HH exposure was repeated (HHabr), followed by COH exposure (COHabr). Under HHint both cbs and abs

went to NTS. Under COHint only abs, to NTS. Under HHabr only cbs, to NTS. Under COHabr neither cbs nor abs, to NTS. The data suggested that both cbs and abs are needed to maintain peak homeostasis in the face of an hypoxic challenge; e.g., to offset the extensive systemic vasodilation. In some cases the cbs seem to exercise a greater influence than the abs; e.g. cardiac output, dP/dtmax, femoral blood pressure. However, the abs do exercise a significant influence; e.g., on pulmonary vascular resistance. Supported by the NHLBI: HL 0-507-12-15.

3.23
PROGRESSION OF CAROTID BODY CHEMOSENSORY POTENTIATION AND CARDIORESPIRATORY ALTERATIONS DURING INTERMITTENT HYPOXIA: THE CHEMO-REFLEX LINK TO AUTONOMIC DYSFUNCTION

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The sleep apnea syndrome, characterized by chronic intermittent hypoxia (CIH) is recognized as an independent risk factor for hypertension. A crucial step in the CIH-induced hypertension is the potentiation of carotid body (CB) chemosensory responses to hypoxia, associated with enhanced hypoxic ventilatory and sympathetic responses, attenuation of spontaneous baroreflex efficiency (SBR) and alterations of heart rate variability (HRV). Since the time-course of the chemosensory and cardiorespiratory alterations are not well known, we hypothesized that CB chemosensory potentiation should precede the autonomic alterations and hypertension. Thus, we studied the effects of CIH on CB chemosensory and ventilatory responses to acute hypoxia, blood pressure (BP), SRB and HRV. Experiments were performed on male Sprague-Dawley rats exposed to 5%O_2, 12 times/hr for 8 hrs, for 7-21 days, or sham condition for 21 days. Exposure to CIH for 7 days enhanced CB chemosensory and ventilatory responses to hypoxia and reduced SBR, effects maintained until 21 days of CIH. After 14 days, CIH shifted the HRV power spectrum toward the low frequency band suggesting a predominance of the sympathetic component. Cardiorespiratory alterations occurred without significant BP elevation until 21 days of CIH. Thus, present results show that the CIH-induced hypertension was preceded by an early potentiation of CB chemosensory and ventilatory responses to hypoxia, reduction of SBR and alterations of HRV. Support by FONDECYT 1100405.

3.24
OBSTRUCTIVE SLEEP APNEA IS ASSOCIATED WITH INCREASED CHEMOREFLEX SENSITIVITY IN PATIENTS WITH METABOLIC SYNDROME

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Objective: We tested the hypothesis that chemoreflex sensitivity is heightened in patients with MetS and OSA. Methods: Forty six newly diagnosed MetS patients (ATP-III) were allocated into: 1) MetS+OSA (n=24, 48±1.8y); and 2) MetS-OSA (n= 22, 44±1.7y). Eleven normal individuals were also enrolled (C, 47±2.3y). OSA was deferred as an apnea/hypopnea index >15 events/hour (polysomnography). We evaluated muscle sympathetic nerve activity (MSNA-microneurography) and peripheral chemoreflex sensitivity by inhalation of 10% O2 and 90% N2 (CO2 titrated), and central by 7% CO2 and 93% O2 for 3 min. Results: MetS and anthropometric data were similar between MetS+OSA and MetS-OSA. MSNA was higher in MetS compared to C, and MSNA was higher in MetS+OSA than MetS-OSA (33±1.3, 28±1.2 and 18±2.2 bursts/min, P<0.05). Despite similar decreases in O2 saturation, MSNA during hypoxia was higher in MetS compared to C and higher in MetS+OSA compared to MetS-OSA (P=0.03). Also, despite similar increases in end-tidal CO2, MSNA during hypercapnia was higher in MetS than C and higher in MetS+OSA than MetS-OSA (P=0.005). Additionally, minute ventilation in response to hypercapnia was higher in MetS+OSA compared to C (P=0.001). Conclusion: OSA is associated with increased peripheral and central chemoreflex sensitivity in patients with MetS. These findings suggest mechanisms to explain the heightened sympathetic outflow in patients with MetS and comorbid OSA.

3.25
C1 AND RTN NEURON STIMULATION PRODUCES CORTICAL AROUSAL IN SLEEPING RATS

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Sleep-disordered breathing is associated with repeated bouts of hypoxia and hypercapnia leading to respiratory, autonomic and cortical arousal. Phox2b-expressing neurons of the retrotrapezoid nucleus (RTN) and C1 adrenergic population in the rostral ventrolateral medulla (RVLM) are important for the cardiorespiratory response to hypoxia and hypercapnia and innervate brain regions that regulate wakefulness. In this study, we evaluate if selective stimulation of Phox2b-expressing neurons is sufficient to produce sleep to wake transitions during non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS) in rats instrumented for recordings of cortical EEG and neck EMG. Channelrhodopsin2 (ChR2) was restricted to C1 and RTN neurons using a lentivirus vector carrying a Phox2b-dependent promoter. Photostimulation (2-20 Hz, 10 ms pulses) produced frequency dependent transitions from NREMS to wakefulness in 72% of trials (P<0.001, N=8). In contrast, stimulation during REMS was not associated with significant transitions to wakefulness (P=0.40). Using plethysmography, we evaluated the respiratory effects of photostimulation during NREMS and REMS. Photostimulation during NREMS increased tidal volume (TV: +34%) and breathing frequency (fR: +57%), whereas only TV was increased (+24%) during REMS (fR: +5%). The ventilatory effect of photostimulation was significantly correlated with the probability of state transitions from NREMS and to a lesser degree REMS. This study demonstrates that photostimulation of Phox2b neurons in the RVLM is sufficient to produce cortical arousal in sleeping rats. This work suggests that C1 and RTN neurons could contribute to the arousal associated with sleep-disordered breathing.

4.0: OXIDATIVE STRESS AND SYMPATHETIC REGULATION

4.1
OXIDATIVE STRESS-ASSOCIATED SIGNALS IN REGULATION OF SYMPATHETIC ACTIVITY AND BLOOD PRESSURE

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Oxidative stress in rostral ventrolateral medulla (RVLM), where sympathetic premotor neurons located, contributes to neural mechanisms of hypertension. In normotensive rats, angiotensin II (Ang II) increases superoxide production and induces redox-sensitive activation of p38 mitogen-activated protein kinase (p38MAPK) and extracellular signal-regulated protein kinase (ERK)1/2 in RVLM. The p38MAPK mediates Ang II-induced acute pressor response via potentiation of glutamatergic neurotransmission, whereas ERK1/2 mediates a long-term pressor response of Ang II by transcriptional upregulation of angiotensin type 1 receptors in RVLM. In RVLM of SHR, redox-sensitive transcription of uncoupling protein 2 (UCP2), an endogenous mitochondrial antioxidant, is downregulated. Transcriptional upregulation of UCP2 alleviates oxidative stress and promotes antihypertension in SHR. Moreover, oxidative stress upregulates transcription of the brain-derived neurotrophic factor (BDNF), this in turn exerts a negative-feedback regulation of superoxide production via upregulation of UCP2. In SHR, this redox-dependent BDNF-UCP2 signaling pathway is suppressed in RVLM, leading to overexcitation of sympathetic vasomotor activity and manifestation of hypertension.

4.2
NANOFORUMULATED ANTIOXIDANTS: DELIVERY TO CENTRAL NEURONS AND MODULATION OF ANGIOTENSIN II INTRA-NEURONAL SIGNALING

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Aberrant angiotensin II (AngII) signaling in the central nervous system (CNS) and neurogenichypertension are linked toexcessive superoxide ($O_2^{\bullet-}$)levels. Previously, we and others reported that adenoviral-mediated overexpression of the $O_2^{\bullet-}$ scavenging enzyme, superoxide dismutase 1 (SOD1), in the brain inhibits Ang II-induced hypertension. However, peripherally administered adenovirus induces toxicity and does not target the brain.To improve CNS delivery of SOD1, we developed SOD nano, a polyion complex nanotechnology delivery system composed of a polyethylene glycol corona and polyethyleneimine core (PEI-PEG) that electrostatically binds SOD1 protein. We hypothesize that SOD nano delivers functional SOD1 protein to neuronsand inhibits AngII intra-neuronal signaling and the central AngII-induced pressor response. Using cultured neurons, we have shown that SOD nano delivers active SOD1 protein intracellularly, via active endocytosis, as evident by a decrease in $O_2^{\bullet-}$ levels and attenuation of the AngII-mediated inhibition of outward K^+ current. Once internalized, SOD nano is distributed into various subcellular compartments including Rab5+ endosomes, mitochondria, lysosomes, and cytoplasm. *In vivo* studies revealed that the central AngII-induced pressor response is inhibited by an intracarotid injection of SOD nano, but not free SOD1 protein, thus suggesting delivery of SOD nano to the brain following peripheral administration. These data demonstrate that SOD1 nano delivers functional SOD1 protein to neurons and suggest therapeutic potential of SOD nano for AngII-dependent neurogenic hypertension.

5.0: MECHANISMS OF BARO AND CHEMORECEPTORS SENSORY TRANS-DUCTION: A LINK TO SYMPATHO-EXCITATION IN DISEASE

5.1
SENSORY NEURONAL SIGNALS THAT ARE POWERFUL REGULATORS OF THE HYPERTENSIVE STATE

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Neuronal signals from baroreceptors, chemoreceptors, vagal afferents, and central neurons have pronounced effects on autonomic drive to the circulation. Their disruption results in sympathetic-vagal efferent imbalances that exacerbate hypertension and cardiovascular mortality. Molecular determinants of activation of nodose neurons with vagal and baroreceptor afferents, and of glomus cells which initiate chemoreceptor activity, were identified by their mRNAs and microRNAs. Changes in expression of ion channels (ASIC2, ASIC3, TASK, Kv's, $^{Cl\text{-}C}$), of NaK-ATPase, methionine sulfoxide reductase, and NADPH oxidase in knockout and transgenic mouse models may account for decreased baro- and increased chemoreceptor sensitivity such as seen in spontaneously hypertensive rats (SHR). Two autonomic efferent signals also modify significantly the course of hypertension in SHR. One is the sympatho-excitatory contribution of peripheral chemoreceptors. By resecting carotid bodies in prehypertensive SHR, we found that over one-third of the subsequent sustained increase in blood pressure was abrogated. The second represents a beneficial anti-inflammatory effect of parasympathetic stimulation and nicotinic cholinergic receptors on innate immune cells which is reversed in SHR. Thus, autonomic dysregulation of the immune system is an important, novel neuropathogenic mechanism in hypertension. Support: NIH HL14388. Reference: Abboud, F.M., Harwani, S.C., and Chapleau, M.W.: Autonomic Neural Regulation of the Immune System: Implications for Hypertension and Cardiovascular Disease. Hypertension, 59:755-762, 2012

5.2
GASEOUS MESSENGERS IN OXYGEN SENSING BY THE CAROTID BODY

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This presentation focuses on the roles of gas messengers in hypoxic sensing by the carotid body. Carbon monoxide (CO) and nitric oxide (NO), generated by heme oxygenase-2 (HO-2) and neuronal nitric oxide synthase (nNOS), respectively, inhibit carotid body activity. Molecular O_2 is a required substrate for the enzymatic activities of HO-2 and nNOS. Stimulation of carotid body activity by hypoxia may reflect *reduced* formation of CO and NO. Glomus cells, the site of O_2 sensing in the carotid body, express cystathionine γ-lyase (CSE), an H_2S generating enzyme. *Cth*$^{-/-}$ mice, which lack CSE, exhibit severely impaired hypoxia-induced H_2S generation, sensory excitation, and stimulation of breathing in response to low O_2. Hypoxia-evoked H_2S generation in the carotid body requires the interaction of CSE with HO-2, which generates CO. Heightened carotid body activity has been implicated in the pathogenesis of autonomic morbidities associated with sleep-disordered breathing, congestive heart failure, and essential hypertension. NIH-HL-76537, HL-90554, and HL-86493. Prabhakar NR et al. 1993. Hypoxia inhibits NO generation in the carotid body and NO is inhibitory to the carotid body sensory activity. *Brain Res* 625:16-22. Prabhakar NR et al. 1995.Hemeoxygenase 2 is expressed in glomus cells and endogenous CO inhibits sensory activity. *Proc Natl Acad Sci USA* 92:1994-1997. Peng YJ et al. 2010. Cystathinine-γ-lyase (CSE), an H_2S generating enzyme is expressed in glomus cells and endogenous H_2S mediates O_2 sensing in the carotid body. *Proc Natl Acad Sci U S A* 107:10719-10724.

6.0: PLENARY LECTURE II

6.1
NEUROMODULATORY PATHWAYS AND CENTRAL CONTROL OF SYMPATHETIC ACTIVITY IN HYPERTENSION AND HEART FAILURE

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The classical neurotransmitters, glutamate and GABA, mediate fast (msec) synaptic transmission, and modulate its effectiveness through slow (sec to min) signaling processes. Activation of angiotensinergic pathways from the lamina terminalis to the PVN/SON and RVLM by stimuli such as circulating Ang II or CSF[Na+] leads to sympatho-excitation largely by decreasing GABA and increasing glutamate release. The aldosterone-"ouabain" pathway is a much slower pathway. Aldosterone enhances "ouabain" release, which then increases chronic activity in angiotensinergic pathways by eg increasing expression of AT1R and NADPH oxidase subunits in the PVN. Blockade of this pathway largely prevents chronic sympatho-excitatory and pressor responses to CSF[Na+] or Ang II. These 2 neuromodulatory pathways allow the CNS to rapidly cause and sustain sympathetic hyperactivity efficiently over hours/days. In models of salt-sensitive hypertension, high salt diet increases CSF[Na+] and hypothalamic aldosterone and "ouabain". The resulting sympatho-excitation and hypertension can be prevented by specific CNS blockade of any of the steps in the pathway from aldosterone synthase to AT1R. Whether this pathway also is activated in other hypertension models, depending on central AT1R stimulation, has not yet been studied. Post MI, AT1R stimulation in the PVN plays a critical role. Chronic activation of the hypothalamic aldosterone-"ouabain" pathway, possibly by plasma Ang II, is the main mechanism contributing to this persistent AT1R stimulation and thereby to sympathetic hyperactivity. How eg cytokines and microglia activation are involved, still needs to be assessed. Integration of rapid, slow and very slow CNS pathways contributing to sympatho-excitation provides a frame-work to understand how different stimuli and mechanisms may interact. Support:CIHR:MOP-74432;13182;119273.

7.0: SYMPATHO-EXCITATORY MECHA-NISMS IN CARDIOVASCULAR DISEASE

7.1
PSYCHOGENIC CARDIOVASCULAR DISEASE–NEURAL MECHANISMS

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Although the mediating mechanisms of psychogenic cardiovascular disease, which bridges the boundary between psychiatry and cardiology are unclear, sympathetic nervous pathophysiology is a prime mover. Severe acute mental stress can trigger heart attacks. This truth is contested, but the remarkable increase in non-traumatic sudden death during earthquakes provides one indisputable example. Sympathetic activation in acute human anxiety occurs preferentially in the cardiac sympathetic outflow. Two mechanisms mediating cardiac events are atherosclerotic plaque rupture from increased shear stress in the arterial wall, and the development of neural cardiac arrhythmias, to which vagal withdrawal also contributes, in people who have underlying, often unrecognised, coronary stenosis. Adverse cardiac events occurring in patients with panic disorder are analogous. Clinical case material includes recurrent emergency room attendances with electrocardiograph ischemia, cardiac arrhythmias, coronary artery spasm, and myocardial infarction. Nerve recording with microneurography during panic attacks captures the high level of sympathetic activation, evident in massive increase in the amplitude of the multiunit bursts. During panic attacks, neuropeptide Y (NPY) is released from sympathetic nerves of the heart, interesting in the context of coronary spasm in that NPY content in sympathetic nerves is high in arteries. We detect reduced neuronal norepinephrine uptake in panic disorder. This magnifies the sympathetic neural signal in the heart, contributing to increased cardiac risk. Reduced abundance of NET protein evident in Western blot analysis of sympathetic nerve proteins accessed via subcutaneous vein biopsy. Major Depressive Disorder (MDD) is a risk factor for coronary heart disease, no less important than hypercholesterolemia or diabetes. Using coronary venous sinus blood sampling we detect in a subset (approximately 40%) of patients with untreated MDD an extraordinarily high level of sympathetic nervous activity in the heart, to the level present in cardiac failure. This is normalised during clinical remission of MDD, on SSRI drugs. Beta-adrenergic blockade is life-saving in cardiac failure. Perhaps there will be a future place for anti-adrenergic cardiac protection also in MDD, especially in drug-resistant patients. Chronic mental stress is probably a cause of essential hypertension. Opinion on this is polarized, no doubt because the occupational health litigation dimensions of the subject are so divisive. Support in my country comes from the ruling of a Governmental body, the Specialist Medical Review Council. The judgment reached, that chronic mental stress is one proven cause of hypertension was based in particular on the neural pathophyiology of essential hypertension: (i) sympathetic activation is commonly present, (ii) noradrenergic brain neurons projecting to the hypothalamus and amygdala are activated, (iii) adrenaline is released as a cotransmitter from the sympathetic nerves of hypertensive patients, (iv) sympathetic nerves (accessed from a subcutaneous forearm vein biopsy) contain PNMT, absent in health, the probable origin of the co-released adrenaline.

7.2
ROLE OF INFLAMMATORY CELLS IN THE PROGRESSION OF CARDIOVASCULAR DISEASE

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Neuroendocrine immune interactions play an important role in the pathophysiology of cardiovascular disease. Each of the systems, namely the nervous system, endocrine system and immune system interact with each other via their mediators to maintain cardiovascular homeostasis. However, in cardiovascular disease this internal milieu is disturbed, resulting in excessive production of mediators and ultimately resulting in cardiovascular disease. In this presentation, we will examine how these neuromodulators contribute to the development of cardiovascular disease. We will examine some of our recent findings using the angiotensin (ANGII) infusion model of hypertension to understand the role played by the brain in the development of hypertension. We will use a comprehensive, whole animal, molecular, cellular and genetic approach to explore the possible mechanism by which cytokines and their transcription factor, nuclear factor kappa B (NFkB), in the paraventricular nucleus of the hypothalamus contribute to hypertension. Finally, we will also present data on the effect of direct manipulation of PVN NFkB and renin-angiotensin system modulation in the development of hypertension. Some of

our findings will suggest that cytokine or NFkB-induced changes within the PVN might be an important modulator of hypertension. The central link between cytokines and neurohumoral system activation in hypertension may lead to a better understanding of the progression of the disease processes and ultimately lead to new and effective strategies to treat hypertension.

8.0: POSTER SESSION II

8.1

KLOTHO AND CENTRAL REGULATION OF SYMPATHETIC NERVE DISCHARGE

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Klotho is a recently identified anti-aging gene and genetic mutation of *klotho* is associated with the presentation of numerous aging phenotypes (e.g., arteriosclerosis, hypoglycemia, hypoactivity).The working hypothesis is that silencing of brain *klotho* significantly potentiates SND responses to acute cold stress.To silence brain *klotho* in vivo we constructed recombinant adeno-associated virus (AAV) carrying short hairpin interference RNA (AAV-*kl*-shRNA) and AAV carrying a scrambled shRNA (AAV-*sc*-shRNA). Sprague-Dawley rats (250-350 g) were anesthetized and microinjected icv witheither AAV-*kl*-shRNA (exp. group) or AAV-*sc*-shRNA (control group)at $7.0x10^{10}$IFU and allowed to recover. Rats completed acute cold stress experiments at either 10, 15 or 20 days following injections. Renal SND was recorded in anesthetized rats while core body temperature was decreased from 38° to 30°C. Preliminary results indicatethat renal SND was decreased~50% at 30°C in each of rats receiving AAV-*sc*-shRNA, regardless of the recovery duration. In contrast, renal SND tended to be increased in response to cooling in the AAV-*kl*-shRNA-treated rats.The AAV-*kl*-shRNA reduced endogenous *klotho* expression ~50-70% compared to the AAV-*sc*-shRNA-treated rats. These preliminary data suggest that brain klotho may influence the responsiveness of sympathetic neural circuits to acute stress. Funding provided by NIH grants HL-091342 and HL-092392.

8.2

A_{2C}-ADRENOCEPTOR STIMULATION RESTORES A_{2A}-ADRENOCEPTOR MALFUNCTION IN HYPERTENSIVE RATS

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α_2-adrenoceptors α_2AR) control blood pressure (BP) by limiting central sympathetic output and peripheral noradrenaline (NA) and adrenaline (A) release and by acting on blood vessels. α_2AR malfunctions may result in high BP. We studied the effect of α_2AR agonists/antagonists, with different subtype profiles and ability to cross the blood-brain-barrier, on catecholamine release and vascular resistance (TPVR) in spontaneously hypertensive (SHR) and normotensive (WKY) rats. The peripheral α_2AR antagonist L-659,066 increased resting NA overflow to plasma when combined with NA-reuptake (NET) inhibitor, particularly in SHR. Tyramine-activated NA release through NET will inhibit reuptake. Effects due to presynaptic release control is therefore superimposed on NET-mediated release. Centrally active α_2AR-agonist (clonidine), but not fadolmidine (peripheral), reduced baseline BP, TPVR and heart rate, and resting and tyramine-stimulated NA overflow in SHR. L-659,066 increased NA overflow and reduced the TPVR-response to tyramine in WKY, but, in SHR, only when combined with peripheral, α_{2C}AR-stimulating agonist. α_2AR-modulation of experiment-induced, central activation of A secretion, mostly paralleled that of NA. Conclusions: α_2AR failed to limit peripheral NA and A release in SHR. Inhibition of smooth muscle α_2AR allowed NA to counter-act α_1AR-mediated vasoconstriction in WKY but not SHR. Peripheral α_{2C}AR-stimulation or lowering central sympathetic output with clonidine repaired these malfunctions in SHR.

8.3

PARAVENTRICULAR NUCLEUS AND RENAL SYMPATHETIC NERVE ACTIVITY IN HYPERADIPOSE RATS: POSSIBLE MECHANISMS FOR OBESITY INDUCED HYPERTENSION

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In the present study we evaluated the renal sympathetic nerve activity (RSNA) and the involvement of paraventricular nucleus (PVN) in hyperadipose rats induced by neonatal administration of monosodium glutamate (MSG). Neonatal Wistar male rats were injected with MSG (4 mg/g body weight ID) or equimolar saline (control) for 5 days. At 90th day, the rats were anesthetized (urethane 1.4g/kg) for catheterization of the femoral artery for mean arterial pressure (MAP) and heart rate (HR) measurements and the renal nerve was dissected and clamped with electrodes to RSNA recordings. We also evaluated the cardiovascular effects of GABAA agonist (muscimol) and antagonist (bicuculline) microinjected in the PVN of conscious control and hyperadipose rats. The anesthetized MSG rats presented baseline hypertension (CT= 90.00 ± 3.65; MSG=110.4 ± 8.25 mmHg) and increased RSNA compared with control (CT=72.01 ± 6.42; MSG= 94.48 ± 7.75 spikes/s). The conscious MSG rat also presented baseline hypertension (CT= 111.7 ± 1.61; MSG= 118.6 ± 1.12 mmHg) and the microinjection of muscimol in the PVN produced a higher decrease in MAP in MSG compared with control rats (CT = -18.26 ± 1.67; MSG= -24.40 ± 1.82 mmHg), with no difference in pressor and tachycardic responses to bicuculine. (CT= 41.27 ± 6.90; MSG= 43.51 ± 2.53 mmHg). Our results suggest the involvement of the renal sympathetic nervous system in the physiopathology of the MSG obesity and a possible involvement of PVN neurons.

8.4

THE SUBFORNICAL ORGAN IS ACTIVATED DURING CHRONIC HEART FAILURE AND EXHIBITS ENHANCED SYMPATHOEXCITATION IN RESPONSE TO ANGIOTENSIN II

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A characteristic feature of chronic heart failure (HF) that increases the risk of mortality is elevated sympathetic drive. The subfornical organ (SFO) is involved in neural control of sympathetic drive and may be influenced by circulating peptides such as angiotensin (Ang) II and endothelin (ET)-1 due to its weak blood-brain barrier.We hypothesized that an activated SFO, by Ang II/ET-1, contributes to enhanced sympathetic activity in HF.Sprague-Dawley rats were subjected to coronary artery ligation to induce HF. HF was confirmed by echocardiography 4 weeks after surgery. The activation of the SFO was assessed by FosB immunohistochemistry. Rats with HF had an increasein FosB-positive cells in the SFO compared to sham rats (101 vs. 29 FosB-positive cells). In urethane-anesthetized rats, microinjection of Ang II (50-200 pmol)into the SFO increased renal sympathetic nerve activity (RSNA), blood pressure, and heart rate to a greater extent in HF than in sham rats (ΔRSNA:31vs. 15% of basal value;100pmol). HF rats also exhibited an elevated protein expression of AT_1(67%), ET_A(69%), ET_B(40%) receptors, while they had areduced level of $GABA_A$ receptor (42%) in the SFO. The enhanced activation of the SFO by circulating peptidessuch as Ang II and ET-1, that are known to be elevated during HF, may contribute to the sympathoexcitation exhibited in HF. Supported by the UNMC Skala Fellowship and NIH grant HL62222.

8.5

PARADOXIC ELEVATIONS IN ANGIOTENSIN II, INDEPENDENT OF PLASMA RENIN, CONTRIBUTE TO THE SUPINE HYPERTENSION OF PRIMARY AUTONOMIC FAILURE

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Despite profound impairments in sympathetic activity, at least 50% of primary autonomic failure [AF]patients exhibit supine hypertension. While the mechanisms are unknown, plasma renin activity is often undetectable suggesting renin mechanisms are not involved. However, the preservation of aldosteroneled us to examine the status and contribution of the renin-angiotensin [Ang] system in AF.Supine plasma Ang peptideswere measured in hypertensive patients [AF-HT, n=18], normotensive patients [AF-NT, n=11] and matched healthy subjects[n=10]. Ang II levels were paradoxically elevated in AF [39±4 AF-HT vs 42±6 AF-NT vs 27±4 pg/mL healthy; $p<0.05$], despite suppressed renin. In contrast, Ang-(1-7) was reduced in AF patients [7±1 AF-HT vs 4±1 AF-NT vs 22±6 pg/mL healthy; $p<0.05$]. Plasma aldosterone was preserved in AF and did not correlate to Ang II levels. To determine the functional relevance of Ang II, we administered nighttime losartan [50mg, PO] to 9 AF-HT patients and measured supine systolic blood pressure q2 hours for 12 hours. Losartan significantly reduced blood pressure [25±15 mmHg at 6 hours after administration]. These findings suggest an imbalance in Ang II and Ang-(1-7) in AF that is independent of hypertensive status. The elevation in Ang II appears to contribute to hypertension in AF patients. Overall, these patients offer a unique model to study blood pressure regulation and the production of Ang II in the absence of both autonomic and renin influences. Funding: AHA 11POST7330010, CTSA UL1 RR024975

8.6

NOREPINEPHRINE INCREASES NADPH OXIDASE-DERIVED SUPEROXIDE PRODUCTION IN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM HEALTHY HUMANS

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Many diseases associated with sympathetic overactivity also exhibit elevated reactive oxygen species (ROS). Although animal studies suggest that exogenous administration of the sympathetic neurotransmitter norepinephrine (NE) increases systemic ROS, the ability of NE to increase ROS in humans is unknown. Thus, we sought to examine the potential contribution of NE via the NADPH oxidase pathway in increasing superoxide production in peripheral blood mononuclear cells (PBMCs) from healthy humans. PBMCs were isolated from blood samples in 7 healthy males. NADPH oxidase ($gp91^{phox}$and $p22^{phox}$) mRNA expression was assessed using real time RT-PCR at 1, 6, 12 and 24 hours following NE (50ng/ml

and 50pg/ml) or vehicle treatment. In addition, intracellular superoxide production was measured at 1, 6, 12, 24 and 36 hours using dihydroethidium following NE only, NE + diphenylene iodonium (DPI; selective NADPH oxidase blocker) and vehicle. At physiological concentrations of NE (50ng/ml and 50pg/ml), expressions of $gp91^{phox}$ and $p22^{phox}$ were increased at 12 and 24 hours (e.g., $gp91^{phox}$; 12±4and 4±3 fold; NE (50ng/ml) vs. vehicle; $P<0.05$). This was followed by an increase in superoxide production at 36 hours (1.4±0.3 fold; NE (50ng/ml) vs. vehicle; $P<0.05$). Importantly, NE-induced increases in superoxide production were attenuated by DPI. These findings suggest that NE increases the expression of NADPH oxidase subunit genes and NADPH oxidase-derived superoxide production in human PBMCs.

8.7

EXAGGERATED PRESSOR RESPONSE TO MENTAL STRESS IN MEN COMPARED TO WOMEN: UNDERLYING HEMODYNAMIC MECHANISMS AND ACUTE EFFECT OF EXERCISE

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Potential mechanisms underlying the sex-dependent blood pressure (BP) responses to mental stress (MS) remain unclear, but previous evidence suggests that it is unlikely related to endogenous levels of sex steroids, sympathetic outflow or differences in stress-induced forearm vasodilation. Importantly, exercise has been proposed as a coping resource for stress management. Given this, the purpose of the present study was to determine the role of cardiac output (CO; ModelFLow) and forearm vascular responses (plethysmography) in mediating the pressor response (Finometer) to MS (3 min, Stroop word–colour test) before and 60 min after a maximal exercise bout (treadmill) in young healthy men (n=15) and women (n=19). Before exercise, BP response was significantly ($P<0.05$) augmented in men (Δ16±2 mmHg) compared to women (Δ11±1 mmHg). This heightened response to MS, was also accompanied by greater increases in CO in men (Δ31±7 %; $P<0.05$) compared to women (Δ11±5 %) and similar forearm vasodilation between sexes (Δ70±20% men vs Δ78±16% women). After exercise, the BP, CO responses to MS were attenuated only in men and, consequently, no sex differences were observed during this period. Vascular responses to MS were not affected by exercise. In summary, these findings highlight for the first time a potential role for CO in mediating the exaggerated BP response in men as well as how exercise could benefit male subjects in regards to the cardiovascular reactivity during a mental stress.

8.8

RELATION OF CARDIOVAGAL BAROREFLEX SENSITIVITY TO IMPAIRED CAROTID ARTERY ELASTIC FUNCTION IN PATIENTS WITH TETRALOGY OF FALLOT

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Background: Sudden cardiac death (SCD) is a common late complication in patients with tetralogy of Fallot (ToF). Reduced cardiovagal baroreflex sensitivity (BRS) was found to be an independent predictor of SCD. Reduced BRS was reported in ToF patients, but the underlying mechanism is not clear. Our laboratory has shown earlier that BRS is related to carotid artery distensibility (DC) in healthy subjects and that DC is reduced in ToF. Considering all above, we aimed to test the hypothesis that reduced BRS is related to impaired carotid artery elastic function. Methods and results: We studied 36 ToF patients (21 ± 11 yrs) and 50 age– and gender–matched healthy control subjects. Carotid artery diastolic diameter and pulsatile distension was determined by echo wall tracking and carotid blood pressure was measured by tonometry. DC was calculated subsequently. Spontaneous blood pressure fluctuations coupled with adequate heart rate responses were used to calculate spontaneous BRS (sBRS). Intravenous phenylephrine–induced blood pressure elevation followed by heart rate reduction was used to determine BRSphe.. Results: (mean±SD) BRS indices were markedly reduced in patients compared with controls (sBRS 9.3±9.2 vs. 17.5±6.8 ms/mmHg; BRSphe 16.8±10.2 vs. 32.6±11.4 ms/mmHg). DC also showed significant difference between groups (5.1±1.8 vs. 6.8±2.8 10-3/mmHg). DC correlated significantly and positively with BRS across patients and control subjects as well (sBRS r=0.49† vs. r=0.42*; BRSphe r=0.31 vs. r=0.73*). Multiple regression analysis indicated that DC is an independent determinant of BRS indices in ToF patients. (†:$p<0.05$; *:$p<0.01$). Discussion: Our data demonstrate that reduced DC can contribute to impairment of BRS in ToF patients. Lifestyle modifications, such as moderate aerobic exercise, sodium restriction and omega-3-fatty acid intake, appear to be efficient interventions in preventing and treating carotid artery stiffness and –indirectly– impaired baroreflex function.

8.9

RHO KINASE INHIBITION LOWERS SYMPATHETIC NERVE ACTIVITY AND RESTORES BAROREFLEX IN CONSCIOUS RABBITS WITH CHRONIC HEART FAILURE

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Rho-Associated protein kinase (RhoK) is a serine/threonine kinase involved in calcium sensitization and vascular smooth muscle cell contraction. RhoK overactivation is implicated in chronic heart failure (CHF) anda potential contributor to the heightened sympathetic nerve activity (SNA) seen in CHF. Thus, we investigated the effect of central RhoK blockade on renal SNA (RSNA) in a pacing rabbit model of CHF. We induced CHF by placement of left ventricular pacing leads and characterized CHF by an ejection fraction of ~45%. Renal nerve recording electrodes and an ICV cannula and osmotic minipump (rate: 1 μL/h) containing sterile saline or 1.5 mg/kg/mL fasudil (Fas, a RhoK inhibitor) were implanted. Arterial baroreflex control was determined by IV infusion of sodium nitroprusside (100μg/kg) until mean arterial pressure (MAP) was lowered to ~40 mmHg and phenylephrine (80μg/kg) until MAP was raised to ~100 mm Hg. Fas infusion significantly lowered resting heart rate by 25 ± 2.1 BPMand improved maximal HR/MAP baroreflex gain in CHF (Fas:2.20 ± 0.13 vs Veh:2.84 ± 0.12, $p<0.05$). Administration of metoprolol prior to performing baroreflex analysis increased slope in the Fas group, suggesting Fas improves vagal tone. Change in RSNA response to oropharyngeal smoke was increased in CHF Fas animals (93 ± 18%)vs CHF Veh (45 ± 9%).These data suggest that central RhoK activation may contribute to sympatho-excitation in the setting of CHF. Supported by PO-1 HL62222.

8.10

BLUNTED ADRENERGIC VASOCONSTRICTION IMPAIRS BLOOD PRESSURE RECOVERY FOLLOWING SEVERE HEMORRHAGE IN OBESE ZUCKER RATS

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Obesity has impaired baroreflex activity and elevated sympathetic tone which may impair the buffer capacity in response to hemorrhage. We hypothesize that blood pressure compensation following severe hemorrhage is impaired in obesity due to a blunted baroreflex and altered sympathetic mediated vasoconstriction. A loss of 35% of total blood volume was induced in conscious lean (LZ) and obese Zucker rats (OZ) (11-12 weeks). Blood pressure (BP) and heart rate (HR) were monitored during the hemorrhage and a 1 hour recovery. The basal BP, HR, and total peripheral resistance (TPR) were not different between groups. During hemorrhage, BP in LZ did not decrease until 15% loss of total blood volume. This was associated with a transient increase in HR. In OZ, BP dropped below basal levels after a 5% loss associated with an absence of tachycardia. After a 1 hour recovery, BP was partially compensated through an increased TPR in LZ and OZ, with the increases in BP and TPR blunted in OZ. Prazosin (selective ¦Á1 antagonist) treatment caused a larger decrease in basal BP in OZ as compared with LZ. Prazosin treatment blocked the BP compensation and increase in TPR in both LZ and OZ. Our results suggest that the compensatory mechanisms mediated by baroreflex and sympathetic vasoconstriction following severe hemorrhage are blunted in OZ.

8.11 Withdrawn.

8.12

C-TYPE NATRIURETIC PEPTIDE IN THE PVN MEDIATES RENAL SYMPATHO-INHIBITION

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Volume expansion produces a reflex decrease in renal sympathetic nerve activity (RSNA) that is mediated by the paraventricualr nucleus (PVN). However, the mechanisms for the sympatho-inhibitory role of the PVN and the neurochemical factors involved remain to be identified. C-type natriuretic peptide (CNP) has the attributes to be a potential candidate as a mediator of this sympathoihbition in the PVN. First, microinjection of CNP into the PVN significantly decreased heart rate (HR) (-23.6±3.5 vs. -0.3±0.9 beats/min), renal sympathetic nerve activity (RSNA) (-25.8±1.8 vs. -3.6±1.5%) and means arterial pressure (MAP) (-15.0±1.9 vs. -0.1±0.9 mmHg) compared with microinjection of artificial cerebrospinal fluid. Second, 19 spontaneously active neurons were recorded in the PVN in normal rats with extracellular single-unit recording in vivo, and 6 units were antidromically activated from the rostral ventrolateral medulla (RVLM). Picoinjection of CNP significantly decreased the basal discharge in 5/6 PVN-RVLM neurons, and in 6/13 neurons that were not antidromically activated from the RVLM. There were no significant changes after picoinjection of artificial cerebrospinal fluid. Third, we determined whether natriuretic peptide receptor type C (NPR-C) was present on PVN neurons that projected to the RVLM. The retrogradely transported fluorescent tracers LatexGreen was injected into the RVLM. The NPR-C was present on PVN neurons that projected to the RVLM as detected by immunohistochemistry. Double-labeled neurons major localized in the parvocellular part of the PVN. These results suggest a potential role for CNP in the PVN in the regulation of renal sympathetic nerve activity.

8.13

NEUROINFLAMMATION IN ROSTRAL VENTROLATERAL MEDULLA CONTRIBUTES TO NEUROGENIC HYPERTENSION FOLLOWING CHRONIC SYSTEMIC INFLAMMATION

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Neuroinflammation, which increases sympathetic drive, contributes to cardiovascular diseases including hypertension. Rostral ventrolateral medulla (RVLM), which regulates central sympathetic outflow, is involved in neural mechanism of hypertension. Kv4.3, one of voltage-gated K+ channels, in RVLM has been demonstrated to regulate sympathetic outflow. We investigated whether neuroinflammation causes downregulation of Kv4.3 ion channel in RVLM to mediate neurogenic hypertension under chronic systemic inflammation (CSI). CSI was induced via a continuous intraperitoneal infusion of E coli. lipopolysaccharide to normotensive Sprague-Dawley rats. Activation of microglia, activation of cyclooxygenase-2 (COX-2), increases in proinflammatory cytokine, NADPH oxidase subunits, and intercellular adhesion molecule-1 expression, and decrease in endothelial nitric oxide synthase expression were observed in RVLM under CSI. A long-term pressor response, accompanied by an increase in tissue level of superoxide and a downregulation of Kv4.3 expression was also detected in the RVLM. Pressor response and cellular events were significantly prevented by inhibition of microglia activation, COX-2 inhibition, cytokine suppression, and superoxide scavenge. Together, these results suggest that CSI activates microglia to evoke a COX-2-dependent neuroinflammation, oxidative stress and Kv4.3 downregulation in RVLM, leading to neurogenic hypertension. (This study was supported by research grants NSC-99-2811-B-075B-001 and NSC-99-2321-B-075B-001 from the National Science Council, Taiwan, Republic of China).

8.14

SYMPATHOEXCITATION INDUCED BY ETHANOL IN THE CENTRAL AMYGDALA INVOLVES LOCAL ACTIVATION OF NMDA RECEPTORS IN ANESTHETIZED RATS

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Evidence indicates that central mechanisms contribute to the increased sympathetic nerve activity (SNA) and arterial pressure in response to ethanol intake. One of the key areas that link ethanol-induced sympathoexcitation is the central nucleus of the amygdala (CeA). However, the underlying neural mechanisms have not been determined. We tested the hypothesis that the sympathoexcitatory response to CeA injection of ethanol requires activation of local ionotropic excitatory amino acid (EAA) receptors. In anesthetized rats, CeA injection of ethanol increased splanchnic SNA (SSNA), lumbar SNA (LSNA), and MAP in a dose-dependent manner. Maximum increases elicited by CeA ethanol (n=6) in SSNA (118±28%), LSNA (59±13%) and MAP (11±4mmHg) respectively. A cocktail containing KYN (7.2 nmol), a non-selective EAA blocker, and ethanol attenuated responses ($p<0.05$; n=5) in SSNA (32±11%), LSNA (23±5%), and MAP (4±1mmHg) compared to that elicited by CeA ethanol alone. Similarly, responses to a cocktail containing AP5 (6 nmol), a NMDA receptor blocker, and ethanol in SNA and MAP were less than ethanol alone ($p<0.05$; n=5) and not statistically different from a cocktail containing KYN and ethanol. The symapthoexcitatory response elicited by a cocktail containing NBQX (2.6 nmol), a non-NMDA receptor blocker, and ethanol (n=5) were not different from CeA ethanol alone. CeA injection of KYN, AP5, and NBQX did not affect baseline parameters. This data indicates that sympathetic responses to CeA ethanol require local action of EAAs at NMDA receptors. Support: AHA 10SDG2640130 (QHC).

8.15

BAROREFLEX CONTROL OF LEG VASCULAR CONDUCTANCE DURING SIMULATED CAROTID HYPERTENSION IN YOUNG AND OLDER WOMEN

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Recent data indicate that β-adrenergic stimulation offsets α-adrenergic vasoconstriction in young women and this effect is lost in post-menopausal women. These findings suggest that sympathetic control of the vasculature differs with age in women. However, the impact of these age-related vascular changes on baroreflex control of blood pressure remains unknown. Thus, the purpose of this study was to examine the effect of baroreflex stimulation on leg vascular conductance (LVC) and mean arterial pressure (MAP). In 7 young (YW; 25±2 yrs) and 5 older women (OW; 60±5 yrs), femoral artery blood velocity and diameter (duplex Doppler ultrasound), MAP (Finometer) and heart rate (HR; ECG) were continuously measured during 5sec pulses of neck suction (-60 Torr) to simulate carotid hypertension. Resting LVC, MAP and HR were similar between groups. In response to neck suction, increases in LVC were significantly less in YW compared to OW (YW, +7±3 vs. OW, +21±4% ml/min/mmHg;$P<0.05$), whereas, YW exhibited greater decreases in HR (YW, -14±2 vs. OW, -8±2 bpm;$P<0.05$). Interestingly, carotid baroreflex-mediated decreases in MAP (YW, -12±1 vs. OW, -11±3 mmHg;$P>0.05$) were similar between groups. These preliminary findings suggest that older women have a greater reliance on changes in vascular conductance to modulate blood pressure during simulated carotid hypertension, whereas younger women rely more on cardiac responsiveness. Supported by R01HL093167

8.16

NUTRITIONALLY-INDUCED CHANGES IN CARDIOVASCULAR PARAMETERS

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This study examined the influence of body mass index (BMI) on heart rate variability (HRV) at rest and examination stress. 123 healthy female students with a mean age of 20.66±0.12 years volunteered for the experiment: 12 thin subjects (TS) (BMI<18.5); 9 pre-obese subjects (PO) (BMI = 25 – 29,99); 102 nonobese controls (NC) (BMI = 18.5 – 24.99). In all participants, we performed 5-minute electrocardiogram recording at rest and shortly before real life stress. Main outcome measures included heart rate (HR) and HRV parameters. Kruskal-Wallis ANOVA was used to assess significance of associations. Baseline characteristics in NC group did not differ significantly from the TS and PO groups. During stress, TS had significantly elevated HR and decreased SDNN (94.18+/-3.95 and 0.036+/-0.005, respectively) when compared with NC (82.93+/- 1.13 and 0.047+/- 0.002, respectively) and PO (73.33+/- 3.12 and 0.063+/- 0.007, respectively). In comparison with the two other groups, TS showed a significant decrease TF (TS= 1797,55+/- 367,53; PO=3551,76 +/- 232,81; NC= 6386,67+/-1092,11), and a significant decrease of the power of the LF (TS=570,65+/- 116,44; P0= 1242,45 +/- 104,15; NC= 2216,11+/- 454,61). There were no differences between the groups in HF and LF/HF. The results are consistent with the hypothesis that low BMI is characterized by a tendency towards heightened stress-induced physiological activation. Supported by the Ministry of Education and Science of Russia (grant N 4.4904.2011) and RGNF (grant N 12-16-21014).

8.17

NOCTURNAL HYPOXEMIA INDUCED BY OBSTRUCTIVE SLEEP APNEA DETERMINES SYMPATHETIC HYPERACTIVATION AND MOOD DISTURBANCE IN PATIENTS WITH METABOLIC SYNDROME

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Objective: We tested the hypothesis that nocturnal hypoxemia (NH) induced by obstructive sleep apnea impairs muscle sympathetic nerve activity (MSNA) and is associated with mood disturbance in patients with metabolic syndrome (MetS). Methods: Seventy-three never-treated patients with MetS (ATP III) were submitted to a polysomnography. Patients were divided into quartiles, based on the time of oxygen saturation (SaO2) below 90% during sleep. We compared the first quartile (without NH, MetS-NH; n= 18) and fourth quartile (19% of the time with SaO2<90%, MetS+NH; n= 19) patients, and healthy control group with SaO2>90% (C, n= 10). We measured MSNA (microneurography) and the total mood disturbance (TMD) by Profile of Mood States questionnaire. Results: MSNA was augmented in MetS+NH compared with MetS-NH and C groups ($P<0.001$). And, MSNA was higher in MetS-NH than in C groups ($P=0.01$). MetS+NH showed high levels of depression ($P<0.001$), hostility ($P<0.001$), fatigue ($P<0.001$), confusion ($P<0.001$) and TMD ($P<0.001$) in relation to MetS-NH and C groups. No difference in the mood symptoms were observed in MetS-NH in relation to C group. In addition, MSNA was associated with TMD score ($R=0.43$ and $P=0.01$). Conclusion: The time of nocturnal hypoxemia determines the sympathetic hyperactivity and mood symptoms in patients with MetS. These results suggest that the prolonged hypoxemia during sleep can be an important risk factor for cardiovascular and mental disturbances in patients with MetS.

8.18

CARDIOVASCULAR RESPONSES OF NIGERIAN PATIENTS WITH CHRONIC HEART FAILURE TO 6-MINUTE WALK TEST

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In clinical practice, objective estimates of performance and fitness can be obtained through standardized exercise tests. This study was to evaluate the cardiovascular responses of Nigerian adult patients with chronic heart failure (CHF) to the 6-minute walk test (6MWT). Participants were 18 adult patients with CHF and 30 age-matched, apparently healthy individuals with no history of cardiovascular disorders. On the day of exercise testing, pre-test heart rate, respiratory rate and BP were taken. The subjects went through the standardised procedures of the 6MWT. The cardiovascular parameters were taken again immediately after the test. For each of the male and female study and control subjects, paired *t*-tests were used to evaluate the differences between the pre-test and post-test mean values of HR, SBP and DBP. After the 6MWT, male patients had 9% increase in HR while the female patients had an 8.5% increase. The male control subjects had a 13.4% increase while the female controls had a 9% increase ($P<0.05$). The male patients had a 14.4% increase in SBP; while the male control subjects had a 16% increase ($P<0.05$). The female patients had a 12.1% increase in SBP while the female

control subjects had an 11.1% increase (P<0.05). DBP was significantly in-creased in male patients, male control subjects and female control subjects. The 6-MWT test is a safe and simple instrument for demonstrating cardiovascular responses to sub maximal exercise in patients with heart disease.

8.19 Withdrawn.

8.20

INTEGRATED CIRCULATION AND RESPIRATION IN PHYSIOLOGY AND MEDICINE II: WHY VARIATIONS OF HR, SBP AND ANATOMIC TONE FOLLOW RESPIRATORY RHYTHM

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INTRODUCTION: The new theory system of respiration-circulation integrated control and regulation appears to be clear for understanding of many questions in physiology and medicine. Second, we try to explain mechanism of the variability of heart rate (HR), systolic blood pressure (SBP) and anatomic tone depending upon breath rhythms. QUESTION: There is variability of HR, SBP and anatomic tone normally following the breath rhythms. However, the mechanism is unclear. HYPOTHESIS: We try to use the continuous dynamic change in ¡°Trinity¡± of PaO2 (dominant), PaCO2 and [H+] in blood, which originally results from lung inspiratory and expiratory ventilation, to explain the mechanism for variability of HR, SBP and anatomic tone. EXPLANATIONS: As we described while introduced the new theory, alveolar gases pressures continuously go up/down during lung inspiratory and expiratory period. The signals of these changes of lung/alveolar PO2 and PCO2, go to arterial side following blood flow, then arterial oscillatory changes of ¡°Trinity¡±, which stimulate the peripheral chemical sensors via the nerve system, to result variability of HR and anatomic tone. Based upon the hyper-oxygen pulmonary vascular relaxation and hypo-O2-construction, alveolar PO2 and PCO2 oscillation results similar patterns of pulmonary blood flow and resistance. As Starling¡¯s principle, afterward preloading of left ventricle makes variability in stroke volume and SBP.

8.21

INTEGRATED CIRCULATION AND RESPIRATION IN PHYSIOLOGY AND MEDICINE III: WHY HF PATIENTS APPEAR OSCILLATORY BREATHING DURING SLEEP AND EXERCISE

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INTRODUCTION: Since APS/EB2011&2012, ACCP2011 and APSR2011, new theory system of respiration-circulation integrated control and regulation appears to be clear for understanding of many questions in cardiovascular physiology and medicine. Third, we try to explain mechanism of oscillatory breathing (OB) in heart failure (HF) patients. QUESTION: There is OB during sleep and exercise in HF. However, mechanism is unclear. HYPOTHESIS: Poor left ventricle function (lower EF, SV and CO) de-creased magnitude of oscillatory information in arterial blood ¡°Trinity¡± of PaO2 (dominant), PaCO2 and [H+], while blood passed left ventricle from lung to artery, can explain mechanism for oscillatory breathing. EXPLANATIONS: As we de-scribed, the next breath is dominantly initiated by this breath, via fast response peripheral chemical receptors; and the gain/sensitivity is adjusted with long time delay (about 20-30s) by slow response central chemical receptors. The poor heart function abnormally decreased magnitude of oscillatory information in PaO2 etc ¡°Trinity¡±. The normal breath information, via HF left ventricle, only generated a smaller initial signal for next breath; and so on¡- the final breath should be very little or disappeared (apnea). Then the delayed averaged/mean signal arrived at central chemical receptors will change gain to adjust the sensitivity to make a larger breath¡- Combined different fast and slow receptors¡¯ rules in breath control clearly explain mechanism of oscillatory breathing pattern in HF patients.

9.0: SYMPATHETIC MECHANISMS IN HUMAN HYPERTENSION

9.1

IMPAIRED AUTONOMIC REGULATION OF BLOOD PRESSURE AND HYPERTENSION

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The autonomic nervous system is not only crucial role in the instantaneous regulation of blood pressure, but also contributes to the chronic maintenance of hypertension, as evidenced by conditions resulting from lesions of autonomic pathways and recent findings in obesity and resistant-hypertension. Lesions of baroreflex pathways in the neck (following surgery or radiation) or the NTS, lead to labile hypertension. Neurovascular compression of the RVLM is associated with hypertension. Neurodegeneration of central autonomic pathways (multiple system atrophy) is accompanied bysevere supine hypertension driven by residual sympathetic tone. These rare disorders support the concept that abnormal autonomic mechanisms can contribute to the maintenance of hypertension. Obesity, the most common cause of hypertension, is characterized by selective activation of sympathetic pathways involved in cardiovascular regulation. Furthermore, blood pressure is virtually normalized in animal models of obesity hypertension with chronic carotid sinus stimulation and in patients by autonomic withdrawal with ganglionic blockade. Current antihypertensives targeting the autonomic nervous system are limited by side effects. This void is being filled by interventional approaches such electrical stimulation of the carotid sinus, and catheter ablation of renal afferent nerves. These novel devices are currently being tested for the treatment of resistant hypertension. REFERENCES: Biaggioni I. Interventional approaches to reduce sympathetic activity in resistant hypertension. Hypertension 2012; 59:194-5.

9.2

ACUTE AND CHRONIC ORTHOSTATIC INTOLERANCE, MALADAPTIVE AUTONOMIC REGULATION

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Vagal withdrawal and sympathetic circulatory control are key to the rapid cardiovascular adjustments that occur within seconds of standing upright (orthostasis) and which are required for bipedal stance. Indeed, patients with ineffective sympathetic adrenergic vasoconstriction rapidly develop "orthostatic hypotension" prohibiting all effective upright activities. One speaks of "orthostatic intolerance" (OI) when signs (e.g. decreased BP) and symptoms of cerebral hypoperfusion (e.g. lightheadedness) and sympathetic activation (e.g. jitteriness) occur when upright and are relieved by recumbence. The experience of transient mild OI is part of daily life. However, many people experience episodic acute OI, in the form of postural faint or chronic OI, in the form of orthostatic tachycardia and postural hyperpnea which significantly reduce quality of life. Potential mechanisms for OI include forms of sympathetic hypofunction, forms of sympathetic hyperfunction ("hyperadrenergic"), orthostatic intolerance that results from regional blood volume redistribution due to selective orthostatic vascular bed inadequacy, and orthostatic intolerance that results from postural hyperpnea with consequent tachycardia, hypertension and cerebral hypoperfusion. Reference: Rowell L. Human Cardiovascular Control. 1993. Oxford University Press, Inc. New York.

11.0: PLENARY LECTURE III

11.1

MUSCLE SYMPATHETIC REFLEXES IN HUMANS

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In this presentation we will discuss cardiovascular regulation during exercise. Two systems, central command and the muscle reflex are predominantly responsible for autonomic engagement. Central command is a feed forward system in which volitional motor activity is thought to be linked to the autonomic response. The exercise pressor reflex is engaged whenmechanical and metabolic stimuli increase the discharge of thin fiber sensory afferents within the active muscle. This is turn leads to an increase in heart rate, blood pressure and ventilation. In this presentation we will focus on the muscle reflex and how it is altered in cardiovascular disease. Funded by: P01 HL096570 (LIS).

12.0: NITRIC OXIDE AND SYMPATHO-VAGALREGULATION

12.1

TARGETING CYCLIC NUCLEOTIDES TO RESCUE CARDIAC SYMPATHOVAGAL PHENOTYPES IN CARDIOVASCULAR DISEASE

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A hall mark of cardiovascular disease is abnormal neurohumoral activation at the end organ level. This phenotype often exists before these disease states have been established. The mechanism responsible for defective transmission may be related to free radical damage that is secondary to oxidative stress. Soluble guanylate cyclase, the key pre-cursor of cGMP-dependent effects of nitric oxide (NO) is down-regulated in diseased hearts as is the bioavailability of NO itself. This is also associated with enhanced levels of tissue cAMP. Therefore strategies aimed at increasing bioavailability of NO could be advantageous in rescuing impaired neural phenoltypes. We have reported that noradrenergic neuron-specific promoter to drive nNOS or enhanced green fluorescence protein expression, to only cardiac sympathetic neurons can inhibit noradrenergic neurotransmission in hypertensive rats and bring their sympathetic responsiveness to levels observed in age matched normotensive controls by decreasing neuronal intracellular calcium transients linked to exocytosis. Similarly, targeted nNOS gene transfer to isolated cardiac pacemaking cells decreases the hyper-responsiveness of I_{CaL} in the SHR by increasing cGMP dependent signaling and decreasing cAMP-PKA activity. Long term suppression of cardiac sympathetic transmissionand upregulation of parasympathetic transmissioncan be sustained following nNOS over expression with

lenti viral gene transfer. Whether this approach is viable to treat hyper-responsive sympathetic and beta adrenergic phenotypes remains to be established.

12.2

THE BLOOD BRAIN BARRIER AND CONTROL OF ARTERIAL PRESSURE

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The mechanisms for long term regulation of arterial pressure in conditions of hypertension remain an enigma. Our goal is to understand the origin of sympathetic over activity that parallels the development/maintenance of hypertension. Our research has focussed on the roles of the endothelium within the brainstem and delivery of blood to this portion of the brain via the vertebrobasilar circulation as major determinants of the set-point of arterial pressure. I will review the importance of brainstem endothelial cell derived nitric oxide and its importance in modulating neuronal function via '*vascular-neuronal signalling*' for the long term regulation of arterial pressure. I will provide evidence that the microcirculation within the brainstem is inflamed in conditions of hypertension and provide evidence for upregulation of adhesion molecules in the trapping of leukocytes. Putative downstream actions of chemokines and cytokines on neural circuitry regulating arterial pressure will be demonstrated in a pre-clinical rodent model of hypertension. Finally, I will demonstrate that the brainstem of the spontaneously hypertensive rat is hypoperfused and that this reflects the situation in hypertensive humans. Our recent evidence supports the provocative hypothesis that brainstem hypoperfusion is causative to the development and maintenance of hypertension. In conclusion, the microcirculation plays a major role in determining the set point of arterial pressure and this includes signalling across the blood brain barrier as well as the rate of blood perfusion. *British Heart Foundation* funded research.

13.0: POSTER SESSION III

13.1

INVOLVEMENT OF PIN IN ANGIOTENSIN II DEPENDENT REGULATION OF NEURONAL NITRIC OXIDE SYNTHASE IN THE PVN OF RATS WITH CHRONIC HEART FAILURE

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Expression of neuronal nitric oxide synthase (nNOS) decreased in the paraventricular nucleus (PVN) of rats with chronic heart failure (CHF), however the molecular mechanism remains unclear. In the present study protein levels of PIN (a protein inhibitor of nNOS, known to dissociate nNOS dimers into monomers) increased (1.12(0.09 vs. Sham 0.76(0.10) with approximately 60% decrease in dimer/monomer ratio in the PVN of rats with CHF (6-8 wks. after coronary artery ligation). In vitro studies using neuronal cell line, NG108 showed that PIN protein expression is 2.3- fold higher in response to angiotensin II (Ang II). Silencing of PIN in NG108 cells leads to 2-fold accumulation of nNOS suggesting a regulatory role of PIN in NO synthesis. Moreover, dimer/monomer ratio of nNOS also increased by 80% with PIN knockdown in NG108 cells. Furthermore, Ang II treatment in NG108 cells in the presence of proteasome inhibitor, lactacystin, led to decreased ubiquitination of PIN (54% decrease vs. lactacystin alone), suggesting that post-translational processes such as protein degradation/stabilization are involved in Ang II dependent up-regulation of PIN. We conclude that post-translational accumulation of PIN, mediated by Ang II, leads to a decrease in the dimeric active form of nNOS as well as protein levels of nNOS which may lead to reduced nitric oxide mediated inhibition of sympathetic tone during CHF. Supported by NIH grant HL62222

13.2

AUTONOMIC/HYPOXEMIA-INDUCED VENTRICULAR FIBRILLATION IN EPILEPTIC RATS

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The effects of seizures on the autonomic activity can be severe and cardiac damage and arrhythmias may be the result of seizures. Rats that undergo status epilepticus (SE) show cardiac myofilament damage. They are more susceptible to ventricular fibrillation (VF) with an arrhythmogenic drug, but these changes do not appear if rats are pre-administered a beta blocker. In normal rats, we have characterized the conditions necessary for extreme autonomic changes to cause VF, and we studied these conditions in epileptic rats.Rats were made epileptic with a single period of kainic acid-induced SE. When rats peaked in seizure frequency, they were anesthetized with urethane. Echocardiography was used to measure left ventricular (LV) mass, the electrocardiogram (EKG) was recorded, and vagotomy and infusion of isoproterenol were performed. Trials of hypoxemia used fixed dead space volumes (1-8 ml) placed over an endotracheal tube.LV mass was greater in epileptic rats (1.06 ± 0.07 g vs. 0.79 ± 0.05, p = 0.004; 22 epileptic, 20 control). During hour-long EKGs, 8/13 of epileptic rats had premature ventricular contractions compared to 0/6 of controls. However, VF was induced in only one epileptic rat (1/7 rats, 26 attempts) compared to 100% (4/4) of controls (8/18 attempts).Epileptic rats have altered susceptibility to autonomic/hypoxemia-induced VF. Seizure-induced cardiac damage may be compensated for by cardiac hypertrophy. This hypertrophy may be related to VF susceptibility.

13.3

EFFECT OF DIETARY OMEGA-3 FATTY ACIDS ON THE HEART RATE VARIABILITY RESPONSE TO PHYSIOLOGICAL CHALLENGES IN A CANINE MODEL OF SUDDEN CARDIAC DEATH

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Although dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs) can increase heart rate variability (HRV), it has not been established if this treatment has the same effect in low and high post-infarction patients. Therefore, HRV (high frequency and total R-R interval variability, indices of cardiac vagal regulation) were evaluated before and 3 months after n-3 PUFA treatment in dogs with healed myocardial infarction that were either susceptible (S, n = 31) or resistant (R, n = 31) to ventricular fibrillation (VF) induced by a 2 min coronary artery occlusion during the last minute of an exercise test. HR and HRV were evaluated at rest, during exercise and in response to acute myocardial ischemia at rest before and after either placebo (1 g/day, corn oil, S, n = 9; R n = 8) or n-3 PUFA (docosahexaenoic acid + eicosapentaenoic acid ethyl esters, 1-4 g/day, S, n = 22; R, n = 23) treatment for 3 months. The n-3 PUFA treatment elicited similar increases in red blood cell, right atrial, and left ventricular n-3 PUFA levels in both groups. The n-3 PUFA treatment also provoked similar reductions in baseline HR and increases in baseline HRV in both groups that resulted in parallel shifts in the response to either exercise or acute myocardial ischemia (i.e., the responses to physiological challenges were not altered after n-3 PUFA treatment). These data demonstrate that dietary n-3 PUFAs decreased HR and increased HRV to a similar extent in animals known to be prone to or resistant to VF. Therefore, changes in cardiac autonomic regulation are not solely responsible for the putative beneficial actions of n-3 PUFAs. [Supported by NIH grant HL086700]

13.4

CAROTID BODY DENERVATION ATTENUATES INCREASED SYMPATHETIC NERVE ACTIVITY IN CONGESTIVE HEART FAILURE

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In congestive heart failure (CHF) the carotid body chemoreflex (CBC) is enhanced and contributes to increased sympathetic nerve activity (SNA) that exacerbates progression of the disease. We hypothesized that SNA is increased in a rabbit model of pacing-induced CHF, and that denervation of the CB (CBD) would ameliorate these changes. Plethysmography was used to measure ventilatory responses to hypoxia (Hx). SNA was measured directly from the renal nerves of conscious animals. Autonomic control of cardiovascular function was assessed indirectly by spectral analysis of blood pressure variability (BPV) using telemetry. We found that RSNA and ventilatory responses to Hx were augmented in CHF, and that CBD nearly abolished the responses to Hx. Spontaneous baroreflex sensitivity was attenuated in CHF (α-coefficient 0.96±0.03 pre-pace vs. 0.70±0.11 CHF), and was improved by CBD (α-coefficient 1.03±0.03). The low frequency component of systolic BPV (reflecting sympathetic tone) increased in CHF (82%±38 above pre-pace) and this was attenuated after CBD (24%±23 above pre-pace). RSNA was greater in CHF (21±1% sham vs. 54±4% CHF), and this increase was not apparent after denervation (23±1% CHF-CBD). Our findings support previous findings that enhanced CBC contributes to increased SNA in CHF, and suggest that CB denervation may be an effective treatment to reduce SNA and improve baroreflex sensitivity in CHF. This work was funded by NIH PO1 HL06222212 and Coridea NC1, Inc.

13.5

HIGH FIDELITY AUTONOMIC NERVE SIGNALS USING BIPOLAR NANOELECTRODE ARRAYS

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Most organs in the body are controlled by sympathetic nerve activity (SNA), suggesting that SNA dysfunction may either contribute to disease pathogenesis or indicate impaired compensation and disease severity. Using existing technology, direct measurement of SNA is limited by the presence of significant noise signals in the recorded SNA signal, because both signals havesimilar microvoltage amplitudes. The objective of this work is to improve the signal-to-noise ratio (SNR) of recorded signals associated with autonomic nerve activity. Using microfabrication techniques, novel bipolar nanoelectrode arrays (BNA) were fabricated with nanoscale features that improve electrical contact with autonomic nerves. We compared the SNA signals recorded from the BNA with aconventional metal hook (MH) electrode.Both electrodes were placed on the left stellate ganglion in canine subjects for simultaneous measurements in the acute setting. The results showed

that BNA consistently exhibited significant improvement in the signal amplitude (77.09μV ± 7.35 vs. 32.11μV ± 6.34 for the MH electrode; $P< 0.001$) and SNR (35.71 dB ±2.44 vs. 25.08 dB ± 2.31 for the MH electrode; $P< 0.001$) of the measured SNA. Moreover, the BNA was capable of recording electrical events lost in the noise floor of the measurements using MH electrodes.We conclude that BNA technology improves the SNR of SNA recordings and significantly advances techniques to investigate the pathophysiologic role of SNA.

13.6

RESPONSE OF INTRACARDIAC GANGLION NEURONS TO NICOTINE IN TYPE-2 DIABETIC RATS

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Clinical studies have shown that the arterial baroreflex was blunted in patients with type-2 diabetes mellitus (T2DM). As a final pathway for the arterial baroreflex control of the cardiac function, intracardiac ganglion (ICG) neurons are excited by acetylcholine acting on the nicotinic acetylcholine receptors (nAChRs). Our recent study has demonstrated that ICG neuron excitability was lowered by the decreased N-type Ca2+ currents in high-fat diet/low-dose streptozotocin-induced T2DM rats. In the present study, we examined whether the sensitivity of ICG nuerons to nicotine (a nAChR agonist) is impaired in T2DM rats. Immunofluorescence data showed that there was no significant difference on the protein expression of nicotinic receptors in ICG neurons from sham and T2DM rats. Using whole-cell patch clamp technique, we found that nicotine concentration-dependently enhanced ICG neuron excitation (action potential frequency) and the sensitivity of ICG neurons to nicotine in diabetic rats was lower than that in sham rats (EC50 value is 2.86 μM in T2DM rats and 0.49 μM in sham rats). Diabetes also decreased the response of Ca2+ channels to nicotine in ICG neurons, compared to sham rats. Additionally, nicotinic receptor antagonist (100 μM hexamethonium) and N-type Ca2+ channel blocker (1 μM omega-conotoxin GVIA) completely blocked the effect of nicotine on ICG neuron excitability and Ca2+ currents in sham and T2DM rats. Our results indicate that T2DM decreases the sensitivity of ICG neurons to nicotine.

13.7

GLUTAMATERGIC RECEPTORS IN SPINAL CORD MEDIATES THE EXAGGERATED EXERCISE PRESSOR REFLEX IN RATS WITH CHF

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Glutamate released by contraction-activated skeletal muscle afferents into thedorsal horn of the spinal cord initiate the central component of the exercise pressor reflex (EPR). However, the role of glutamate as well as glutamatergic receptors in mediating the exaggerated EPRinthe chronic heart failure (CHF) state remainsto be determined. To address this issue, we performed local microinjection of glutamatergic receptor antagonists into the ipisilateral L4/L5 dorsal horns to investigate their effects on the pressor response to static contraction in sham and CHF rats. As shown in the Table, microinjection of either thebroad spectrum glutamate receptor antagonistkynurenate (KYN, 50 mM/100nl), or the NMDA receptor antagonistAP-5 (50 mM/100nl), or the AMPA receptor antagonistCNQX (5 mM/100nl) into the L4/5 dorsal hornsdecreased the pressor response to contraction in CHF rats to a greater extent than in sham rats, suggesting that glutamatergic receptors in spinal cordmediates the exaggerated EPR in CHF.

Table. The Effects ofglutamatergic receptor antagonists on the pressor response tocontractionin sham and CHF rats.

	Sham		CHF	
	Before	After	Before	After
KYN	17.5±2.0	9.3±1.1*	32.3±2.6†	8.5±0.8*
CNQX	16.1±2.0	7.5±1.0*	28.3±3.0†	11.8±1.8*
AP-5	20.0±2.6	14.3±1.8*	34.5±3.0†	17.6±2.0*

Mean±SE, n=8-10 in each group,*P<0.05 vs.Before, † P<0.05 vs.CHF.

13.8

SYMPATHETIC NERVE RECORDINGS: A GLIMPSE OF THE RECENT PAST WITH AN EYE ON THE FUTURE

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The sympathetic nervous system plays an important role in cardiovascular function and a critical mechanistic relationship exists between altered sympathetic neural mechanisms and the fundamental processes of cardiovascular disease. The state of the literature was assessed regarding studies that have used direct recordings of sympathetic nerve discharge (SND) as peripheral SND recordings provide a measure of central neural-generated sympathetic nerve outflow. The majority of studies reporting SND recordings in rats have been completed using anesthetized preparations, although a substantial number of studies have involved conscious rats. However, few studies have employed longer-term (>5 days) SND recordings in freely-behaving rats, and even fewer studies have used experimental preparations that combine longer-term nerve recordings with the capacity for completing central neural microinjections, or have completed chronic SND recordings in animal models of cardiovascular disease. These are critical barriers as the translational significance of animal research to human medicine and disease cannot be fully realized without maximizing experimental conditions in animal preparations that closely match those in human subjects. Further development and implementation of techniques to complete long-term SND recordings in rodent models of cardiovascular disease will substantially enhance the translational exchange of clinically-relevant information from animal models to human patients.

13.9

UNILATERAL RENAL DENERVATION ENHANCES BAROREFLEX FUNCTION IN CONSCIOUS RABBITS WITH CHRONIC HEART FAILURE

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Renal nerve denervation (DNx) is currently being assessed as a therapy for drug-resistant hypertension and other disorders characterized by sympatho-excitation, such as chronic heart failure (CHF). We hypothesized that renal DNx enhances arterial baroreflex (BR) control of heart rate (HR) in normal and CHF rabbits. All animals were instrumented with ventricular pacing leads and an arterial pressure (AP) radiotelemetry transducer. After recovery the left kidney was denervated by stripping the renal artery of all visible fibers. Intact animalswere subjected to a sham operation. Two weeks later, CHF animals were subjected to rapid ventricular pacing. BR changes in HR and AP were inducedby iv sodium nitroprusside and phenylephrineinfusionsalone and after injection of atropine or metoprolol. BR function was determined by fitting mean AP and HR data to a 4 parameter logistic equation. Renal DNx increased HR range in sham animals (intact: 156± 34 bpm;DNx: 298± 39 bpm, p = 0.022). HR range was also enhanced in CHF DNx animals (CHF, intact: 110 ± 16 bpm; CHF, DNx: 294 ± 15 bpm, p = 0.002). Preliminary data suggestsrenal DNx enhances HR range after atropine or metoprolol blockade, potentially improving both vagal and sympathetic components of BR function.These data indicate renal DNx enhances the autonomic components of BR control of HR in the normal and CHF states. Supported by: P01-HL62222.

13.10

INTEGRATED CIRCULATION AND RESPIRATION IN PHYSIOLOGY AND MEDICINE IV: WHY AND HOW BODY BLOOD FLOW REDISTRIBUTION DURING EXERCISE?

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INTRODUCTION: During maximal exercise, muscles blood flow increased 20-40 folds, which comes from 3-5 folds increase in cardiac output (CO) and 6-10 folds from blood redistribution. New theory appears to be clear in physiology. Fourth, we try to explain mechanism of muscle blood flow increase due to blood flow redistribution. QUESTION: The mechanism of muscle blood flow increase during exercise is unclear. HYPOTHESIS: We try to use exercise tissues¡¯ changes PO2 (dominant) ¡°Trinity¡± to explain blood flow re-distribution. EXPLANATIONS: At rest, opened capillary, came in higher PO2 arterial blood (low PCO2 and low [H+]) and then resulted in this capillary closed. After time passed, mitochondria used more O2, lower PO2 to re-open the capillary, i.e. only partial capillaries are alternatively opened and more closed. During exercise, mitochondria materials oxygenate rate increased to match energy demand, resulted in fast PO2 decrease (PCO2 and [H+] increases). They progressively increase capillary opened rate and time, and relax more arterial vascular structures. At peak exercise, all arterial vascular structures maximally opened and all capillaries continues opened. But O2 supply still less than demanded, body via nerve and blood systems to increase blood vascular tone and contraction, then decrease blood flow into other no exercise tissues. Finally, at peak, exercise muscles¡¯ blood flow relative percentage of total CO increased from ~10% up to 85-90% of CO while the CO increased 3-5 folds.

13.11

INTEGRATED CIRCULATION AND RESPIRATION IN PHYSIOLOGY AND MEDICINE V: WHY AND HOW TO INCREASE THE CARDIAC OUTPUT (CO) DURING EXERCISE?

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INTRODUCTION: In physiology, ventilation control and regulation, cardiovascular and metabolic regulation was discussed separately but none of combining discussion. New theory appears be able to. Fifth, we try to explain mechanism of exercise muscles blood flow increase due to CO increase. QUESTION: The mechanism of CO increase during exercise is unclear. HYPOTHESIS: We try to use O2 (dominant) etc ¡°Trinity¡± dynamic balance between demand and supply to explain CO increase during exercise. EXPLANATIONS: At rest, low and dy-

namically matching mitochondria oxygenation rate with energy demand, so return blood has relatively normal (i.e. high) PvO2. During exercise, progressively increased capillary opened rate and time, relax arterial vassals increase venous return. However, O2 supply is still less than demand, higher metabolic [H+] (above anaerobic threshold) helps to unload more O2 at tissues and higher percentage of blood passed muscles results in lower PvO2. Lower PvO2 arrive at lung, larger PA-vO2 and faster loading O2 in blood, then larger magnitude of PaO2 up-down wave inspiratory-expiratory period. It, via fast peripheral sensors, increases both ventilation and blood flow in dynamically matching. During exercise, relatively higher averaged/mean PaCO2 and [H+]a, via central chemical sensors, increase gain too. All together, CO increases 3-5 folds for optimal matching with ventilation for optimal O2 exchange.

13.12
AUTONOMIC MODULATION: EMERGING PARADIGM FOR CARDIOVASCULAR TREATMENT?

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Objective: Consider physiological interventions of the autonomic nervous system (ANS) as they relate to treatments for cardiovascular diseases and note a developing theme for *autonomic modulation.* **Summary:** Increasingly, experimental and clinical data on ANS denervation or stimulation are reporting therapeutic effects: a) Regional radiofrequency catheter ablation of atrial ganglionated plexi (GP) restored sinus rhythm in 71% of patients with atrial fibrillation (AF); b)Low level electrical stimulation of the vago-sympathetic trunks significantly suppresses AF inducibility in the canine; c) Likewise, we demonstrated that polymeric nanoparticles (110 nm)delivering a neurosuppressantpayload and targeted by an external magnetic field to GP, suppressed/prevented AF inducibility; d)Vaso-vagal syncope (intrinsic cardiac ANS dysreflexia) had no recurrence in patients with partial GP ablations;e). Drug resistant hypertension was significantly reduced out to 24 months, with improved glucose metabolism and insulin sensitivity in patients receiving renal nerve catheter ablation.Additionally, probable slowing of chronic kidney disease progression occurred following renal nerve ablation. **Conclusion**: Together these observations suggest that targeted ANS denervation or suppression, by devices or nanoformulations, may present as future therapeutic cardiovascular interventions.

13.13
CARDIOVASCULAR AUTONOMIC CONTROL IN THE FIRST YEAR AFTER SPINAL CORD INJURY

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Autonomic pathways that travel in the spinal cord are susceptible to spinal cord injury (SCI) and their disruption can result in a range of cardiovascular dysfunctions. The development and evolution of these complications remains poorly understood. Here we sought to evaluate cardiovascular function in the first yearafter traumatic SCI using spectral analyses. Resting supine beat-to-beat blood pressure and 3-lead electrocardiography were recorded during supine rest for 15 minutes at several time points in the first year post-injury. Here we present results from recordings performed in the first two weeks post-injury, and again at one-year, on the same eightsubjects: four with cervical SCI and four with low thoracic or lumbar SCI. Autonomic function was quantified using spectral analysis of heart rate variability (HRV) and blood pressure variability (BPV). Individuals also completed a questionnaire at each visit evaluating symptoms of cardiovascular dysfunction after SCI. All subjects showed increased total HRV at one year post-injury compared to the first timepoint. Our initial BPV analyses show two different patterns. Individuals with low level lesions show frequency domain analyses that are essentially normal and do not show significant changes over time post-injury. Individuals with cervical SCI show evidence of impaired cardiovascular autonomic function that spontaneously improves over time. It remains to be determined whether this reflects autonomically complete lesions that recover, or incomplete lesions with altered autonomic function associated with the initial trauma. The early period after SCI appears to be a time when autonomic control of the cardiovascular system can change significantly. Clinically, it may be wise to assess the cardiovascular system at several stages in the first year after injury in order to get a clearer picture of the level of cardiovascular autonomic control.

13.14
HEART RATE VARIABILITY RESPONSES TO EXERCISE IN THAI BRUGADA SYNDROME SURVIVORS

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Brugada syndrome is one of major causes of sudden death in male Southeast Asian population. Previous studies suggested that an abnormality of autonomic modulation may be related to the syndrome. Therefore, the objective of this study was to assess and compare responses of autonomic nervous system to exercise testing between Thai Brugada syndrome survivors and age-match healthy subjects. Fifteen males per group performed an incremental exercise testing on electromagnetic cycle ergometer. Electrocardiogram was recorded throughout the process and was analyzed for Heart rate variability (HRV) to identify autonomic function. The procedure conformed to the Declaration of Helsinki and was approved by the local ethics committee. There was no difference in autonomic activity between the groups during resting. However, Brugada survivor group showed a significantly higher parasympathetic activity ($p<0.05$) during a final stage of testing, 1 min of HRR and cool down periods (survivors = 53.84 ± 5.13%, 56.99 ± 4.85%, 58.67 ± 4.45% and healthy = 42.91 ± 4.12%, 42.73 ± 4.72%, 43.58 ± 5.11%). Moreover, this difference still existed during five minutes after exercise. The high frequency component (HF) and ratio of low to high frequency component of HRV (LF/HF ratio) of survivors and healthy groups were 37.81 ± 3.54, 1.77 ± 0.36 and 25.13 ± 2.66, 3.23 ± 0.49 ($p<0.05$). Our results suggest that parasympathetic activity tends to be dominant in Brugada syndrome survivors during and after exercise.

14.0: DEVICE THERAPY FOR HYPERTENSION AND HEART FAILURE

14.1
INSIGHT INTO LONG-TERM NEURAL CONTROL OF ARTERIAL PRESSURE BY CHRONIC BAROREFLEX ACTIVATION

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Chronic electrical activation of the carotid baroreflex produces sustained reductions in sympathetic activity and arterial pressure and is currently being evaluated as therapy for resistant hypertension. Since the kidneys play a key role in long-term control of arterial pressure, observations indicating increased renal sympathetic nerve activity (RSNA) in primary hypertension suggest that the renal nerves likely represent the critical link between increased central sympathetic outflow and impaired renal function that sustains hypertension. Furthermore, because the natural activation of the baroreflex during hypertension inhibits RSNA and promotes sodium excretion, carotid baroreflex activation may chronically lower arterial pressureby suppressing RSNA. Surprisingly, the presence of intact renal nerves is not an obligate requirement for lowering arterial pressure during baroreflex activation. Experimental studies and computer simulations indicate that in addition to baroreflex-mediated suppression of RSNA, hormonal and hemodynamic mechanisms also contribute toincreases in renal excretory function that lead to long-term reductions in arterial pressure. Further, the contribution of these redundant mechanisms to lowering of arterial pressure is increased in the absence of the renal nerves. However, activation of these redundant natriuretic mechanisms occurs at the expense of excessive fluid retention. Support: NIH HL-51971. REFERENCE: Lohmeier TE, Iliescu R. Chronic lowering of blood pressure by carotid baroreflex activation: mechanisms and potential for hypertension therapy. Hypertension 2011; 57:880-886.

14.2
WHEN THE LEVEE BREAKS: SYMPATHETIC CONTROL OF SPLANCHNIC VESSELS LEADING TO ACUTE HEART FAILURE

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A growing body of evidence reveals that most patients do not experience net weight gain prior to an episode of acute heart failure (AHF). However, filling pressures clearly do become elevated, in many cases weeks prior to AHF. This suggests that redistribution rather than net gain of volume must occur. Under normal conditions 70% of intravascular volume resides in the venous system, mostly in the splanchnic bed. These beds (predominantly in the liver and spleen) serve as a reservoir under exquisite control by the sympathetic nervous system, and can be recruited rapidly to auto-transfuse large amounts of fluid into the effective circulatory volume within seconds. Baroreflexes exert powerful inhibitory influences over sympathetic outflow, leading to changes in vasomotor tone. In the setting of intact reflexes, changes in intravascular volume can be buffered so that filling pressures remain low. However, in the setting of abnormal baroreflexes (such as in HF), the ability to buffer changes in volume adequately is lost, leading to increases in cardiac filling pressure. Many comorbidities (including sleep disordered breathing, anemia, and chronic kidney disease) contribute to heightened sympathetic tone, abnormal fluid shifts and AHF. Understanding these mechanisms is essential to developing novel approaches to detect and adequately treat AHF. Fallick C., Sobotka P.A., Dunlap M.E.: Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail. 2011 4(5):669-75.

14.3
BEYOND BP REDUCTION, CLINICAL IMPLICATIONS OF RENAL DENERVATION

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Therapeutic renal denervation (RDN) has theoretical applicationin conditions where excess renal sympathetic efferent signaling may contribute to progression of chronic renal disease and cardio-renal syndrome and when renal afferent contribution to central sympathetic drive contributes to insulin resistance, heart failure and arrhythmias. Insulin resistance measured with either Euglycemic Clamp or HOMA-IR reveal improvement following RDN in patients with either essential hypertension or polycystic ovary syndrome. RDN in animal models of volume and

pressure overload demonstrate Podocyte protection and reversal of renal perfusion abnormalities and normalization of expression of angiotensin receptors in heart failure. Trials of RDN in patients with HFrEF, HFpEF, and atrial fibrillation are in progress. References: Rafiq K., et. al. Renal Sympathetic Denervation Suppresses De Dovo Podocyte Injury and Albuminuria in Rats with Aortic Regurgitation. Circulation. 2012;125:1402-1413.; Clayton S.C., Haack K.K., Zucker I.H. Renal denervation modulates angiotensin receptor expression in the renal cortex of rabbits with chronic heart failure. Am J Physiol Renal Physiol. 2011Jan 300(1):F31-9; Mahfoud F., et. al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation 2011 May 10, 123(18):1940-6. Schlaich, M. et. al. Renal Denervation a potential new treatment modality for polycystic ovary syndrome? J Hypertens 2011 May; 29(5):991-6. Sobotka PA, et. al. The role of renal denervation in the treatment of heart failure. Curr Cardiol Rep. 212 March 7.

NOTES

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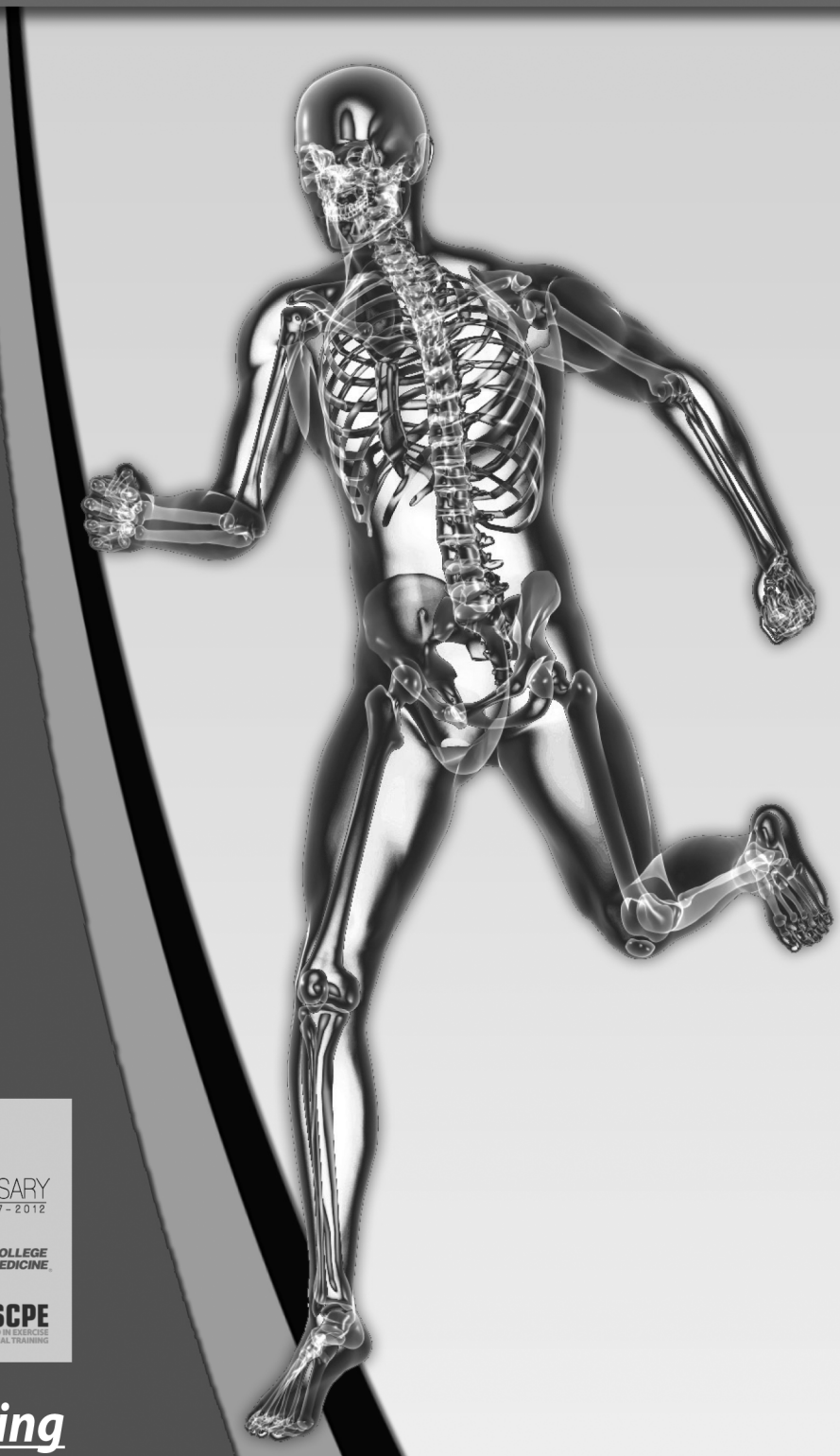

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GlaxoSmithKline
Seahorse Bioscience

2012 APS Intersociety Meeting
The Integrated Biology of Exercise VI
October 10—13, 2012
Westminster, Colorado

Registration Opens at 5:00 PM on Wednesday, October 10, 2012
Opening Reception at 6:00 PM

	Thursday October 11	Friday October 12	Saturday October 13
8:30-10:45 AM Concurrent Symposia 11:00 AM-12:00 Noon Plenary Lecture/Discussion	*Personalized Medicine Track* **Integrating Human "Omics" to the Molecular Physiology of Exercise** Chair: William J. Kraus *Exercise Adaptations Track* **Mechanisms Behind Adaptations to Physical Activity/Inactivity** Chair: Henriette Pilegaard **Towards Personalized Lifestyle Medicine** Speaker: Geoffrey Ginsburg	*Cardiovascular Track* **Cardiovascular Benefits of Exercise: Insight from Animal Studies** Chair: David A. Brown *Lipid Metabolism Track* **Fit, Fat and Lean Liver: Exercise Adaptations in Non-Traditional Tissues** Chair: Espen Spangenburg **Adaptations of the Heart: Traditional and Non-Traditional Research** Speaker: Leslie Linewand	**Physical Activity is Necessary for Optimal Brain Function** Chair: Michael J. Joyner **The Impact of Heat Shock Protein Expression on Muscle Metabolism, Exercise Capacity and Disease Prevention** Chair: Paige C. Geiger **Town Hall Meeting** Led by: Jim Whitehead Martin Frank
Afternoon Activities	12:00-1:15 PM Lunch 1:15-3:15 PM **Poster Presentations and Exhibits**	12:00-1:15 PM Lunch	12:00-1:15 PM Free Time 1:15-3:15 PM **Poster Presentations and Exhibits**
3:15-5:30 PM Concurrent Symposia	*Personalized Medicine Track* **Personalized Exercise Prescription Based Upon Integrative Biology** Chair: Frank Booth *Exercise Adaptations Track* **Acetylation: Linking Changes in NAD to Metabolism and Growth** Chair: Keith Baar	*Cardiovascular Track* **Cardiovascular Benefits of Exercise: Insight from Human Studies*** Chair: Judy Muller-Delp *Lipid Metabolism Track* **Skeletal Muscle Lipid Droplet Biology in Exercise and Disease*** Chair: Deborah M. Muoio	**Hot Topics in Exercise Physiology** Chair: P. Darrell Neufer **Unified Cellular and Molecular Mechanism of Muscle Hypertrophy** Chair: Keith Baar
Evening Events	5:30-7:00 PM **Poster Presentations** **Evening Free** Explore the urban city of Westminster or visit the nearby vibrant city of Boulder.	3:30-6:00 PM **Recreational Activities** Challenge your colleagues to a friendly game of bowling, soccer, or even ice skating at nearby locations. 7:00-8:00 PM **Dinner** 8:00-9:30 PM **Poster Presentations and Exhibits**	7:00-10:00 PM **Banquet and Awards Presentation** *(*Included with registration).

***Friday Afternoon Concurrent Sessions begins at 1:15-3:30 PM**

Location:

The 2012 APS Intersociety Meeting: The Integrative Biology of Exercise VI will be held October 10—13, 2012 at the Westin Westminster Hotel, 10600 Westminster Blvd., Westminster, CO 80020, telephone (303) 410-5000, FAX: (303) 410-5005.

Onsite Registration Hours:

Wednesday, October 10…….5:00—8:30 PM
Thursday, October 11……..7:00 AM—6:00 PM
Friday, October 12……...7:30 AM—3:30 PM
Saturday, October 13……..8:00 AM—5:00 PM

On-Site Registration Fees:

APS Member	$600
ACSM Member	$600
CSEP Member	$600
APS Retired Member	$400
Nonmember	$700
Postdoctoral	$450
Student	$400

The registration fee includes entry into all scientific sessions, opening reception, lunches and dinners.*

*Must get ticket for entry. Dinners are scheduled for Friday and Saturday evenings only.

Payment Information:

Registrants may pay by institutional or personal check, traveler's check, MasterCard, VISA or American Express. 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.**

Press:

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.

Ancillary Session:

Career Workshop: This special session entitled: "The *Ins* and *Outs* of Authorship" will be presented by Lacy A. Holowatz, Pennsylvania State University. Discuss the criteria for authorship and various roles authors can play during the research process and preparation and publication of a manuscript. Through case studies, explore real-life scenarios and how best to deal with the various issues that can arise with authorship.

Program Objective:

This meeting is designed to bring together scientists from all over the world who have been involved in research interest in the broad area of exercise physiology. The meeting is designed to provide a strong scientific program with participant interaction and emphasize emerging research performed by young investigators.

The participants will likely focus on recent important advances in the traditional areas of interest in exercise (e.g. metabolic control, cell signaling, satellite/stem cells biology, hypertrophy, vascular adaptations) as well as significant new developments in emerging areas of science that have great relevance to investigators interested in exercise (e.g. mechanical signal transduction, AMPK, cytokines).

The goal is to provide an in-depth understanding of exercise physiology and interdisciplinary efforts to assess its impact on the systems of the body. In addition, the goal is to outline directions for future work and to interest new investigators and students in pursuing research opportunities to understand the integrative biology of exercise and its relation to gender and aging.

Target Audience:

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

Please note that photography is forbidden in all session rooms

THURSDAY, OCTOBER 11, 2012

Symposia I *Personalized Medicine Track*

1.0 INTEGRATING HUMAN "OMICS" TO THE MOLECULAR PHYSIOLOGY OF EXERCISE

Thurs., 8:30 - 10:45 AM, Standley Ballroom.

Chair: **William J. Kraus,** *Duke Univ*.

8:30 AM **1.1** Introduction. **William J. Kraus.** *Duke Univ. Med. Ctr.*

8:35 AM **1.2** Modulation of Small Molecule Metabolites in Peripheral Blood and Skeletal Muscle. **Kim Huffman.** *Duke Univ. Med.Ctr.*

9:05 AM **1.3** Modulation of Skeletal Muscle Global Gene Expression. **Monica Hubal.** *Children's Natl. Med. Ctr.*

9:35 AM **1.4** Modulation of the Proteome by Exercise. **Dustin Hittel.** *Univ. of Calgary, Canada.*

10:05 AM **1.5** Putting it all Together: Integrative Molecular Physiology of Exercise. **Eric Hoffman.** *Children's Natl. Med. Ctr.*

Symposia II *Exercise Adaptations Track*

2.0 MECHANISMS BEHIND ADAPTATIONS TO PHYSICAL ACTIVITY/INACTIVITY

Thurs., 8:30 - 10:45 AM, WB III/IV.

Chair: **Henriette Pilegaard,** *August Krogh Inst., Denmark.*

8:30 AM **2.1** Introduction. **Henriette Pilegaard.** *August Krogh Inst., Denmark.*

8:35 AM **2.2** Role of PGC-1α in Exercise-Induced Adaptations in Skeletal Muscle. **Christophe Handschin.** *Univ. of Basel.*

9:05 AM **2.3** Exercise-Induced Autophagy in Skeletal Muscle Adaptations. **Zhen Yan.** *Univ. of Virginia.*

9:35 AM **2.4** Role of DNA Methylations in Exercise-Induced Adaptations. **Romain Barres.** *Univ. of Copenhagen, Denmark.*

10:05 AM **2.5** Molecular Mechanisms Regulating Insulin Sensitivity in Skeletal Muscle with Activity/Inactivity. **Jørgen Wojtaszewski.** *Univ. of Copenhagen, Denmark.*

Plenary Lecture

P1 PLENARY LECTURE

Thurs., 11:00 AM - 12:00 Noon, WB III/IV.

11:00 AM **P1** The Exposome in Health and Disease. **Geoffrey Ginsburg.** *Duke Univ. Med. Ctr.*

Poster Session

3.0 GENOMICS/PROTEOMICS

Thurs., 1:15 - 3:15 PM, WB I/II.

Board #

1 **3.1** Global Muscle Gene Expression After Sprint Exercise. **A. Montelius, H. Rundqvist, M. Esbjörnsson, and E. Jansson.** *Karolinska Inst., Stockholm, Sweden.*

2 **3.2** Molecular Signatures of Adipose Tissue in an Ossabaw Swine Model of Childhood Obesity Using Transcriptome Analysis. **R. Toedebusch, K. Wells, F. Booth, and J. S. Rector.** *Univ. of Missouri, Columbia.*

3 **3.3** Association of Bone Density with Estrogen Receptor Gene 1 Polymorphisms and Environmental Factors in Japanese Young Women. **H. Kondo, H. Fujino, S. Murakami, N. Fujita, F. Nagatomo, and A. Ishihara.** *Nagoya Womens Univ., Kobe Univ., and Kyoto Univ., Japan.*

Poster Session

4.0 GENDER DIFFERENCES

Thurs., 1:15 - 3:15 PM, WB I/II.

Board #

4 **4.1** Maximal Force and Motor Unit Recruitment Patterns are Altered across the Human Menstrual Cycle. **M. Tenan, Y-L. Peng, A. Hackney, and L. Griffin.** *Univ. of Texas, Austin, and Univ.of North Carolina, Chapel Hill.*

5 **4.2** Sex-based Differences in Salivary α-amylase and IgA Responses Following Submaximal Cycling Exercise. **R. Teraoka, T. Tanioka, and N. Yasuda.** *Intl. Pacific Univ., Okayama, Japan, and Showa Univ., Hatanodai, Japan.*

6 **4.3** Gender Differences in Muscle Fiber Characteristics After 8 Weeks of Resistance Training. **T. Moro, F. Pacelli, L. Toniolo, M. Canato, P. Cancellara, C. Reggiani, and A. Paoli.** *Univ. of Padova, Italy.*

Poster Session

5.0 PHYSICAL INACTIVITY AND CHRONIC DISEASE

Thurs., 1:15-3:15 PM, WB I/II.

Board #

7 **5.1** Habitual Physical Activity Predicts Dietary Fat Oxidation and Trafficking. **A. Bergouignan, I. Momken, E. Antoun, D. Schoeller, C. Platat, H. Vidal, M. Laville, E. Lefai, C. Simon, and S. Blanc.** *IPHC/CNRS, Strasbourg, France, Univ. of Wisconsin, and Ctr. Hosp. Lyon Sud, Pierre Benite, France.*

8 **5.2** Sedentary Women with Overweight and Obesity: Effects of a Dietary Intervention, Circuit Resistance Training and Aerobic Training in the Metabolic and Ventilatory Parameters. **M. Rodrigues Barbosa, S. Perez, D. Bertucci, I. Wenzel, A. Duarte, C. Papini, L. Carvalho, E. Silva, and F. Ferreira.** *Univ. Fed. de São Carlos, Brazil.*

9 **5.3** Restoring Metabolic Homeostasis in Type 2 Diabetes with Exercise-Hyperthermic Mimetics. **P. Hooper.** *Univ. of Colorado, Denver.*

10 **5.4** Compensatory Responses of Insulin Signal-ing Restore Muscle Glucose Uptake Following Long Term Inactivity. **Z. Callahan, E. Cassell, J. Wheatley, M. Oxendine, A. Bartos, P. C. Geiger, and P. Schaeffer.** *Miami Univ., and Kansas Univ. Med. Ctr.*

11 **5.5** Effect of Chronic Swim Exercise on Adi-posity and Metabolic Function in Mice. **D. Hyman, A. Carneiro, M. Morris, and R. Pohlman.** *Wright State Univ.*

12 **5.6** Inflammatory Pathways Leading to Non Alcoholic Fatty Liver Disease are Blunted by Regular Running Exercise in Mice. **S. Hofmann, J. Weber, T. Ograjek, O. Al Massadi, E. Donelan, and M. Tschöp.** *Helmholtz Zentrum Muen-*

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chen, Munich, Germany, and Univ. of Cincinnati.

13 **5.7** High Intrinsic Aerobic Capacity is Associ-ated with Greater Liver Fatty Acid Oxidation Adaptability. **E. M. Morris, G. M. E. Meers, T-W. Liu, M. L. Kearney, A. L. Blandon, J. A. Fletcher, L. G. Koch, S. L. Britton, R. S. Rector, and J. P. Thyfault.** *Univ. of Missouri, and Univ. of Michigan.*

14 **5.8** Phenotypic Differences Between Generation 8 Rats Selectively-bred to Voluntarily Run High Versus Low Nightly Distances with an Emphasis on Using Voluntary Running to Prevent the Develop-ment of Juvenile Obesity. **M. Roberts, J. Brown, J. Company, T. Childs, L. Gilpin, and F. Booth.** *Univ. of Missouri, Columbia.*

15 **5.9** Intramuscular Expression of Mechanosensor Ankrd2 and Myokine Angptl4 During an Acute Bout of Inactivity. **J. Brown, M. Roberts, T. Childs, C. Cruthirds, and F. Booth.** *Univ. of Missouri, Columbia.*

16 **5.10** The Ubiquitin-Protein Ligase Nedd4 Contributes to the Skeletal Muscle Atrophy Induced by 14 Days of Immobilization. **L. MacNeil, E. Habib, J. Crane, M. Nilsson, and M. Tarnopolsky.** *McMaster Univ., Hamilton, Canada.*

Poster Session

6.0 EXERCISE AND DRUG INTERACTIONS

Thurs., 1:15 - 3:15 PM, WB I/II.

Board #

17 **6.1** Rat Metabolic Responses During Treadmill Running Following Doxorubicin Injections in Sedentary and Exercise Trained Rats. **K. Kenefick, J. Smith, E. Bredahl, and D. Hydock.** *Univ. of Northern Colorado.*

18 **6.2** A Pilot Study: Acute Effects of Doxorubicin on Hind-limb Gait Kinematics in Rats. **J. Smith, J. Yager, N. Gibson, and D. Hydock.** *Univ. of Northern Colorado.*

19 **6.3** Effects of Treadmill Training on Doxo-rubicin and Goserelin Acetate-Induced Bone De-generation. **E. Bredahl, D. Hydock, U. Iwaniec, R. Turner, T. Parry, C. Schneider, and R. Hayward.** *Univ. of Northern Colorado, and Oregon State Univ.*

20 **6.4** Tissue Specific Effects of Acetaminophen and Treadmill Exercise on Collagen Content in Male Wistar Rats. **C. Carroll, A. Peterson, and T. Broderick.** *Midwestern Univ.*

21 **6.5** Chronic Oral -(-)Epicatechin does not Affect Rat Hindlimb Skeletal Muscle Vascular Function During Exercise. **S. Copp, D. Hirai, T. Inagaki, M. White, G. Sims, C. Holdsworth, S. Ferguson, D. Poole, and T. Musch.** *Kansas State Univ.*

22 **6.6** Influence of Chronic Ethanol Ingestion on Compensatory Muscle Hypertrophy in the Rat. **J. Blank, D. Brim, V. Tomlinson, A. Tadros, J. Lewis, and J. Dyal.** *California Poly. State Univ.*

23 **6.7** MAC25 Promotes Muscle Hypertrophy by Coordinating both IGFII and Tgf beta Pathways. **B. Yaden, A. Ryan, G. Dai, and V. Krishnan.** *Indiana Univ., Perdue Univ., Indianapolis, and Eli Lilly and Co.*

24 **6.8** Influence of Nrf2 Activator Supplementation on Physiological Responses to Short Term Sprint

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Interval Training. **R. Scalzo, G. Peltonen, S. Binns, D. Hartley, A. Klochak, M. Lonac, S. Szallar, L. Wood, K. Hamilton, B. Miller, and C. Bell.** *Colorado State Univ.*

25 **6.9** Effects of the Phosphodiesterase-5 Inhibitor Tadalafil on Physiological Responses During Submaximal Exercise in Normoxia. **C. Buzzachera, L. Guidetti, L. Di Luigi, M. C. Gallotta, P. Sgrò, G. P. Emerenziani, E. Franciosi, and C. Baldari.** *Univ. of Rome Foro Italico, Italy, and North Univ. of Parana, Brazil.*

26 **6.10** Nitrous Oxide Narcosis and Hyperthermia Effect the Pattern of Breathing During Light Exercise. **K. Henderson, S. Ghaffari, P. L. L. McDonald, M. L. Walsh, and M. D. White.** *Simon Fraser Univ., Burnaby, Canada.*

Poster Session

7.0 MUSCLE FUNCTION AND ADAPTATION I

Thurs., 1:15 - 3:15 PM, WB I/II.

27 **7.1** Prolonged Mechanical Ventilation Results in Diaphragm Hypoxia and a Down-Regulation of Resistance Artery eNOS Expression. **B. Behnke, R. Davis III, and C. Bruells.** *Univ. of Florida, Gainesville, and Aachen Univ. Hosp. of the Rhenish-Westphalian Tech. Univ., Aachen, Germany.*

28 **7.2** Effects of Heat Stress on Diaphragmatic Atrophy Induced by 12 h Mechanical Ventilation in Rat. **N. Ichinoseki-Sekine, T. Yoshihara, R. Kakigi, T. Sugiura, S. Powers, S. Kawai, and H. Naito.** *Juntendo Univ., Tokyo, Japan, Yamaguchi Univ., Japan, and Univ. of Florida, Gainesville.*

29 **7.3** The Combined Effects of Inspiratory Muscle Training and Cycling on Diaphragm Muscle Activity. **N. Hellyer, A. Kakuk, I. Folsom, J. Mack, and J. Ver Mulm.** *Mayo Clinic.*

30 **7.4** Effect of Intermittent Activity During Cardiothoracic Surgery on Human Diaphragm Mitochondrial Respiration. **D. Martin, B. Smith, A. M. Jospeh, T. Beaver, T. Martin, H. Deoghare, and C. Leeuwenburgh.** *Univ. of Florida, Gainesville, and California State Univ., Fresno.*

31 **7.5** A 28 day Sojourn to 3454m Diminishes Skeletal Muscle Respiratory Capacity but Enhances Efficiency in Humans. **R. Jacobs, A-K. Meinild, and C. Lundby.** *Univ. of Zurich, Switzerland.*

32 **7.6** Acute In Vitro Statin Exposure Alters Mitochondrial Function in Permeabilized Skeletal Muscle from Healthy Humans. **C-T. Lin, B. Cathey, C. Perry, W. Mayo, L. Gilliam, K. Fisher-Wellman, D. Lark, C. Smith, and P. D. Neufer.** *East Carolina Univ.*

33 **7.7** Acute Exposure to Lovastatin Diminishes Tension Development in Intact Isolated Myofibers. **Q. Soltow, P. Gandra, L. Nogueira, and M. Hogan.** *Univ. of California; San Diego.*

34 **7.8** Three-dimensional Dynamic Organization of Mitochondria in Skeletal Muscle: Effects of a Single Bout of Voluntary Exercise. **M. Picard, K. White, S. Gartside, and D. Turnbull.** *Newcastle Univ., United Kingdom, and McGill Univ., Montreal, Canada.*

35 **7.9** Glycolytic Skeletal Myofibers Display Higher P/O Ratios than Cardiac Myofibers Due to Adenylate Kinase: Preliminary Findings Using a Novel

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Oxi-Fluorometer Apparatus. **D. Lark, P. D. Neufer, and E. Anderson.** *East Carolina Univ.*

36 **7.10** Effects of Aerobic Training and Overtraining on DNA Damage and Oxidative Stress in Swiss Mice. **B. Pereira, G. Alves, L. Antunes, M. Almeida, V. Venâncio, E. Freitas, J. Pauli, M. Saad, and A. Silva.** *Univ. São Paulo, Brazil and Univ. of Campinas, Brazil.*

37 **7.11** Sarcolipin Ablation does not Affect Exercise Training-Induced Adaptation of Oxidative Metabolism in Skeletal Muscle. **A. Trinh, V. A. Fajardo, D. Gamu, E. Bombardier, and R. Tupling.** *Univ.of Waterloo, Canada.*

38 **7.12** NFATc3 Regulates Muscle Fiber-Type Transition Independently From the Activation of Calcineurin During Long-Term Endurance Training in Rats. **A. Aguiar, I. Vechetti-Júnior, F. Almeida, and M. Dal-Pai-Silva.** *North Univ. of Paraná, Brazil, and São Paulo State Univ., Brazil.*

39 **7.13** Phospholamban Overexpression Causes Irregular Distribution and Size of Slow-Twitch and Fast-Twitch Fibres in Mouse Soleus and Diaphragm. **V. A. Fajardo, E. Bombardier, R. Mariani, I. Smith, B. Wadsworth, and R. Tupling.** *Univ. of Waterloo, Canada.*

40 **7.14** Phospholamban Regulates Both SERCA1a and SERCA2a in Human Skeletal Muscle. **E. Bombardier, V. A. Fajardo, C. Vig-na, T. Devji, D. Gamu, and R. Tupling.** *Univ. of Waterloo, Canada.*

41 **7.15** Assessment of the Intracellular Calcium Transient Using High and Low Affinity Fluorescent Indicators in Potentiated Mouse Lumbrical Muscle. **I. Smith, W. Gittings, R. Tupling, and R. Vandenboom.** *Univ. of Waterloo, Canada, and Brock Univ., St. Catherines, Canada.*

42 **7.16** Changing Myoglobin's Paradigm: A Novel Link Between Lipids and Myoglobin. **A. Schlater, M. De Miranda Jr., and S. Kanatous.** *Colorado State Univ.*

Poster Session

8.0 MOLECULAR REGULATORY MECHANISMS

Thurs., 1:15 - 3:15 PM, WB I/II.

Board #

43 **8.1** Effect of Exercise and Dietary Fat on Ge-netic Regulators of Knee Osteoarthritis in Mice. **T. Griffin, J. DeMoe, W-P. Chang, M. B. Frank, M. Bebak, and E. Hutchison.** *Oklahoma Med. Res. Fdn., Oklahoma City, and Univ. of Oklahoma Hlth. Sci. Ctr.*

44 **8.2** Skeletal Muscle Mass Regulators with and Without Contractile Activity in Spinal Cord-Injured vs. Able-Bodied Individuals. **N. Kelly, C. Yarar, C. S. Bickel, S. Windham, and M. Bamman.** *Univ. of Alabama at Birmingham.*

45 **8.3** Growth Hormone Deficiency has Tissue-Specific Effects on Protein Synthesis. **J. Drake, F. Peelor, L. Biela, R. Miller, K. Hamilton, and B. Miller.** *Colorado State Univ., and Univ. of Michigan.*

Don't forget to visit the exhibits—open daily during the Poster Sessions

Board #

46 **8.4** AICAR Inhibits Ceramide Biosynthesis in Skeletal Muscle. **B. Bikman, K. A. Erickson, M. E. Smith, and C. R. Hancock.** *Brigham Young Univ.*

47 **8.5** Modulation of Cardiac Mitochondrial Bioenergetics by Endurance Training and Intermittent Hypobaric Hypoxia. **J. Magalhães, I. Falcão-Pires, I. Gonçalves, J. Lumini-Oliveira, I. Marques-Aleixo, E. dos Passos, S. Rodrigues, A. C. Moreira, N. Machado, D. Mirada-Silva, A. Leite-Moreira, P. Oliveira, J. Torrella, and A. Ascensão.** *Univ. of Porto, Portugal, Fac. of Med., Porto, Portigal., Univ. of Coimbra, Portugal, and Univ. of Barcelona, Portugal.*

48 **8.6** Ovariectomy Increases Hepatic Mito-chondrial ROS Production in Mice. **A. Valencia, M. Morris, J. Thyfault, and E. Spangenburg.** *Univ. of Maryland, and Univ, of Missouri, Columbia.*

49 **8.7** Treatment of Cultured Myotubes with Rapamycin Activates AMP-Activated Protein Kinase. **D. Reuland, J. C. Drake, S. Khademi, B. F. Miller, and K. L. Hamilton.** *Colorado State Univ.*

50 **8.8** Skeletal Muscle Adaptation in Response to Mechanical Stress in p130Cas Mice. **T. Akimoto, K. Okuhira, K. Aizawa, S. Wada, H. Honda, T. Fukubayashi, and T. Ushida.** *Univ. of Tokyo, Japan, Waseda Univ., Tokorozawa, Japan, and Hiroshima Univ., Japan.*

51 **8.9** Phosphatidic Acid and Mechanical Stimuli Activate mTOR Signaling via an ERK-independent Mechanism. **J-S. You, J. Frey, and T. Hornberger.** *Univ. of Wisconsin, Madison.*

52 **8.1** mTOR Pathway Activation in the Desmin Knockout Mouse. **D. Nelson, M. Leavitt, B. Benson, G. Mack, and A. Parcell.** *Brigham Young Univ.*

53 **8.11** Withdrawn.

54 **8.12** Targeted Inhibition of Calcineurin Signaling with the Ca+2-Buffering Protein Parvalbumin Reduces Utrophin A Expression and Exacerbates the Dystrophic Pathology in mdx Mice. **M. Al Zein, E. Chin, B. Jasmin, and R. Michel.** *Concordia Univ., Montreal, Canada, Univ. of Maryland, and Univ. of Ottawa, Canada.*

55 **8.13** Deptor Expression is Altered by Mechanical Loading in Skeletal Muscle of Rats. **K. Shimkus, E. Wudeck, Y. Shirazi-Fard, H. Hogan, and J. Fluckey.** *Texas A&M Univ.*

56 **8.14** Differential Expression of HDAC Genes During Skeletal Muscle Atrophy. **A. Beharry; P. Sandesara, S. Senf, B. Roberts, and A. Judge.** *Univ. of Florida, Gainesville.*

57 **8.15** Exploring Ribosomal Regulation of Human Skeletal Muscle Hypertrophy. **M. Stec, A. Thalacker-Mercer, and M. Bamman.** *Univ. of Alabama at Birmingham.*

58 **8.16** Skeletal Muscle Fiber Type-Specific Transcriptional Response to Aerobic Exercise. **M. Undem, A. Konopka, U. Raue, B. Jemiolo, S. Trappe, and M. Harber.** *Ball State Univ.*

Poster Session

9.0 AGING

Thurs., 1:15 - 3:15 PM, WB I/II.

Board #

59 **9.1** Markers of "SR Stress" in Aging and Exercised Muscle. **D. Russ, J. Krause, A. Wills, and E. Klein.** *Ohio Univ., and Ohio Musculoskeletal & Neurological Inst.*

60 **9.2** Identification of Differentially Expressed mRNAs Between Young and Old Rats During Muscle Regeneration. **T. Itaka, Y. Miyagoe-Suzuki, and S. Machida.** *Tokai Univ., Hiratsuka, Japan, and Natl. Inst. of Neuroscience, Kodaira, Japan.*

61 **9.3** RAGE and STAT3 Signaling in Chronic AICAR-Treated Young Adult and Old Skeletal Muscle. **M. Jacobs, S. Hardman, T. Moore, J. Lew, P. Reynolds, and D. Thomson.** *Brigham Young Univ.*

62 **9.4** Age-Related Decrements in Human Whole Muscle Performance Correlate with Slower Myosin-Actin Cross-Bridge Kinetics. **M. Miller, N. Bedrin, D. Callahan, P. Ades, D. Maughan, B. Palmer, and M. Toth.** *Univ. of Vermont.*

63 **9.5** Age-Specific Adaptations in Myofiber Contractile Function in Response to Aerobic Exercise Training in Young and Older Men. **M. Harber, A. Konopka, M. Undem, J. Hinkley, K. Minchev, L. Kaminsky, T. Trappe, and S. Trappe.** *Ball State Univ.*

64 **9.6** Changes in Muscle Strength and Bone Mineral Density Following Exercise Training in Old Adults. **M. Welsch, N. Johannsen, D. Credeur, B. Hollis, T. Church, E. Ravussin, and J. Allen.** *Louis-iana State Univ., Pennington Biomedical Res. Ctr., Baton Rouge, Univ. of Missouri, and Duke Univ. Med. Ctr.*

65 **9.7** Novel Peripheral Training as a Primer for Increased Gains in Functional Capacity in Frail Elderly. **J. Allen, N. Johannsen, M. VanBruggen, J. Robbins, D. Credeur, T. Church, W. Kraus, C. Pieper, and M. Welsch.** *Duke Univ. Med. Ctr., Pennington Biomedical Res. Ctr. Baton Rouge, and Louisiana State Univ.*

66 **9.8** Long-Term Creatine Supplementation Combined with Resistance Training Improves Functional Capacity but not Maximal Strength in Older Women. **R. Januario, A. Aguiar, R. Pires Junior, A. Mendes Gerage, F. L. Cheche Pina, M. Amarante do Nascimento, and E. Serpeloni Cyrino.** *North Univ. of Parana, Londrina, Brazil, and Londrina State Univ., Brazil.*

67 **9.9** Effect of Increasing Essential Amino Acid Availability Following Resistance Exercise on Skeletal Muscle Let-7 miRNA Expression in Older Men. **J. Dickinson, D. Gundermann, M. Drummond, D. Walker, P. Reidy, M. Arora, E. Volpi, and B. Rasmussen.** *Univ. of Texas Med. Branch.*

68 **9.10** Essential Amino Acid Ingestion Following Aerobic Exercise in Older Adults Enhances Skeletal Muscle Amino Acid Transporter Expression. **M. Markofski, K. Timmerman, J. Dickinson, P. Reidy, M. Borack, D. Walker, B. Rasmussen, and E. Volpi.** *Univ. of Texas Med. Branch.*

69 **9.11** Aerobic Exercise Attenuates the Age-Associated Deterioration of Human Skin. **J. Crane, L. MacNeil, I. Braur, D. Ogborn, and M. Tarnopolsky.** *McMaster Univ., Hamilton, Canada.*

Symposia III *Personalized Medicine Track*

10.0 PERSONALIZED EXERCISE PRESCRIPTION BASED UPON INTEGRATIVE BIOLOGY

Thurs., 3:15 - 5:30 PM, Standley Ballroom.

Chair: **Frank Booth,** *Univ. of Missouri, Columbia.*

3:15 PM **10.1** Introduction. **Frank Booth.** *Univ. of Missouri, Columbia.*

3:20 PM **10.2** Adverse and Enhanced Responders to the Same Exercise Exposure. **Claude Bouchard.** *Pennington Biomedical Res. Ctr., Baton Rouge.*

3:50 PM **10.3** Gene-Activity/Inactivity Interaction. **Flemming Dela.** *Univ. of Copenhagen, Denmark.*

4:20 PM **10.4** High Resolution Physiologically-Based Phenotyping Along with an Integrated Medical Record System to Provide Insight About Individual Patients. **Michael J. Joyner.** *Mayo Clinic.*

4:50 PM **10.5** Lifestyle Medicopharmacogenetics. **William J. Kraus.** *Duke Univ. Sch. of Med.*

Symposia IV *Exercise Adaptations Track*

11.0 ACETYLATION: LINKING CHANGES IN NAD TO METABOLISM AND GROWTH

Thurs., 3:15 - 5:30 PM, WB III/IV.

Chair: **Keith Baar,** *Univ. of California, Davis.*

3:15 PM **11.1** Introduction. **Keith Baar.** *Univ. of California, Davis.*

3:20 PM **11.2** Pathophysiological Significance and Therapeutic Potential of NAMPT-Mediated NAD^+ Biosynthesis in Metabolic Diseases. **Jun Yoshino.** *Washington Univ. Sch. of Med.*

3:50 PM **11.3** Regulation of the Adaptive Response to Exercise by the Acetyltransferase GCN5. **Keith Baar.** *Univ. of California Davis.*

4:20 PM **11.4** Sirtuins: Regulating Metabolism Within the Mitochondria. **Matt Hirschey.** *Duke Univ. Med. Ctr.*

4:50 PM **11.5** Sirtuins: Central Control of Metabolism. **Raul Mostoslavsky.** *Massachusetts Genl. Hosp., Harvard Med. Sch.*

Plan to Attend the Welcome and Opening Reception
Wednesday, October 10
6:00 – 10:00 PM
The Lake House

FRIDAY, OCTOBER 12, 2012

Symposia V — *Cardiovascular Track*

12.0 CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM ANIMAL STUDIES

Fri., 8:30 - 10:45 AM, Standley Ballroom.

Chair: **David Brown,** *East Carolina Univ.*

8:30 AM **12.1** Introduction. **David Brown.** *East Carolina Univ.*

8:35 AM **12.2** Exercise and Cardiac Arrhythmias. **George Billman.** *Ohio State Univ.*

9:05 AM **12.3** Potassium Channels and Physiological Remodeling Following Exercise. **Scott Powers.** *Univ. of Florida, Gainesville.*

9:35 AM **12.4** Exercise, Sarcolemmal KATP Channels and Cardioprotection. **Leonid Zingman.** *Univ. of Iowa.*

10:05 AM **12.5** Cardiac KATP Channels and Exercise Cardioprotection. **John Quindry.** *Auburn Univ.*

Symposia VI — *Lipid Metabolism Track*

13.0 FIT, FAT AND LEAN LIVER: EXERCISE ADAPTATIONS IN NON-TRADITIONAL TISSUES

Fri., 8:30 - 10:45 AM, WB III/IV.

Chair: **Espen Spangenburg,** *Univ. of Maryland, College Park.*

8:30 AM **13.1** Introduction. **Espen Spangenburg.** *Univ. of Maryland, College Park.*

8:35 AM **13.2** Contribution of Glucagon to Exercise-Induced Reversal of Fatty Liver. **David Wasserman.** *Vanderbilt Univ.*

9:05 AM **13.3** Intrinsic Fitness and Exercise Prevent Hepatic Lipotoxicity. **John Thyfault.** *Univ. of Mis-souri, Columbia.*

9:35 AM **13.4** Exercise, IL-6 and Adipose Tissue Metabolism. **David Wright.** *Univ. of Guelph.*

10:05 AM **13.5** Energetic Regulation of White Adipose Tissue Metabolism. **Rolando Ceddia.** *York Univ., Toronto, Canada.*

Plenary Lecture

14.0 PLENARY LECTURE

Fri., 11:00 AM - 12:00 Noon, WB III/IV.

11:00 AM **14.1** Adaptations of the Heart: Traditional and Non-Traditional Research Approaches. **Leslie Leinwand.** *Univ. of Colorado, Boulder.*

Symposia VII — *Cardiovascular Track*

15.0 CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM HUMAN STUDIES

Fri., 1:15 - 3:30 PM, Standley Ballroom.

Chair: **Judy Muller-Delp,** *Univ. of Florida, Gainesville.*

1:15 PM **15.1** Introduction. **Benjamin Levine.** *Texas Hlth., Presbyterian Hosp.*

1:20 PM **15.2** Improving Exercise Tolerance in Heart Failure. **Dalane Kitzman.** *Wake Forest Univ.*

1:50 PM **15.3** Impaired Cardiac Function in Obese Adolescents: Reversal by Aerobic Interval Training. **Charlotte Ingul.** *Norwegian Univ. of Sci. & Tech., Trondheim, Norway.*

2:20 PM **15.4** Effects of Interventional and Lifelong Exercise on Left Ventricular Compliance and Diastolic Function in Aged Subjects. **Benjamin Levine.** *Texas Hlth., Presbyterian Hosp.*

2:50 PM **15.5** Exercise Attenuates the Premature Cardiovascular Aging Effects of Type 2 Diabetes Mellitus. **Amy Huebschmann.** *Univ. of Colorado Sch. of Med.*

Symposia VIII — *Lipid Metabolism Track*

16.0 SKELETAL MUSCLE LIPID DROPLET BIOLOGY IN EXERCISE AND DISEASE

Fri., 1:15 - 3:30 PM, WB III/IV.

Chair: **Deborah Muoio,** *Duke Univ.*

1:15 PM **16.1** Introduction. **Deborah Muoio.** *Duke Univ.*

1:20 PM **16.2** Role of Adipose Tissue Triglyceride Lipase in Exercise and Diabetes. **Matt Watt.** *Monash Univ., Australia.*

1:50 PM **16.3** Exercise-Induced Regulation of Lipid Droplet Proteins in Humans. **Patrick Schrauwen.** *Maastricht Univ. Med.Ctr., The Netherlands.*

2:20 PM **16.4** Cardiac Coordination of Lipid Storage and Utilization. **Carole Sztalryd.** *Univ. of Maryland, Baltimore.*

2:50 PM **16.5** PAT Proteins and Gene Expression. **Perry Bickel.** *Univ. of Texas Southwestern.*

Career Session

17.0 THE *INS* AND *OUTS* OF AUTHORSHIP

Fri., 3:45 - 4:45 PM, Standley Ballroom.

Chair: **Lacy A. Holowatz,** *Penn State Univ.*

3:45 PM **17.1** The *Ins* and *Outs* of Authorship. **Lacy A. Holowatz.** *Penn State Univ.*

Poster Session

18.0 MICROCIRCULATION

Fri., 7:00 - 9:30 PM, WB I/II.

Board #

1 **18.1** Chronic -(-)Epicatechin Administration does not Affect Contracting Skeletal Muscle Microvascular Oxygenation. **C. Holdsworth, S. Copp, T. Inagaki, D. Hirai, S. Ferguson, G. Sims, M. White, D. Poole, and T. Musch.** *Kansas State Univ.*

2 **18.2** Relation of Arterio-Venous Differences in Nitrate and Nitrite to Oxygen Content and Acid Base Status. **N. Maassen, K. Sutmoeller, H. Starke, M. Maassen, and D. Tsikas.** *Univ. Hannover, Germany, and Med. Sch. Hannover, Germany.*

3 **18.3** FoxO1 and FoxO3a are Involved in the Regulation of Exercise Induced Angiogenesis. **D. Slopack, S. Liu, E. Roudier, O. Birot, A. Montelius, T. Gustafsson, and T. L. Haas.** *York Univ., Toronto, Canada, and Karolinska Univ. Hosp., Stockholm, Sweden.*

Board #

4 **18.4** Myocyte-Derived VEGF Regulates Adaptations to Increased Blood Flow in Skeletal Muscle. **C. Uchida, E. Nwadozi, A. Hasanee, E. Gee, S. Olenich, I. M. Olfert, and T. L. Haas.** *York Univ., Toronto, Canada, and Univ. of West Virginia.*

5 **18.5** The Impact of Neuronal Nitric Oxide Synthase Expression on Running Performance and the Capillary System in Skeletal Muscle of Mice. **O. Baum, and H. Hoppeler.** *Univ. of Bern, Switzerland.*

6 **18.6** Ameliorative Effects of Antioxidant Astaxanthin on Capillary Regression in Hindlimb Unloading-Induced Atrophied Muscle. **H. Fujino, M. Kanazashi, H. Kondo, S. Murakami, F. Nagatomo, N. Fujita, and A. Ishihara.** *Kobe Univ., Japan, Nagoya Women's Univ., Japan, and Kyoto Univ., Japan.*

7 **18.7** Chronic Heart Failure and Muscle Microvascular Oxygenation: Effects of Exercise Training. **D. Hirai, S. Copp, S. Ferguson, C. Holdsworth, G. Sims, T. Musch, and D. Poole.** *Kansas State Univ.*

8 **18.8** The Effects of Acute Dietary Nitrate Supplementation on Muscle Microvascular Oxygenation in Contracting Rat Muscle. **S. Ferguson, D. Hirai, S. Copp, C. Holdsworth, T. Musch, and D. Poole.** *Kansas State Univ.*

Poster Session

19.0 BLOOD FLOW REGULATION

Fri., 7:00 - 9:30 PM, WB I/II.

9 **19.1** Central Command Contributes to Increasing Blood Flow to Non-Contracting Muscle During Motor Imagery and Voluntary One-Legged Exercise. **K. Ishii, K. Matsukawa, N. Liang, A. Oue, A. Hirasawa, K. Sato, and T. Sadamoto.** *Hiroshima Univ., Japan, and Japan Women Coll. of Physical Ed., Tokyo, Japan.*

10 **19.2** Alterations in Cerebral Blood Flow During Exercise at High Altitude. **K. Smith, D. Macleod, C. Willie, K. Ikeda, N. Lewis, and P. Ainslie.** *Univ. of British Columbia, Canada, and Duke Univ. Med. Ctr.*

11 **19.3** Effect of PCO_2 Clamping on Brain Blood Flow, Oxygenation and Performance During 15 km Time Trial Cycling in Severe Hypoxia. **J-F. Fan, N. Bourdillon, and B. Kayser.** *Univ. of Geneva, Switzerland.*

12 **19.4** Contribution of Nitric Oxide to Exercise Hyperemia in Obese Adults. **R. Johansson, J. Limberg, J. Harrell, M. Crain, J. Sebranek, B. Walker, and W. Schrage.** *Univ. of Wisconsin, Madison.*

13 **19.5** Effect of β-Adrenergic Blockade on Exercise Hyperemia in Metabolic Syndrome. **J. Harrell, J. Limberg, J. Sebranek, L. Proctor, M. Eldridge, B. Morgan, and W. Schrage.** *Univ. of Wisconsin, Madison.*

14 **19.6** Effect of Endurance Training on Splanchnic Circulation During Head-Up Tilt. **C. Ray, E. Conboy, and C. Sauder.** *Penn State Univ. Coll. of Med.*

Don't forget to visit the Exhibits—open daily during the Poster Sessions

Board #

15 **19.7** Vasoconstrictor Responsiveness During Hyperbaric Hyperoxia in Contracting Human Muscle. **D. Casey, M. J. Joyner, P. Claus, M. Bigelow, W. Fuqua, and T. Curry.** *Mayo Clinic.*

16 **19.8** Alterations in Endothelial Function with Physical Inactivity: A Preliminary Report. **L. Boyle, D. Credeur, S. Holwerda, H. Leidy, J. Padilla, J. Thyfault, and P. Fadel.** *Univ. of Missouri, Columbia.*

Poster Session

20.0 CARDIOVASCULAR

Fri., 7:00 - 9:30 PM, WB I/II.

Board #

17 **20.1** Regular Exercise Reverses Suppressions of SERCA Activity and α-MHC Expression in the Heart of Orchidectomized Rat. **P. Vutthasathien, T. Bupha-Intr, and J. Wattanapermpool.** *Mahidol Univ., Bangkok, Thailand.*

18 **20.2** Regular Exercise Prevents the Cardiac Myofilament Ca2+ Hypersensitivityin Angiotensin II-Infused Ovariectomized Rat. **T. Bupha-Intr, S. Pandit, and J. Wattanapermpool.** *Mahidol Univ., Bangkok, Thailand.*

19 **20.3** Sarcolipin and Phopholamban Protect Sarco Plasmic Reticulum Ca2+-ATPase Function During Heat Shock. **D. Gamu, E. Bombardier, and A. Tupling.** *Univ. of Waterloo, Canada.*

20 **20.4** Synergistic Impact of Endurance Training and Intermittent Hypobaric Hypoxia on Heart Mitochondrial Susceptibility to Permeability Transition Pore Opening and Apoptotic Signaling. **A. Ascensao, I. Falcao-Pires, I. Oliveira-Gonçalves, J. Lumini-Oliveira, I. Marques-Aleixo, E. Passos, S. Rocha-Rodrigues, A. C. Moreira, N. Machado, A. Leite-Moreira, P. Oliveira, J. Torrella, and J. Magalhaes.** *CIAFEL, Porto, Portugal, Fac. of Med, Porto, Portugal, Univ. of Coimbra, Portugal, and Fac. of Biology, Barcelona, Spain.*

21 **20.5** Endurance-Training in Early Life Results in Long-Term Programming of Cardiac Hypertrophy in Rats. **G. Wadley, R. Laker, G. McConell, and M. Wlodek.** *Deakin Univ., Burwood, Australia, Univ. of Melbourne, Australia, and Victoria Univ., Australia.*

22 **20.6** High Fat Diet-Induced Hyperinsulinemia Induces Early Cardiac Adaption to Insulin Resistance. **A. Gupte, L. Minze, M. Reyes, X. Wang, K. Ding, Z-Z. Shi, D. Hamilton, and W. Hsueh.** *The Methodist Hosp. Res. Inst., Houston.*

23 **20.7** Apocynin Prevents Exercise-Induced Cardiac Dysfunction and Ca2+ Leak From the Sar-coplasmic Reticulum of Rat Myocardium. **C. Vigna, D. Gamu, E. Bombardier, J. W. Rush, and A. Tup-ling.** *Univ. of Waterloo, Canada.*

24 **20.8** Post-Exercise Flow-Mediated Dilation is Influenced by Retrograde and Oscillatory Shear. **B. Johnson, K. Mather, S. Newcomer, T. Mickleborough, and J. Wallace.** *Indiana Univ., and Purdue Univ.*

25 **20.9** Differential Vasodilator Effects of Insulin Between Gastrocnemius and Soleus Muscle Feed Arteries: Role of Endothelin-1. **N. Jenkins, J. Padilla, J. Martin, J. Crissey, J. Thyfault, R. Rector, and M. Laughlin.** *Univ. of Missouri, Columbia.*

Board #

26 **20.10** Effects of Flexibility Levels on Stretching Exercise-Induced Reduction in Arterial Stiffness. **Y. Gando, K. Yamamoto, H. Kawano, R. Hara, and I. Muraoka.** *Waseda Univ., Tokorozawa, Japan, and Univ. of North Texas Hlth. Sci. Ctr., Fort Worth.*

27 **20.11** Long-Term Aerobic and Resistance Training Differentially Impact Conduit Artery Structural Properties. **C. Mikus, K. Ham, C. Slentz, W. Kraus, and J. Allen.** *Duke Univ. Med.Ctr.*

28 **20.12** Acute Exercise and Activation of Nitric Oxide Synthase in Aorta of Rats: Role of Reactive Oxygen Species, Akt and AMP-Activated Protein Kinase. **C. De Souza, T. Luciano, S. Marques, D. Souza, and R. Pinho.** *Univ. do Extemo Sul Catarinense, Criciúma, Brazil.*

29 **20.13** Effects of Voluntary Wheel Running on Aortic Doxorubicin Accumulation and Dysfunction. **N. Gibson, S. Greufe, D. Hydock, and R. Hayward.** *Univ. of Northern Colorado.*

30 **20.14** The Temporal Nature of Cardioprotection in Voluntary Wheel Running Mice. **B. Budiono, L. See Hoe, J. Peart, S. Sabapathy, K. Ashton, J. Head-rick, and L. Haseler.** *Griffith Univ., Southport, Australia.*

31 **20.15** The Transient Cardioprotective Effects of Training, Detraining and Retraining of Acute Voluntary Wheel-Running Mice. **B. Budiono, L. See Hoe, J. Peart, S. Sabapathy, K. Ashton, J. Headrick, and L. Haseler.** *Griffith Univ., Southport, Australia.*

32 **20.16** Chronic Low-Intensity Interval Exercise Training Increases Cardiac Torsion and is Associated with Enhanced Systolic and Early Diastolic Strain Rate in Mini-Swine with Compensated Heart Failure. **K. Marshall, C. Weimer, and C. Emter.** *Univ. of Missouri, Columbia.*

33 **20.17** Effects of Deployment-Related Exposures on Cardiopulmonary Function. **M. Falvo, J. Witkowski, A. Acosta, M. Blatt, and J. Serrador.** *VA NJ Hlth. Care Sys., and New Jersey Med. Sch.*

34 **20.18** Moderate-Intensity Resistance Training Improves Vascular Function in Obese Women. **N. Franklin, M. Ali, P. McGinty, E. Norkeviciute, and S. Phillips.** *Univ. of Illinois at Chicago.*

35 **20.19** Effects of High Intensity Intermittent Training on Aerobic Capacity, Endurance Capacity and Short Term Recovery. **J. Eigendorf, and N. Maassen.** *Leibniz Univ., Hannover, Germany.*

36 **20.20** Factors Limiting Aerobic Capacity: Cardiopulmonary or Peripheral? **G. Crocker, and J. Jones.** *Univ. of California, Davis.*

Poster Session

21.0 CHO/LIPID METABOLISM

Fri., 7:00 - 9:30 PM, WB I/II.

Board #

37 **21.1** Identification of Circulating Biomarkers of Muscle Fatty Acid Oxidation. **C. Aguer, O. Fiehn, M. Padilla, D. Bickel, E. Seifert, S. H. Adams, and M-E. Harper.** *Univ. of Ottawa, Canada, Univ., of California, Davis, and U.S. Dept. of Agriculture.*

38 **21.2** Insulin Signaling in Myotubes Derived from Obese Adults was not Impaired in Response to a Mixture of Fatty Acids Resembling that Found in Human Plasma. **S. Park, J. P. Gumucio, A. Hinko, S. A.Newsom, and J. F. Horowitz.** *Univ. of Michigan.*

Board #

39 **21.3** Skeletal Muscle Fatty Acid Synthase Modulates Sarcoplasmic Reticulum Phospholipid Composition to Regulate Insulin Sensitivity and Muscle Strength. **K. Funai, H. Song, X. Wei, I. J. Lodhi, and C. F. Semenkovich.** *Washington Univ.*

40 **21.4** Post-Exercise Values for Muscle AS160 Phosphorylation and Insulin-Stimulated Glucose Uptake are Greater for Chow-Fed vs. High Fat Fed Rats. **C. Castorena, E. Arias, Y. Xiao, and G. Cartee.** *Univ. of Michigan.*

41 **21.5** Perilipin 2 and 5 are not Modulated by Physiological Stressors Affecting Triacylglycerol Storage or Utilisation in Skeletal Muscle. **R. Mason, R. Meex, B. Canny, and M. Watt.** *Monash Univ., Clayton, Australia.*

42 **21.6** Divergent Effects of L-Carnitine on Pyruvate-Supported O_2 Consumption and H_2O_2 Emission Within Permeabilized Myofibers. **K. Fisher-Wellman, L. Gilliam, B. Cathey, C-W. Lin, and P. D. Neufer.** *East Carolina Univ.*

43 **21.7** Reduced Respiration in Skeletal Muscle Mitochondria from Obese Mice is Associated with Decreased Sirt3 Expression and Hyperacetylation of Mitochondrial Proteins. **N. Turner, L. Wright, B. Osborne, A. Brandon, M. Montgomery, and G. Cooney.** *Garvan Inst. of Med. Res., Darlinghurst, Australia.*

44 **21.8** Acute Heat Treatment Alters Adipose Tissue Fatty Acid Handling. **R. Rogers, M-S. Beaudoin, J. Wheatley, D. C. Wright, and P. C. Geiger.** *Univ. of Kansas Med. Ctr., and Univ. of Guelph, Canada.*

45 **21.9** The Upregulation of Genes Involved in Fatty Acid Oxidation is Depressed with Severe Obesity. **J. Maples, J. Brault, T. Weber, G. Battaglia, S. Alavi, G. Dubis, L. Consitt, and J. Houmard.** *East Carolina Univ., Univ. of Illinois at Chicago, and Ohio Univ.*

46 **21.10** Postprandial Hepatic Triacylglycerol Secretion and Fatty Acid Oxidation are not Altered by Prior Aerobic Exercise in Obese-Susceptible Sprague-Dawley Rats. **T. Heden, E. M. Morris, M. L. Kearney, T. W. Liu, F. W. Booth, J. A. Kanaley, and J. P. Thyfault.** *Univ. of Missouri, Columbia.*

47 **21.11** Activation of the Fat Metabolism by High-Intensity Sprint Exercise. **M. Maassen, H. Starke, K. Sutmoeller, and N. Maassen.** *Leibniz Univ., Hannover, Germany, and Med. Sch. of Hannover, Germany.*

48 **21.12** Erythropoietin Increases Mitochondrial Capacity in White Adipose Tissue in Mice. **V. Díaz, R. A. Jacobs, C. Lundby, and M. Gassmann.** *Univ. of Zurich, Switzerland.*

49 **21.13** Resveratrol Supplementation Improves Glucose Homeostasis and White Adipose Tissue Metabolism in a Depot-Specific Manner in Zucker Diabetic Fatty Rats. **M-S. Beaudoin, G. P. Holloway, L. A. Snook, I. R. Ritchie, and D. C. Wright.** *Univ. of Guelph, Canada.*

50 **21.14** Hemolysis Due to Lactate Infusion: Is pH or Osmolarity the Culprit? **J. McDonald, G. Oldenbeuving, M. Goodwin, Y. Sun, K. Lee, M. W. Nijsten, G. M. van Dam, and B. Gladden.** *Auburn Univ., Univ. Med. Ctr. Groningen, The Netherlands, and Weill Cornell Med. Coll.*

Board #

51 **21.15** Verification of an Intracellular Lactate Shuttle in Human Skeletal Muscle. **R. Jacobs, A-K. Meinild, N. Nordsborg, B. Saltin, and C. Lundby.** *Univ. of Zurich, Switzerland, and Univ. of Copenhagen, Denmark.*

52 **21.16** Effects of Dietary Induced Obesity and Exercise Training on Hepatic CIDE Expression. **J. Donohue, A. Frulla, A. Robinson, and T. Reynolds.** *Skidmore Coll.*

Poster Session

22.0 MUSCLE INJURY

Fri., 7:00 - 9:30 PM, WB I/II.

53 **22.1** Role of LKB1 in Skeletal Muscle Regeneration After Injury. **S. Anderson, C. Tanner, S. Hardman, B. Nelson, Z. Oleskey, M. Price, and D. Thomson.** *Brigham Young Univ.*

54 **22.2** Mesenchymal Stem Cells Contribute to Exercise-Induced Skeletal Muscle Hypertrophy and Strength. **K. Zou, H. Huntsman, and M. Boppart.** *Univ. of Illinois; Urbana-Champaign.*

55 **22.3** Proliferation of Human Myoblasts Cultured in Serum Obtained After Sprint Exercise. **H. Fischer, S. Alam, B. Norman, H. Rundqvist, M. Esbjörnsson, and E. Jansson.** *Karolinska Univ., Stockholm, Sweden.*

Poster Session

23.0 MUSCLE FUNCTION AND ADAPTATION II

Fri., 7:00 - 9:30 PM, WB I/II.

Board #

56 **23.1** Space Radiation Environment Creates Ion-Specific Increases in Muscle Mass in Simulated Lunar Gravity. **K. Shimkus, M. Wiggs, B. Macias, F. Lima, R. Boudreaux, Y. Shirazi-Fard, E. Greene, L. Braby, H. Hogan, S. Bloomfield, and J. Fluckey.** *Texas A&M Univ.*

57 **23.2** Short-Term Intense Exercise Training Reduces Markers of Cellular Stress in Human Skeletal Muscle. **C. Wolff, J. M. Hinkley, A. Konopka, M. Undem, B. Jemiolo, T. Trappe, S. Trappe, and M. Harber.** *Ball State Univ.*

58 **23.3** Effects of 12-wks of Aerobic Exercise Training on Skeletal Muscle Insulin Sensitivity, Mitochondrial Bioenergetics, Substrate Utilization, and Energy Expenditure in Premenopausal Women. **G. Fisher, B. Gower, D. Moellering, F. Ovalle, and G. Hunter.** *Univ. of Alabama at Birmingham.*

59 **23.4** Skeletal Muscle of Extremely Obese Women is Insensitive to Atrophic Stimuli. **L. Bollinger, and J. Brault.** *East Carolina Univ.*

60 **23.5** Acetaminophen has no Effect on Integrin Signaling Following 5-weeks of Treadmill Exercise in Rat Soleus Muscle. **Z. Graham, C. Carroll, T. Broderick, and P. Gallagher.** *Univ. of Kansas, and Midwestern Univ.*

61 **23.6** SIRT1 and AMPK Activators Promote Phenotypic Adaptations in Dystrophic Skeletal Muscle and Represent Pre-Clinical Therapeutics for DMD. **V. Ljubicic, M. Burt, S. Brunette, L. A. Megeney, and B. J. Jasmin.** *Univ. of Ottawa, Canada, and Ottawa Hlth. Res. Inst., Canada.*

62 **23.7** miR-23a Targets PGC-1α and Regulates Mitochondrial Content in Skeletal Muscle. **S. Wada, A. Russell, Y. Kato, T. Ushida, and T. Akimoto.** *Univ. of Tokyo, Japan, Deakin Univ., Burwood, Australia, and Nat. Inst. of Advanced Ind. Sci. and Tech., Tsukuba, Japan.*

Board #

63 **23.8** PGC-1α is Required for Exercise Training and Resveratrol Induced Effects on Oxidative Capacity of Mice Skeletal Muscle. **S. Ringholm, J. T. Pedersen, J. Olesen, Y. Hellsten, and H. Pilegaard.** *Univ. of Copenhagen, Denmark.*

64 **23.9** Thrombospondin-1 Influences Skeletal Muscle Mitochondrial Respiratory Enzyme Activity. **G. Audet, D. Fulks, D. Thapa, and I. M. Olfert.** *West Virginia Univ.*

65 **23.10** Lack of Alpha-Actinin-3 Attenuates m-TOR Signaling in Human Skeletal Muscle After Sprint Exercise. **B. Norman; M. Esbjörnsson, T. Österlund, H. Rundqvist, and E. Jansson.** *Karolinska Inst., Stockholm, Sweden.*

66 **23.11** Resistance Exercise Acutely Induces the Unfolded Protein Response in Skeletal Muscle. **D. Ogborn, B. McKay, J. Crane, G. Parise, and M. Tarnopolsky.** *McMaster Univ., Hamilton, Canada.*

67 **23.12** Effects of AICAR and/or Exercise on Muscle Function and Hsp25 and 70 Expression in Mice. **K. Huey, and B. Moeller.** *Drake Univ., Des Moines, Iowa.*

68 **23.13** Effects of Unloading on Myosin Heavy Chain Phenotypes of Soleus Muscle in Heat Shock Transcription Factor 1-Null Mice. **K. Goto, A. Nakai, T. Sugiura, Y. Ohira, and T. Yoshioka.** *Toyohashi SOZO Univ., Toyohashi, Japan, Yamaguchi Univ., Ube and Yamaguchi, Japan, Osaka Univ., Toyonaka, Japan, and Hirosaki Gakuin Univ., Hirosaki, Japan.*

69 **23.14** Effects of Aging and Endurance Training on the Muscle-Tendon Complex Behavior. **K. Hirose, M. Tsutsumi, and K. Ogiso.** *Kogakkan Univ., Ise, Japan.*

70 **23.15** ICAM-1 Promotes Skeletal Muscle Hypertrophy. **Q. Goh, C. Dearth, J. Marino, M. J. Torres-Palsa, P. Cicinelli, B. Hammer, and F. Pizza.** *Univ. of Toledo.*

71 **23.16** Changes in Muscle Atrophy and Pro-Inflammatory Cytokines in Patients Undergoing ACL Reconstruction and Rehabilitation. **C. Mendias, E. Lynch, S. Roche, E. Sibilsky Enselman, M. Davis, and A. Bedi.** *Univ. of Michigan Med. Sch.*

Poster Session

24.0 EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE

Fri., 7:00 - 9:30 PM, WB I/II.

Board #

72 **24.1** Low-Intensity Interval Training Attenuates Increased mRNA Expression of Extracellular Matrix Regulating Biomarkers in Mini-Swine with Compensated Heart Failure. **B. Muller, K. Marshall, C. Weimer, and C. Emter.** *Univ. of Missouri, Columbia.*

73 **24.2** Mechanical Loading and TGF-β Regulate the Expression of Multiple miRNAs in Tendon Fibroblasts. **J. Gumucio, E. Lynch, and C. Mendias.** *Univ. of Michigan Med. Sch.*

Don't forget to visit the Exhibits—open daily during the Poster Sessions

Poster Session

25.0 FATIGUE

Fri., 7:00 - 9:30 PM, WB I/II.

Board #

74 **25.1** Behavior of the Tibialis Anterior Muscle-Tendon Complex During Repeated Maximum Isometric Dorsiflexion. **K. Ogiso, Y. Kobayashi, K. Hirose, and M. TsuTsumi.** *Kogakkan Univ., Ise, Japan.*

75 **25.2** What Determines the Time-Course of Performance Loss and Muscle Fatigue in Different Modes of Dynamic Exercise? **C. W. Sundberg, S. F. Barrett, and M. W. Bundle.** *Univ. of Montana, and Univ. of Wyoming.*

76 **25.3** The Effect of Metabolic Alkalosis on Localised Neuromuscular Fatigue During Intermittent, High-Intensity Cycling at a Fixed Cadence. **J. Siegler, P. Marshall, S. Raftry, C. Brooks, B. Dowswell, R. Romero, K. Mathews, and M. Knox.** *Univ. of Western Sydney, Penrith, Australia.*

77 **25.4** Influence of Altered Duty Cycle on Critical Power During Handgrip Exercise. **R. Broxterman, C. Ade, S. Wilcox, S. Schlup, and T. Barstow.** *Kansas State Univ.*

SATURDAY, OCTOBER 13, 2012

Symposia IX

26.0 PHYSICAL ACTIVITY IS NECESSARY FOR OPTIMAL BRAIN FUNCTION

Sat., 8:30 - 10:45 AM, Standley Ballroom.

Chair: **Michael Joyner,** *Mayo Clinic.*

8:30 AM **26.1** Introduction. **Michael Joyner.** *Mayo Clinic.*

8:35 AM **26.2** Brain Blood Flow and Epidemiology of Cognitive Decline. **Michael Joyner.** *Mayo Clinic.*

9:00 AM **26.3** What Mechanisms Explain the Protective Effects of Exercise on Brain Function. **Carl Cotman.** *Univ. of California, Irvine.*

9:25 AM **26.4** Potential Neurobiological Mechanisms Between Physical Activity and Cognitive Function. **Rong Zhang.** *Univ. of T Southwestern.*

9:50 AM **26.5** How Does Aerobic Exercise Protect Against Dementia? **Neill Graff-Radford.** *Mayo Clinic Jacksonville.*

10:15 AM **26.6** Why and How Physical Activity Promotes Physical Activity-Induced Brain Plasticity. **Laura Baker.** *Univ. of Washington.*

Symposia X

27.0 THE IMPACT OF HEAT SHOCK PROTEIN EXPRESSION ON MUSCLE METABOLISM, EXERCISE CAPACITY AND DISEASE PREVENTION

Sat., 8:30 - 10:45 AM, WB III/IV.

Chair: **Paige C. Geiger,** *Univ. of Kansas Med. Ctr.*

8:30 AM **27.1** Introduction. **Paige C. Geiger.** *Univ. of Kansas Med. Ctr.*

8:35 AM **27.2** Mechanisms and Functional Effects of Attenuation of Exercised-Induced HSP Production During Aging. **Anne McArdle.** *Liverpool Univ., United Kingdom.*

9:05 AM **27.3** The Role of HSP72 in Regulating Mitochondrial Function and Capacity in Skeletal Muscle. **Mark Febbraio.** *Baker Heart Res. Inst., Melbourne, Australia.*

9:35 AM **27.4** Sex Differences in the Exercise Stress Response and Potential Implications for Myocardial Protection. **Kevin Milne.** *Univ. of Windsor, Canada.*

10:05 AM **27.5** Targeting Heat Shock Proteins in the Prevention of Insulin Resistance. **Paige C. Geiger.** *Univ. of Kansas Med. Ctr.*

Discussion

28.0 TOWN HALL MEETING

Sat., 11:00 AM - 12:00 Noon, WB III/IV.

Chairs: **Jim Whitehead,** *American Coll. of Sports Med.*, and **Martin Frank,** *American Physiological Soc.*

11:00 AM **28.1** Town Hall Meeting. **Jim Whitehead.** *American Coll. of Sports Med.*, and **Martin Frank,** *American Physiological Soc.*

Poster Session

29.0 INTEGRATED EXERCISE RESPONSE

Sat., 1:15 - 3:15 PM, WB I/II.

Board #

1 **29.1** Jumping Ability of Long-Distance Runners. **M. Tsutsumi, K. Hirose, and K. Ogiso.** *Kogakkan Univ., Ise, Japan.*

2 **29.2** Peak Heart Rate and Performance in Severe Hypoxia: Differences Between Tibetans and Han Chinese. **B. Kayser, J-L. Fan, and T-Y. Wu.** *Univ. of Geneva, Switzerland, and Nat. Key Lab. of High Altitude Med., Qinghai, People's Rep. of China.*

3 **29.3** Short-Term Effects of Intentional Biodynamic Craniosacral Therapy on VO2max and Heart Rate Recovery: A Pilot Study. **M. Armeni, R. D'Onofrio, P. Sommaiuolo, and G. Giusva.** *Still Osteopathic Inst., Rome, Italy, and Univ. Degli Studi di Roma Tor Vergata, Rome, Italy.*

4 **29.4** The Effects of Different Modes of Exercise on the Associations Between Appetite and Appetite-Related Gut Hormones. **H. Kawano, M. Mineta, M. Asaka, M. Miyashita, S. Numao, Y. Gando, T. Ando, S. Sakamoto, and M. Higuchi.** *Waseda Univ., Tokorozawa, Japan, Tokyo Gakugei Univ., Koganei, Japan, and Kyoto Pharmaceutical Univ., Japan.*

5 **29.5** Voluntary Wheel Running that Enhances Neurogenesis Does Not Activate Microglia in the Mice Hippocampus. **T. Nishijima, H. Tamata, and I. Kita.** *Tokyo Metropolitan Univ., Hachioji, Japan.*

6 **29.6** Blood Pressure Response to Exercise is Not Related to Vascular Endothelial Function in Overweight/Obese Adults. **D. Templeton, T. Califf, J. Greiner, B. Stauffer, and C. DeSouza.** *Univ. of Coloardo, Boulder, and Univ. of Colorado, Denver.*

7 **29.7** Reflex Sympathetic Nerve Activity During Static Handgrip Exercise in Human Metabolic Syndrome. **J. Limberg, B. Morgan, and W. Schrage.** *Univ. of Wisconsin, Madison.*

8 **29.8** Influence of Duty Cycle on Muscle Deoxy-(Hb+Mb) During Ramp Hand Grip Exercise. **C. Ade, R. Broxterman, S. Schlup, S. Wilcox, and T. Barstow.** *Kansas State Univ.*

Board #

9 **29.9** Changes in Glucagon Receptors with Fasting and Exercise: Similar Results but Different Mechanisms. **C. Lavoie, A. Melançon, D. Foucher, E. Charest, M. Dumont-Légacé, J. Lamanque, C. G Unson, and M. Cadrin.** *Univ. of Quebec, Trois-Riviéres, Canada, and Rockefeller Univ.*

10 **29.10** The Metabolic Responses to Exercise Mode in Overweight/Obese Asthmatics. **W. Kist**. *Louis Coll. of Pharmacy.*

11 **29.11** Effect of Interval Training on Changes in VO2max: A Meta-Analysis. **A. Bacon, R. Carter, E. Ogel, and M. Joyner.** *Mayo Clinic, and Creighton Univ.*

12 **29.12** An Alternative Approach to Matching Relative Work and Intensity Domains During Interval and Continuous Exercise. **E. Harris, A. Weeks, A. Khalil, G. Birk, C. Ferguson, and K. Birch.** *Univ. of Leeds, United Kingdom.*

13 **29.13** Influence of Exercise Modality on Physiological Adaptations to Short-Term Sprint Interval Training. **R. Scalzo, G. Peltonen, S. Binns, G. Giordano, A. Klochak, H. Paris, M. Schweder, K. Sevitz, S. Szallar, L. Wood, and R. Reiser; C. Bell.** *Colorado State Univ.*

14 **29.14** A Single Session of Sprint Interval Training Increases Total Daily Energy Expenditure. **K. Sevits, E. Melanson, T. Swibas, G. Peltonen, R. Scalzo, S. Binns, A. Klochak, C. Melby, and C. Bell.** *Colorado State Univ., Univ. of Colorado, Anschutz Med. Campus, Denver.*

15 **29.15** A Single Bout of Sprint Interval Training in Normoxia Does Not Improve Endurance Exercise Performance in Hypoxia. **G. Peltonen, R. Scalzo, S. Binns, A. Klochak, S. Szallar, L. Wood, D. Irwin, T. Schroeder, K. Hamilton, and C. Bell.** *Colorado State Univ., Univ. of Colorado, Denver, and Duke Univ. Sch. of Med.*

16 **29.16** Hypoxic Exercise Performance Following Intravenous Glucose Administration: Influence of Sympathetic Inhibition. **R. Scalzo, G. Peltonen, S. Binns, A. Klochak, M. Schweder, S. Szallar, L. Wood, D. Irwin, T. Schroeder, K. Hamilton, M. Hickey, and C. Bell.** *Colorado State Univ., Univ. of Colorado, Denver, and Duke Univ. Sch. of Med.*

17 **29.17** Short-Term Training Improves Glucose Tolerance and Increases Muscle GLUT4, cytc and COXI Protein in Elderly Men. **R. Biensø, N. Iversen, J. Olesen, M. Matzen, M. Matzen, L. Jensen, J. Schmidt, Y. Hellsten, and H. Pilegaard.** *Univ. of Copenhagen, Denmark.*

18 **29.18** The Advantages/Disadvantages to Using Cultured Single Muscle Fibers as an In Vitro Model to Mechanistically Research Skeletal Muscle. **K. Jackson, L. Wohlers, C. Ward, and E. Spangenburg.** *Univ. of Maryland.*

19 **29.19** Acute Exercise Regulates AMPK in Breast Cancer Cells. **P. Hojman, G. Westergaard Hojfeldt, L. Pedersen, and B. Pedersen.** *Copenhagen Univ. Hosp., Denmark.*

20 **29.20** Lactate and mTORC1 Activation in C2C12 Myotubes. **D. Gundermann, D. Walker, M. Borack, and B. Rasmussen.** *Univ. of Texas Med. Branch., Galveston.*

21 **29.21** Effect of Protein Blend vs Whey Protein Post-Exercise Ingestion on Human Skeletal Muscle Amino Acid Transporter Expression Following Resistance Exercise. **P. Reidy, J. Dickinson, D. Walker, D. Gundermann, M. Drummond, K. Timmermann, M. Cope, R. Mukherjea, E. Volpi, and B. Rasmussen.** *University of Texas Medical Branch, Galveston, and Solae LLC, St. Louis, Missouri.*

22 **29.22** Counter-Intuitive Increase in Plasma Myostatin After Resistance Training with Hig h Protein Diet in Young Healthy Subjects. **A. Paoli, F. Pacelli, L. Toniolo, D. Faggian, M. Plebani, and C. Reggiani.** *Univ. of Padova, Italy.*

23 **29.23** The Effect of Muscle Contraction on Cachectic Muscle mTOR Signaling and Protein Synthesis in ApcMin/+ Mouse. **S. Sato, M. Puppa, S. Gao, and J. Carson.** *Univ. of South Carolina.*

24 **29.24** Exercise Training Improves Exercise Capacity Despite Persistent Muscle Mitochondrial Dysfunction in the taz shRNA Mouse Model of Human Barth Syndrome. **M. Claiborne, C. Le, K. Hamilton, and A. Chicco.** *Colorado State Univ.*

25 **29.25** Effects of the Menstrual Cycle Phase on Oxidative DNA Damage Following Submaximal Cycling Exercise. **N. Yasuda, and T. Tanioka.** *Intnl. Pacific Univ., Okayama, Japan, and Showa Univ., Shinagawa-ku, Japan.*

26 **29.26** Impaired Exercise Capacity in Life-Long Skeletal Myofiber-Specific VEGF Gene Deleted Mice. **K. Tang, Y. Gu, N. Dalton, K. Peterson, H. Wagner, P. Wagner, and E. Breen.** *Univ. of California, San Diego.*

27 **29.27** Effect of Post-Myocardial Infarction Exercise Training on Angiogenesis. **J. Zhang, and B. Wilson.** *Univ. of Texas at San Antonio.*

28 **29.28** Increased Baseline but Reduced Endothelial Progenitor Cells After Aerobic Exercise in Subjects at Cardiometabolic Risk. **N. Rocha, R. Miranda, S. Carvalho, M. Silva, R. Alves, V. Garcia, A. Sales, J. Silva, B. Silva, A. Santos, and A. Nobrega.** *Fluminense Fed. Univ., Niteroi, Brazil.*

29 **29.29** Exercise Decreases the Lipogenic Capacity of Adipose Tissue During Weight Regain. **E. Giles, A. Steig, M. Jackman, J. Higgins, G. Johnson, H. Wyatt, E. Melanson, J. Hill, and P. MacLean.** *Univ. of Colorado Anschutz Med. Campus.*

30 **29.30** Effect of Daily Exercise on Thermal Preference and Heat-Escape/Cold-Seeking Behavior in Mice. **K. Nagashima, and C-H. Lin.** *Waseda Univ., Tokorozawa, Japan.*

31 **29.31** The Cardiovascular Response to Acute Exercise in Hypoxia and Hypobaria. **D. DiPasquale, G. Strangman, A. Gunn, and S. Muza.** *Massachusetts Gen. Hosp., Harvard Univ., and U.S. Army Res. Inst. of Environmental Med.*

32 **29.32** Nitric Oxide and Human Sweat Gland Function During Direct Sudomotor Nerve Activation. **G. Mack, J. Kunz, B. Scott, and J. Gifford.** *Brigham Young Univ.*

33 **29.33** The Activity of Cyclooxygenase-1 and -2 in Human Skeletal Muscle is Elevated After Acute Resistance Exercise Independent of Cyclooxygenase-1 and -2 Protein Content. **C. Carroll, R. Steinmeyer, D. O'Connor, and R. Gonzales.** *Midwestern Univ., and Univ. of Arizona, Phoenix.*

Board #

34 **29.34** 17-Allylamino-17-Demethoxygeldanamycin Inhibits HSP70 Response in Rat Skeletal Muscle Following Prolonged Eccentric Exercise. **C. H. Ooi, M. Thompson, P. Ruell, K. Rooney, R. Boadle.** *Univ, of Sydney, Lidcombe, Australia, and Westmead Res. Hub, Westmead, Australia.*

Poster Session

30.0 SIGNALLING

Sat., 1:15-3:15 PM. WB I/II.

Board #

35 **30.1** Glucose Metabolism and Effects of Contractile Activity on Skeletal Muscle Glucose Uptake Signaling in Spinal Cord-Injured vs. Able-Bodied Individuals. **C. Yarar, S. Bickel, S. Windham, and M. Bamman.** *Univ. of Alabama at Birmingham.*

36 **30.2** TSC2/Rheb Signaling Mediates ERK-Dependent Regulation of mTORC1 Activity in Skeletal Muscle Cells. **M. Miyazaki, and T. Takemasa.** *Hlth. Sci. Univ. of Hokkaido, Ishikari-gun, Japan, and Univ. of Tsukuba, Japan.*

37 **30.3** Metabolic Signaling in L6 Muscle Cells in Response to Heat Treatment and Resveretrol. **J. Wheatley, K. S. White, and P. C. Geiger.** *Univ. of Kansas Med. Ctr.*

38 **30.4** Aerobic Exercise Training Increases APPL1 Expression and Improves Insulin Signaling in the Liver of Obese Mice. **R. Marinho, E. C. Ropelle, D. Cintra, L. Pauli, C. Souza, A. Silva, L. Moura, E. Ropelle, and J. R. Pauli.** *State Univ. of São Paulo, Rio Claro, Brazil, and Estate Univ. of Campinas, Limeira, Brazil.*

39 **30.5** The Indispensible Role of the Neuronal Nitric Oxide Synthase in the Adaptive Cardiac Effects of Exercise. **S. Roof, T. Ho, L. Tang, J. Ostler, M. Periasamy, S. Gyorke, G. Billman, and M. Ziolo.** *Ohio State Univ.*

40 **30.6** Smad3 is Sufficient to Inhibit Protein Synthesis and Induce Muscle Fiber Atrophy In Vivo. **C. Goodman, R. McNally, M. Hoffmann, and T. Hornberger.** *Univ. of Wisconsin, Madison.*

41 **30.7** Role of LKB1 in the Regulation of Gene Expression After Skeletal Muscle Contraction. **S. Madsen, D. Hallowell, C. Rindlisbach, T. Moore, J. Bradshaw, and D. Thomson.** *Brigham Young Univ.*

42 **30.8** Vps34 Activity in Human Skeletal Muscle: Effects of Exercise and Oral Amino Acids. **E. Jansson, H. C. Rundqvist, M. R. Lilja, J. T. Murray, O. Rooyackers, and M. Esbjörnsson.** *Karolinska Inst., Stockholm, Sweden, and Queen´s Univ., Belfast, United Kingdom.*

43 **30.9** The Effect of Sprint Exercise on Expression of Myostatin and SMAD7 in Skeletal Muscle. **M. Esbjörnsson, H. C. Rundqvist, T. Osterlund, A. Montelius, and E. Jansson.** *Karolinska Inst., Stockholm, Sweden.*

Poster Session

31.0 INFLAMMATION

Sat., 1:15-3:15 PM. WB I/II.

Board #

44 **31.1** PGC-1a is Required to Prevent an Age-Associated Increase in TNFa and for Decreased TNFa Protein in Skeletal Muscle with Combined Exercise Training and Resveratrol. **J. Olesen, C. Brandt, J. Pedersen, K. Weihe, S. Ringholm, and H. Pilegaard.** *Univ. of Copenhagen, Denmark.*

45 **31.2** Exercise Reverses High-Fat Diet Induced Neuropathy in Pre-Diabetic Mice. **B. Guilford, A. Groover, J. Ryals, R. Swerdlow, and D. Wright.** *Univ. of Kansas Med.Ctr.*

46 **31.3** Acute Exercise Improves Insulin Signaling and Reduces Inflammatory Proteins in Skeletal Muscle of Aged Rats. **L. Moura, R. Marinho, E. C. Ropelle, D. Cintra, L. Pauli, B. Rodrigues, A. Silva, E. Ropelle, M. A. Mello, and J. R. Pauli.** *State Univ. of São Paulo, Rio Claro, Brazil, Estate Univ. of Campinas, Limeira, Brazil, and São Paulo Univ., Ribeirão Preto, Brazil.*

47 **31.4** Fractalkine–Induced in Exercised Human Skeletal Muscle and Stimulates Myoblast Proliferation. **A. Strömberg, K. Olsson, and T. Gustafsson.** *Karolinska Inst., Stockholm, Sweden.*

48 **31.5** Inflammation and the Hypertriglyceridemic Waist Phenotype. **G. Ruegsegger, C. Miller, K. McNulty, M. Greenwood, and M. Miles.** *Montana State Univ.*

49 **31.6** Influence of Fitness and Adiposity on Whole Blood Response to α MSH Treatment. **M. Phillips, A. Adams, M. Unthank, J. J. Barbee, M. Chumley, D. Cheek, and J. B. Mitchell.** *Texas Christian Univ., Fort Worth, and JPS Health Network, Fort Worth.*

50 **31.7** The Influence of Fitness and Adiposity on Melanocortin-1 and Melanocortin-3 Receptors on Monocytes. **M. Unthank, J. Woodson, G. Bratton, J. Butler, J. J. Barbee, C. Michael, D. Cheek, J. B. Mitchell, and M. Phillips.** *Texas Christian Univ., Fort Worth, and JPS Health Network, Fort Worth.*

51 **31.8** Effect of Exercise on T Cells in Cancer Survivors. **L. Bilek, D. Shackelford, G. Sharp, G. Thiele, C. Quinn, and C. Schneider.** *Univ. of Nebraska Med. Ctr., and Univ. of Northern Colorado.*

52 **31.9** Estrogen Status and the IL-6 Response to Prolonged Endurance Exercise. **A. C. Hackney, K. Koltun, and A. Kallman.** *Univ. of North Carolina.*

53 **31.10** Effects of Habitual Physical Activity Level and Acute Exercise on Markers of Systemic Inflammation and Cardiometabolic Risk in Overweight/Obese Adults. **R. Nelson, D. Van Pelt, and J. Horowitz.** *Univ. of Michigan.*

54 **31.11** Anti-Inflammatory Medications and Other Potential Confounding Variables for Strength Gain from Resistance Training for Older Adults. **R. Dennis, K. Garner, P. Kortebein, C. Parkes, M. Bopp, K. Padala, P. Padala, P. Dubbert, and D. Sullivan.** *Central Arkansas Vet. Healthcare, North Little Rock, Univ. of Arkansas for Med. Sci.*

55 **31.12** Effects of Prior Exercise on the Inflammatory Response to a High-Fat Meal in Young Men. **R. Landers-Ramos, J. Brandauer, N. Jenkins, E. Spangenburg, J. Hagberg, and S. Prior.** *Univ. of Maryland, Gettysburg Coll., Univ. of Missouri, Columbia, Univ. of Maryland Sch. of Med., and Baltimore VA Med. Ctr.*

56 **31.13** Influence of Short Term Sprint Interval Training On Skeletal Muscle Inflammation. **M. Schweder, J. Richards, M. Hickey, and C. Bell.** *Colorado State Univ.*

Poster Session

32.0 LATE BREAKING ABSTRACTS

Sat., 1:15-3:15 PM. WB I/II.

Board #

57 **32.1** Absence of Malonyl-CoA Decarboxylase Impacts Endurance Exercise Capacity and Reprograms Skeletal Muscle Mitochondrial Metabolism. **T. Koves, S. Seiler, K. DeBalsi, A. Wittmann, and D. Muoio**. *Duke Univ.*

58 **32.2** Reductions of PEPCK in Adipose Tissues from CD36 KO Mice. **Z. Wan, S. Matravadia, D. J. Philbrick, Graham P. Holloway, and D. C. Wright.** *Univ. of Alberta, Edmonton, Canada, and Univ. of Guelph, Canada.*

59 **32.3** Induction of SIRT1 by Reloading on Atrophied Soleus Muscle in Mice. **A. Goto, Y. Ohno, T. Egawa, T. Sugiura, Y. Ohira, T. Yoshioka, and K. Goto.** *Toyohasji SOZO Univ., Japan, Japan Soc. For the Promotion of Sci., Tokyo, Japan, Yamaguchi Univ., Japan, Osaka Univ., Japan, and Hirosaki Gakuin Univ., Japan.*

60 **32.4** A Pilot Study of Physiologic Correlates to Submaximal and Maximal Exercise in Patients with IBF. **R. M. Jackson, L. P. Cahalin, C. F. Ramos, D. D.Cardenas, C. M. Sol, M. I. Cohen, I. A. Gaurnaud, N. D. Eustis, and O. W. Gómez-Marín.** *Miami VAHS, Univ. of Miami, Florida, and Nova Southeastern Univ., Davie, Florida.*

61 **32.5** Impact of Voluntary Wheel Running and Treadmill Exercise Training on Hepatic Mitochondrial Metabolism and Function. **J. A. Fletcher, G. M. E. Meers, M. A. Linden, M. L. Kearney, E. M. Morris, J. P. Thyfault, and R. S. Rector.** *Univ. of Missouri, Columbia, and Harry S. Truman Mem. Vet. Med. Ctr., Columbia, Missouri.*

62 **32.6** Acute Resistance Training Affects Apoptosis and Migration of Lymphocytes. **S. E. A. Perez, G. B. Pereira, J. Prestes, R. A. Tibana, G. E. Shiguemoto, and J. Navalta.** *Univ. Fed. de São Carlos, São Paulo, Brazil, Univ. Cathólica de Brazília, Brazil, and Western Kentucky Univ.*

63 **32.7** Bronchodilation During Exercise in Patients with Cystic Fibrosis, Comparison to Albuterol Administration. **M. C. McCue, C. M. Wheatley, S. E. Baker, M. A. Morgan, E. C. Wong, M. Sattler, and E. M. Snyder.** *Univ. of Minnesota.*

64 **32.8** Critical Load Estimation by Different Mathematical Models in Swimming Rats. **C. A. Gobatto, P. P. Menezes Scariot, L. F. P. Ribeiro, and F. de Barros Manchado-Gobatto.** *Univ. of Campinas, São Paulo, Brazil.*

65 **32.9** Interluken-6, Epinephrine and the Regulation of Skeletal Muscle Lipolysis. **T. MacDonald, Z. Wan, D. J. Dyck, and D. C. Wright.** *Univ. of Guelph, Canada, and Univ. of Alberta, Edmonton, Canada.*

66 **32.10** Hsp70 Regulates the Skeletal Muscle Inflammatory Response Following Injury. **S. M. Senf, T. M. Howard, and A. R. Judge.** *Univ. of Florida, Gainesville.*

67 **32.11** Role of the Novel Tissue-Specific PGC-1 and ERR-Induced Regulator PERM1 in Muscle. **Y. Cho, B. Hazen, A. Russell, and A. Kralli.** *Scripps Res. Inst., La Jolla, California, and Deakin Univ., Burwood, Australia.*

Board #

68 **32.12** Interleukin-6 and Adipose Tissue Insulin Resistance During the Recovery from Exercise. **L. Castellani, C. G. R. Perry, J. Root-McCraig, and D. C. Wright.** *Univ. of Guelph, Canada, and York Univ. Canada.*

69 **32.13** Elucidating the Role of Histone Deacetylases in Skeletal Muscle Atrophy. **M. E. Walsh, A. Bhattachrya, and H. Van Remmen.** *Univ. of Texas Hlth. Sci. Ctr., San Antonio, and South Texas Vet. Hlth. Care Sys., San Antonio.*

Symposia XI

33.0 HOT TOPICS IN EXERCISE PHYSIOLOGY

Sat., 3:15 - 5:30 PM. Standley Ballroom.

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

3:15 PM **33.1** Introduction. **P. Darrell Neufer.** *East Carolina Univ.*

3:20 PM **33.2** Glycolytic Muscle Development and Metabolic Homeostasis. **Jiandie Lin.** *Univ. of Michigan.*

3:50 PM **33.3** Mitochondria, Hyperglycemia, Redox and Cardiac Dysfunction in Type 2 Diabetes. **Miguel Aon.** *Johns Hopkins Univ.*

4:20 PM **33.4** X-ROS Signaling in Striated Muscle. **Christopher Ward.** *Univ. of Maryland.*

4:50 PM **33.5** Skeletal Muscle Fatty Acid Synthase Modulates Sarcoplasmic Reticulum Phospholipid Composition to Regulate Insulin Sensitivity and Muscle Strength. **Katsuhiko Funai.** *Washington Univ.* **(21.3).**

Symposia XII

34.0 UNIFIED CELLULAR AND MOLECULAR MECHANISM OF MUSCLE HYPERTROPHY

Sat., 3:15-5:30 PM. WB III/IV.

Chair: **Keith Baar,** *Univ. of California, Davis.*

3:15 PM **34.1** Introduction. **Keith Baar.** *Univ. of California, Davis.*

3:20 PM **34.2** The Role of mTOR in Skeletal Muscle Hypertrophy. **Troy Hornberger.** *Univ. of Wisconsin, Madison.*

3:50 PM **34.3** Myostatin and the Control of Muscle Size. **David L. Allen.** *Univ. of Colorado.*

4:20 PM **34.4** Satellite Cells as Mediators of Skeletal Muscle Hypertrophy. **Marcus Bamman.** *Univ. of Alabama at Birmingham.*

4:50 PM **34.5** Molecular Connections Underlying the Hypertophic Response to Loading. **Keith Baar.** *Univ. of California, Davis.*

Don't Forget…
Pick up a ticket for the Closing Banquet Dinner by 10:00 AM on Thursday
This banquet is free but you MUST have a ticket for Entry

2012 APS Intersociety Meeting
The Integrative Biology of Exercise - VI

Abstracts of Invited and Contributed Presentations

Thursday, October 11

Friday, October 12

Saturday, October 13

1.0: INTEGRATING HUMAN "OMICS" TO THE MOLECULAR PHYSIOLOGY OF EXERCISE

1.2
MODULATION OF SMALL MOLECULE METABOLITES IN PERIPHERAL BLOOD AND SKELETAL MUSCLE

Kim Huffman[1,2]
[1]Dept. of Med., Duke Univ. Med. Ctr., Box 3327, Durham, NC, 27701, [2]Physical Med. and Rehabilitation, VA Med. Ctr., 508 Fulton St., Durham, 27705.

Mass spectroscopy-based quantification of metabolic intermediates, or metabolic profiling, is increasingly providing insight into the pathways and underlying mechanisms for exercise mediated improvements in metabolic health. Metabolomic platforms can measure concentrations of metabolic intermediates including amino acids, fatty acids, and acylcarnitines, which are by-products of fatty acid and amino acid catabolism. Using plasma and skeletal muscle from participants of STRRIDE, a randomized controlled exercise training intervention, we are evaluating training-induced responses in metabolic intermediates. In this session, we will discuss analytic issues associated with tissue-based analyses and data complexity. We will summarize responses observed in metabolic intermediates as a result of training and how metabolite modulation relates to change in insulin sensitivity after six months of exercise training or sedentary activity. For example, we found that reductions in plasma free fatty acids and increases in glycine and proline are related to improvements in insulin action. Also, modulation of succinate in skeletal muscle is associated with improvements in insulin action, identifying amino acid metabolism as a key component of metabolic adaptations to even aerobic exercise training. Last, we will discuss how these findings might inform our understanding of how exercise training improves metabolic health and guide future studies to derive more knowledge about exercise-mediated metabolic benefits.

1.4
MODULATION OF THE PROTEOME BY EXERCISE

Dustin Hittel[1], Jane Shearer[1]
[1]Kinesiology, Univ. of Calgary, 2500 University Dr. NW, Calgary, AB, T2N 1N4, Canada.

An integrative model of the molecular physiology of exercise needs to account for all concurrent processes in a cell, tissue or organism. This will only be possible when all biomolecular interactions can be quantified in a single biological sample. In my talk I will discuss the many contributions and current limitations of proteomics as it is applied to our understanding of the biology of exercise. Specifically, I will discuss two current projects in my lab that attempt overcome the complexity of the proteome by focusing on the modulation of post-translational modifications. The first project involves the quantification of the phospho-proteome of muscle cells in response to the atrophy-inducing protein myostatin. The goal of this project is to use proteomics to better understand the cellular signaling events that govern both muscle atrophy and hypertrophy. The second project involves the quantification of O-linked N-acetylglucosamine (O-GlcNAc) erythrocyte proteins in response to glycemic status and exercise. O-GlcNAc levels are, in part, responsive to cellular glucose supplies and linked to metabolic diseases with perturbed glucose homeostasis such as type 2 diabetes. O-GlcNAc levels can also be mediated by exercise, as exercise results in a number of beneficial changes such as improved glycemic control. As such, we are currently determining if O-GlcNAc is more sensitive than HbA1c as an early marker for pre-diabetes.

2.0: MECHANISMS BEHIND ADAPTATIONS TO PHYSICAL ACTIVITY/INACTIVITY

2.2
ROLE OF PGC-1α IN EXERCISE-INDUCED ADAPTATIONS IN SKELETAL MUSCLE

Christoph Handschin[1]
[1]Biozentrum, Univ. of Basel, Div. of Pharmacology/Neurobiology, Klingelbergstrasse 70, Basel, 4056, Switzerland.

Skeletal muscle cells exhibit high plasticity upon stimulation, e.g. a profound remodeling of myofibrillar and metabolic properties induced by regular exercise. The transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) is one of the key regulators of endurance exercise adaptation in skeletal muscle. Many of the major signaling pathways that are activated in a contracting muscle fiber converge on PGC-1α by inducing gene expression, promoting posttranslational modifications of the PGC-1α protein, or by doing both. In turn, elevated expression and enhanced activity of PGC-1α result in the coordinated regulation of the transcriptional programs that mediate exercise adaptation in muscle. We now provide evidence that muscle-specific expression of PGC-1α is sufficient to promote an oxidative phenotype of skeletal muscle cells by remodeling of the neuromuscular junction, modulation of calcium homeostasis, coordinated regulation of catabolic and anabolic metabolic pathways and regulation of the contractile properties. Moreover, we delineated the transcriptional network that controls these adaptations involving the specific antagonistic action of coactivator and corepressor protein complexes. These findings have important implications for our understanding of skeletal muscle cell biology, plasticity in inactive and trained muscle, as well as the therapeutic application of potential "exercise mimetics", pharmacological agents that elicit exercise-like effects in muscle, in various muscle diseases. Supported by the Swiss National Science Foundation, Gebert-Rüf Foundation and the University of Basel. Summermatter, S. and Handschin, C. (2012) *Int J Obes*, epub ahead of print.

2.3
EXERCISE-INDUCED AUTOPHAGY IN SKELETAL MUSCLE ADAPTATION

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Autophagy, a catabolic process for clearance of aggregate proteins and damaged organelles (e.g. mitochondria), is required for normal muscle function. Acute exercise activates autophagy in skeletal muscle; however, it is unknown whether exercise training promotes autophagy and whether autophagy is required for skeletal muscle adaptation. Here, we report that long-term (4 weeks) voluntary wheel running promotes basal autophagy in recruited plantaris muscle in mice as shown by increased protein expression of autophagy related genes (Atg6/Beclin1, Atg8/LC3), a mitophagy gene (Bnip3) and increased autophagy flux (increased LC3-II and decreased p62/Sqstm1). Similar directional changes were found when comparing slow-twitch, oxidative soleus muscle with intermediate plantaris and fast-twitch, glycolytic white vastus lateralis muscles. We also found that transgenic mice with muscle-specific overexpression of PGC-1α have increased basal autophagy with elevated Bnip3 expression, but not significant increases in Atg6 and LC3, suggesting that PGC-1α is sufficient to promote autophagy likely through other mechanism(s). Finally, voluntary exercise-induced improvement of endurance capacity is absent in heterozygous Atg6 knockout mice ($Atg6^{+/-}$) along with attenuated increases in markers of mitochondrial biogenesis, autophagy and autophagy flux in plantaris muscle and blunted improvement of whole body glucose clearance. These findings suggest that endurance exercise training promotes basal autophagy in skeletal muscle and that autophagy is required for mitochondrial biogenesis, as well as improved exercise capacity and insulin sensitivity.

3.0: GENOMICS/PROTEOMICS

3.1
GLOBAL MUSCLE GENE EXPRESSION AFTER SPRINT EXERCISE

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Objective: We hypothesized that sprint exercise increases the transcription of a large number of genes due to the profound metabolic and endocrine stress. The objective of measuring global gene expression was to enable a broad assessment of the physiological responses to sprint exercise. **Methods:** Fourteen healthy subjects performed three 30-s sprints exercise with 20 minutes rest in-between. Vastus lateralis samples were obtained at rest and 120 minutes after the third sprint. RNA was analyzed on Human Gene 1.0 ST Array. Differential expression was calculated by ANOVA. An FDR cut off of 10% yielded 928 differentially expressed genes. Downstream analysis was performed using IPA (Ingenuity Pathway Analysis), comprising tests for canonical pathways, genetic networks and transcription regulators. **Results:** Gene ontology analysis revealed tissue remodeling processes, involving effects on gene expression, cell cycle, growth and proliferation. Pathway analysis pointed to changes in hormonal and cytokine signaling. A transcription factor activity analysis showed recurring physiological themes. The downstream gene lists of HIF1A, CREB, NOTCH, FOXC2, BRACA1, affect energy metabolism, angiogenesis and mitochondrial biogenesis. **Conclusion:** Acute bouts of sprint exercise seem to initiate muscle tissue remodeling, possibly stimulated by hypoxia together with activity of growth factors and hormones.

3.2
MOLECULAR SIGNATURES OF ADIPOSE TISSUE IN AN OSSABAW SWINE MODEL OF CHILDHOOD OBESITY USING TRANSCRIPTOME ANALYSIS

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Childhood (6-11 yrs old) obesity has increased more than 3-fold in the U.S. since 1980. The study objective was to gain an understanding for mechanisms by which adipose tissue expands in young growing animals as a result of a positive caloric balance. Juvenile (8-week old), female Ossabaw swine (n = 6/group) were fed either a high-fat, high-fructose (43.0% fat and 17.8% high fructose corn syrup) or low-fat (10.5% fat) diet for 16 weeks. The high-fat, high-fructose fed animals were fed ~2.5x the number of calories as the low-fat group, resulting in greater body mass (47.1 vs. 25.1kg), greater percent body fat (30.4% vs. 20.4%), and insulin resistance when compared with low-fat fed pigs. While complete transcriptomic analyses utilizing RNA Sequencing are underway, preliminary analysis with DAVID 6.7 of omental adipose tissue from high-fat, high-fructose fed animals (n = 3/group) provided an initial list of five enriched functional-related gene modules that included: growth factors, cytochrome c 450, cytoskeletal proteins, S100 calcium binding proteins, and transcription factors. Funded by Mizzou Advantage and by the Departments of Biomedical Sciences, Food Sciences, Internal Medicine, and Nutrition and Exercise Physiology.

3.3
ASSOCIATION OF BONE DENSITY WITH ESTROGEN RECEPTOR GENE 1 POLYMORPHISMS AND ENVIRONMENTAL FACTORS IN JAPANESE YOUNG WOMEN

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Japan, [3]Human and Environmental Studies, Kyoto Univ., Yoshida Nihonmatsu, Sakyou-ku, Kyoto, 606-8501, Japan.
PURPOSE: Osteoporosis is a systemic skeletal disease characterized by low density and fragile in bone. Estrogen is essential for mechanotransduction, and estrogen receptor 1 (ER1) is a genetic candidate for a prime regulator of bone metabolism. The purpose of the present study was to assess the interactive effects of habitual exercise, calcium intake and ER1 gene polymorphisms on bone density in young women. METHODS: Eighty Japanese healthy young women (20-23 years old) were chosen in this study. Habitual exercise and nutrient intake were assessed using a questionnaire. Bone mass was measured by quantitative ultrasound measurement. ER1 polymorphisms at intron I (rs2234693 and rs9340799) were genotyped using the TaqMan SNP method. RESULTS: The subjects with habitual exercise and high milk intake were significantly higher bone density than those with non-habitual exercise and low milk intake. In addition, the subjects with ER1 genotype (CC or CTAG) and habitual exercise had significantly higher bone density than their non-habitual exercise counterparts. CONCLUSIONS: These results suggest that habitual exercise and calcium intake are more important for bone mass metabolism in young women carrying C and AG allele in ER1, respectively. Supported by Grants-in-Aid for Science Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

4.0: GENDER DIFFERENCES

4.1
MAXIMAL FORCE AND MOTOR UNIT RECRUITMENT PATTERNS ARE ALTERED ACROSS THE HUMAN MENSTRUAL CYCLE

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The excitability of the central nervous system may be altered with hormonal fluctuations. This study sought to determine if motor unit (MU) firing rates at recruitment were altered across the female menstrual cycle and in comparison with a male cohort. Female participants (n=7) were tested in each of the five menstrual phases (pseudo-counterbalanced design). Males (n=11) were tested once. The test was a maximal isometric knee extension (MVC) followed by a slow ramp up to 30% MVC. Fine wire EMG was collected from the vastus medialis and the vastus medialis oblique muscles. There was a 19.1% decrease in MVC at mid luteal phase which was significantly ($p < 0.05$) different from the late follicular, ovulation and late luteal phases. During the ramp contraction, the MU firing rate at recruitment was altered across the menstrual cycle ($p < 0.05$), but was not different from the male cohort ($p > 0.05$). Late luteal MU firing rate (9.11±0.31 Hz) was signify-cantly higher than early follicular (8.16±0.31 Hz) and late follicular (8.01±0.30 Hz). Menstrual phase and gender accounted for 5.1% of the variance in firing rate at recruitment after controlling for the effects of force generation, whereas force accounted for only 1.7%. To our knowledge, this is the first study to show that MU firing patterns are altered across the menstrual cycle and that hormonal status is more important than force generation for MU firing rate at recruitment.

4.2
SEX-BASED DIFFERENCES IN SALIVARY α-AMYLASE AND IGA RESPONSES FOLLOWING SUBMAXIMAL CYCLING EXERCISE

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PURPOSE: The purpose of this study was to clarify the effects of prolonged cycling exercise on salivary α-amylase and IgA responses in men and women. **METHODS:** Recreationally active men (M; n=13) and women (W; n=12) served as the subjects. At the 10-minute period before (Pre) and after (Post) 2 hours of cycling exercise corresponding to constant power output at 60% of peak oxygen uptake, unstimulated saliva was obtained for later analysis of salivary α-amylase and IgA secretion. **RESULTS:** In terms of salivary α-amylase levels (U/mL), two-way (time x sex) analysis of variances (ANOVA) showed significant main effects for time (Pre= 69.7±43.5, Post=243.0±184.4 for M; Pre=86.0±53.7, Post=189.3±109.4 for W, $p<0.05$), but not for sex or interaction. The percent increase of salivary α-amylase activity was four-fold higher in men than in women. With regard to salivary IgA levels (mg/dL), there were no main effects for sex and time or interaction (Pre= 9.1±3.0, Post=8.3±4.2 for M; Pre=7.4±3.7, Post=7.0±3.4 for W). **CONCLUSIONS:** These findings indicate that salivary α-amylase secretion following submaximal cycling exercise appears to be lesser in women than in men. Supported partly by funds from the Grant-in-Aid for Scientific Research (C) in Applied Health Sciences (Grant No.23500867) of Japan Society for the Promotion of Science.

4.3
GENDER DIFFERENCES IN MUSCLE FIBER CHARACTERISTICS AFTER 8 WEEKS OF RESISTANCE TRAINING

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Introduction: Heavy resistance training (RT) promote skeletal muscle hypertrophy decreasing MHC IIx and MHC I and increasing MHC IIa expression. But gender differences in these changes are not known. The aim of this study was to analyse the differences in gender response after two months of RT comparing the changes in muscle fibres characteristics with the mechanical measurement. Methods: Eighteen healthy volunteers participated in 8-week progressive RT for upper limbs muscles. One repetition maximal (1RM) test and mechanical and myosin characterization of latissimus dorsi muscle fibres were analysed pre and post- training using a fine needle biopsy technique. Results: The increase in 1RM was significantly greater in women (+24%) compared to men (+13%). The electrophoretic analysis showed an increased in MHC IIa (male +13% and female +33%) and a decrease in MHC IIx (male -8% and female -26%) while the MHC I expression in male tends to decrease (-5%) and in female tends to increase (+6%). The two-way ANOVA analysis (time x gender) showed a gender significant difference for female only in MHC IIa expression. Training increased significantly the cross sectional area (CSA) and fibre strength in male and muscle fibre tension in both groups. Discussion: The greater increase of 1RM performance with a substantial unchanged fibre CSA in female subjects could be explained by an improved motor units recruitment whilst males showed a greater hypertrophic response. Moreover also myosin changes showed a gender related difference. Taken together our results suggest that resistance training effects on muscle are gender specific.

5.0: PHYSICAL INACTIVITY AND CHRONIC DISEASE

5.1
HABITUAL PHYSICAL ACTIVITY PREDICTS DIETARY FAT OXIDATION AND TRAFFICKING

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INTRODUCTION: The relationship between energy and lipid balances suggests a key role of physical activity energy expenditure (PAEE) in dietary fat partitioning. This hypothesis still needs to be tested. **METHODS:** Sedentary (n=10) and active (n=9) lean men were respectively trained for 2 months and detrained for 1 month. PAEE, oxidation and fate of [d_{31}] palmitate and [1-^{13}C]oleate in triglycerides-rich lipoproteins and FFA, and muscle mRNA expressions were measured before and after interventions. **RESULTS:** Detraining decreased palmitate and oleate oxidations by 31 and 13%, while training increased them by 27 and 20%, respectively ($p<0.05$ for all). Variations in PAEE positively correlated with changes in oleate ($R^2=0.62$, $p<0.001$) and palmitate ($R^2=0.66$, $p<0.0001$) oxidations. Coordinated variations in CD36, FABPpm, FATP1, CPT1 and ASCL1 gene expressions regulated the between-organs fat trafficking and explained changes in dietary fat oxidation. Variations in meal-induced insulin response after interventions were associated with PAEE ($R^2=0.32$, $p=0.02$), oleate ($R^2=0.52$, $p<0.01$) and palmitate ($R^2=0.62$, $p<001$) oxidations. **CONCLUSION:** Physical activity, independent of measurable changes in energy balance, predicts dietary fat oxidation through a better trafficking and uptake by the muscle, while dietary fat oxidation negatively predicts whole body insulin sensitivity. **FUNDING**: Fondation Coeur et Artères, Plan National de Recherche en Nutrition, CNRS, University of Strasbourg and CNES.

5.2
SEDENTARY WOMEN WITH OVERWEIGHT AND OBESITY: EFFECTS OF A DIETARY INTERVENTION, CIRCUIT RESISTANCE TRAINING AND AEROBIC TRAINING IN THE METABOLIC AND VENTILATORY PARAMETERS

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This study and analyze aimed compared to the effect of aerobic training on a treadmill velocity in the ventilatory threshold (VT), circuit resistance training (CRT) and Nutritional Intervention on body composition, fasting glucose (GLU) levels and lipid profile, peak of oxygen uptake (VO2peak), respiratory compensation threshold (RCT), respiratory quotient (QR) at incremental treadmill test in sedentary and overweight/obese women. The inclusion criteria: women 25-45years, sedentary and body mass index (BMI) of 25-34,9 (overweight/obesel). The body composition by bioelectrical impedance (Biodynamics®Model310). The respiratory parameters during the treadmill incremental test by Gas analyzer (VO2000). Waist and hips circumferences were measured. The lipid and glucose levels by enzymatic methods (Laborlab). The CRT will have 3 sessions (se)/wk, 2 rounds in 9 stations, one set of 8-12RM for 10 wks. The aerobic treadmill will have 3 se/wk, walking 40 minutes at VT for 10 wks and nutritional standard by 24h dietary recall. Use Student´s t test or Wilcoxon's test to compare the variables (α=0.05) and ANOVA to measures repeated ($p<0,05$). 32 sedentary women 43±5,9years. BMI 28kg/m2±2,8; fat-free mass 50±9,4; % fat-free mass 59%±8,5 Fat mass 27±5,6; %FM 37%±3,9 water content 69%±0,6; basal metabolic rate 1383kcal±162,4 GLU 86mg/dL±5,9; total cholesterol 180mg/dL±36,8; HDL-c 48mg/dL±9,2; triglycerides 89mg/dL±45,4; VO2peak 29ml/kg/min±3,7; VTload 5km/h±0,8. **FINANCING:** CAPES e CNPq. **KEYWORDS:** chronic diseases, exercise and nutritional intervention.

5.3
RESTORING METABOLIC HOMEOSTASIS IN TYPE 2 DIABETES WITH EXERCISE-HYPERTHERMIC MIMETICS

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The metabolic effects of exercise are ideal for therapy of type 2 diabetes. Heat shock can mimic many of these beneficial effects. The present armamentarium of pharmacologic agents to treat type 2 diabetes is woefully inadequate. The issues of today's drugs range from loss of efficacy with time, failure to protect from complications, weight gain, hypoglycemia, and sometimes major side effects like heart failure, pancreatitis. We need

agents that are like exercise and heat that can restore the low heat shock proteins state of diabetes. Exercise-hyperthermic mimetics improve glycemic control, reduce body weight, restore mitochondrial function, improve insulin signalling, reduce inflammatory cytokines, improve lipid parameters, enhance beta-cell function, and reduce diabetic complications. Reversing an impaired cellular stress response of diabetes corrects a defect that is close to the very pathogenesis of the disease and spawns the development of therapeutic options that are both safe and effective.

5.4

COMPENSATORY RESPONSES OF INSULIN SIGNALING RESTORE MUSCLE GLUCOSE UPTAKE FOLLOWING LONG TERM INACTIVITY

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We investigated the role of muscle activity in maintaining normal glucose homeostasis via transection of the sciatic nerve, an extreme model of inactivity. Mice were sacrificed either 3 days, 10 days, 28 days or 56 days post transection or sham surgery. There was no difference in muscle mass between sham and transected limbs at 3 days post-surgery, but there was a significant reduction following transection at the other three time points. Muscle weight stabilized by 28 days post-surgery with no further loss. Glucose uptake of isolated muscle was blunted 3 days after transection, but returned to normal at later time points. In transected muscle there was reduced expression for transcriptional regulators of metabolism (PGC1α, PGC1β, PPARδ), glycolysis (PFK), glucose uptake (GLUT4), fatty acid transport (M-CPT 1), and mitochondrial oxidation (CS) genes at 3 and 10 days post-surgery but this decrease was reduced at 56 days. Western blot analysis showed reduced expression of AS160 in transected muscle with a compensatory increase in expression of AKT2. While inactivity may initially lead to reduced glucose sensitivity, compensatory responses of insulin signaling restored normal function. These data suggest that necrosis and/or apoptosis may prevent an accurate assessment of the role of inactivity in maintaining glucose homeostasis. This work was supported by NIH grant number 1R15DK085 497-01A1.

5.5

EFFECT OF CHRONIC SWIM EXERCISE ON ADIPOSITY AND METABOLIC FUNCTION IN MICE

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Diabetes is a major health concern today. Concomitantly, the American diet is composed more and more of fat and fructose. Chronic exercise has been recommended as a way to attenuate metabolic changes and prevent obesity. This study was undertaken to determine the effects of moderate swim exercise on body fat and metabolic parameters in response to a high fat/high fructose diet in mice. Mice were assigned to one of three groups: Control (standard chow, without exercise, n=10); Sedentary (fat/fructose, without exercise, n=9); and Exercise (fat/fructose, with exercise, n=9). In the Exercise group, mice swam 1 hour/day, 3 days/week for 8 weeks. In humans, this is equivalent to a low/moderate training program. The fat/fructose diet produced a syndrome similar to human diabetes. The sedentary mice developed hyperglycemia, insulin resistance, high body fat (up to 40 percent), and increased metabolic hormones (insulin and leptin). The exercise paradigm prevented the pathological effects for glucose, insulin, leptin, and glucose tolerance. Exercise did not improve body fat or fat cell size. Glycogen storage and tissue morphology were examined in the liver. The high fat/fructose diet depleted glycogen and caused tissue damage, effects which were partially corrected by the moderate exercise program. Results document the beneficial effects of even moderate exercise on diet-induced diabetes. This study was funded by NIH R01 HL093567.

5.6

INFLAMMATORY PATHWAYS LEADING TO NON ALCOHOLIC FATTY LIVER DISEASE ARE BLUNTED BY REGULAR RUNNING EXERCISE IN MICE

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Maintenance of normal body weight by being more physically active is associated with reduced incidence of nonalcoholic fatty liver disease (NAFLD) and liver fibrosis. However, the underlying mechanisms have not been fully investigated. Here we investigated the effects of exercise on inflammatory and cellular pathways important in the pathogenesis of NAFLD. WT mice were divided in two groups (n=5). The 'training' (T) group was subjected to 30 min treadmill running 5 d/ week at 5 m/min for 5 min, then 15 m/min for 25 min for 6 wks, The 'sedentary' (S) group was not forced to run except during exercise exhaustion tests. No difference in body weights (T= 24.74 ± 1.307 g, S= 25.58 ± 1.696 g) was observed. Mice were run to exhaustion after 6 wks; T mice outperformed S mice in distance covered (498.1 ± 35.09 m vs. 207.1 ± 46.91 g). Gene expression was analyzed in liver tissues via RT-PCR using LDA from ABI in mice fasted for 24h. Inflammatory markers Il-6 (248.8 ± 50.0 vs. .95 ± .256, p=.00255) and Il-10 (496.51 ± 120.8 vs. .82 ± .43, p=.00635) as well as the ER stress protein Ddit3 (9.41 ± 1.64 vs. .94 ±.056, p=.0021) were significantly increased in S mice compared to T mice. S mice also exhibited a markedly increased MMP-9 expression compared to T mice (12.13 ± 1.00 vs. .91 ± .519 p=.00006). Collagen expression, a marker for liver fibrosis, was increased in S mice (930.24 ± 286.2 vs. 2.48 ± .590, p=.0178). Running exercise reduces expression of genes that are involved in liver inflammation and fibrosis in mice. We propose that regular running exercise maintains a healthy liver metabolism by keeping inflammatory signaling pathways in check.

5.7

HIGH INTRINSIC AEROBIC CAPACITY IS ASSOCIATED WITH GREATER LIVER FATTY ACID OXIDATION ADAPTABILITY

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Aerobic capacity is inversely associated with diabetes and non-alcoholic fatty liver disease. We previously observed elevated hepatic fatty acid oxidation (FAO) in rats bred for high aerobic capacity [high capacity runners (HCR)] compared to rats bred for low aerobic capacity [low capacity runners (LCR)]. We hypothesized that high aerobic capacity would result in greater hepatic flexibility in lipid metabolism in response to an acute high-fat diet (HFD) challenge. We examined FAO in liver homogenate and isolated mitochondria of HCR/LCR rats following a 3 day HFD (45% fat). In both strains, HFD resulted in increased daily weight gain (73% HCR, 1.5-fold LCR; $p<0.05$) and increased feeding efficiency (49% HCR, 63% LCR; $p<0.05$). In liver homogenates, HCR rats had 50% higher complete FAO to CO_2 regardless of diet ($p<0.05$). Also, HCR rats demonstrated a 15% increase in incomplete FAO on the HFD ($p<0.05$), with no change observed in LCR rats. In isolated hepatic mitochondria, HCR rats display 73% greater complete FAO compared to LCR ($p<0.05$), with HFD producing a 40% reduction in HCR ($p<0.05$) but no change in LCR rats. The reduced complete FAO in HCR mitochondria on HFD was reversed with the addition of ADP or uncoupling agent FCCP to the assay. In conclusion, HCR rats show greater FAO and adaptability to a HFD than LCR rats suggesting that differences in intrinsic aerobic capacity confer differences in hepatic metabolic flexibility for lipid metabolism.

5.8

PHENOTYPIC DIFFERENCES BETWEEN GENERATION 8 RATS SELECTIVELY-BRED TO VOLUNTARILY RUN HIGH VERSUS LOW NIGHTLY DISTANCES WITH AN EMPHASIS ON USING VOLUNTARY RUNNING TO PREVENT THE DEVELOPMENT OF JUVENILE OBESITY

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We phenotyped generation 8 (G8) rats that possess high (HVR) versus low (LVR) motivations to voluntarily run under two conditions: a) those that voluntarily ran during 28-34 days of age (runners), or b) those that never ran until sacrifice at 34 days of age (sitters). RNA-seq data from the nucleus accumbens of these animals will also be presented. HVR male runners ran longer (22.5 vs. 4.1 km, $p < 0.001$), spent more time running (625 vs. 142 min, $p < 0.001$), and ran faster (34.7 vs. 28.8 m/min, $p < 0.001$) than LVR male runners. HVR female runners ran longer (28.3 vs. 5.9 km, $p < 0.001$), spent more time running (770 vs. 194 min, $p < 0.001$), and ran faster (36.2 vs. 29.5 m/min, $p < 0.001$) than LVR female runners. Comparing day 34 body compositions ($n = 5$-7 families) revealed that LVR male and female sitters possessed a 14-36% higher body fat percentage than HVR female sitters ($p = 0.003$-0.11) despite similar body weights. Visceral adipose tissue weights were 1.5-5.0-fold greater in G8 HVR/LVR male and female sitters versus their runner counterparts. However, running significantly reduced body fat percentage in both lines by 35-52% ($p < 0.001$). Importantly, while HVR runners ran 4.7-5.5-fold higher than LVR runners, body composition and visceral adipose tissue weights between lines were similar after the 6-day running period. Hence, these findings suggest that a range of physical activity is beneficial in preventing the onset of body fat accrual in young rats.

5.9

INTRAMUSCULAR EXPRESSION OF MECHANOSENSOR ANKRD2 AND MYOKINE ANGPTL4 DURING AN ACUTE BOUT OF INACTIVITY

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Risk factors for metabolic disorders, cardiovascular disease, and obesity can be initiated within 2 weeks of lowering physical activity. Based upon previous literature, skeletal mechanosensory and myokine mRNAs/proteins are logical targets to examine processes promoting these conditions during acute bouts of inactivity. Specifically, polyribosomal mRNA microarray results demonstrated that the mechanosensor ankyrin repeat domain 2 (Ankrd2) and the myokine angiopoetin-like protein 4 (Angptl4) were downregulated and upregulated within 53 hours of inactivity, respectively. A wheel lock (WL) model of inactivity was utilized to observe the effects of acute inactivity (WL0, WL5, WL29, and WL53 hours) after 21 days of voluntary wheel running in selectively-bred high voluntary running Wistar rats (HVR). Sedentary littermates were used for comparison. We used nuclear isolation with Western blot and quantitative PCR to determine mRNA/protein content in slow oxidative soleus (SOL) and fast oxidative-glycolytic plantaris (PLT) muscles. All time points were compared to WL0. Nuclear Ankrd2 protein tended ($p=0.09$) to be increased in SOL by WL29. SOL Angptl4 and LPL mRNAs were not

different between SED and WL0 but decreased by WL5 and WL29, respectively. Wheel running increased PLT LPL mRNA at WL0, but values decreased to SED levels by WL5. These results, while not conclusive, show the potential importance and need to further study Ankrd2 and Angptl4 gene expression during acute inactivity. Funded by anonymous gifts.

5.10

THE UBIQUITIN-PROTEIN LIGASE NEDD4 CONTRIBUTES TO THE SKELETAL MUSCLE ATROPHY INDUCED BY 14 DAYS OF IMMOBILIZATION

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Reductions in physical activity induce skeletal muscle atrophy. The primary mechanism for protein breakdown is the ubiquitin-proteosome pathway, a process relying on ubiquitin ligases (E3s) to target specific proteins for degradation. Recent work shows that the E3 Nedd4 contributes to disuse atrophy; however this has not been investigated in humans. **PURPOSE:** To investigate how disuse from immobilization affects Nedd4 gene expression and protein content. **METHODS:** Healthy men and women (10♂, 9 ♀) completed 14d of single leg immobilization. Muscle biopsies of the vastus lateralis collected before (PRE) and immediately after (POST) immobilization were processed to isolate protein and mRNA and quantified by Western Blotting and q-PCR. Immunohistochemistry confirmed protein changes and identified the predominant localization site. **RESULTS:** Following 14d of disuse Nedd4 protein content increased 24% ($p < 0.01$), similar to the 26% increase in total ubiquitination ($p < 0.001$). Although mRNA levels POST were not different from PRE levels ($p = 0.3$), immunohistochemistry confirmed increased (3.5-fold) sarcolemmal localization of Nedd4 ($p = 0.03$). **CONCLUSION:** These results suggest that Nedd4 continues to contribute to the total protein ubiquitination occurring after 2 weeks of disuse. This research was funded jointly by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Institutes of Health Research (CIHR).

6.0: EXERCISE AND DRUG INTERACTIONS

6.1

RAT METABOLIC RESPONSES DURING TREADMILL RUNNING FOLLOWING DOXORUBICIN INJECTIONS IN SEDENTARY AND EXERCISE TRAINED RATS

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The purpose of this study was to determine the effects of 10 weeks of treadmill training prior to doxorubicin (DOX) administration on resting and submaximal exercise metabolic parameters. Twenty male adult (~12 weeks of age) Sprague-Dawley rats were randomly assigned to one of four groups: 1) sedentary saline, 2) sedentary DOX, 3) exercise saline and 4) exercise DOX. Exercise groups underwent a 10 week progressive treadmill training protocol, and sedentary groups maintained normal cage activity for 10 weeks. Following the activity treatment period, baseline resting and submaximal exercise (50 cm/s) metabolic data were collected, and rats received either a bolus 15 mg/kg DOX injection or saline as a control. Seventy two hours after injection, resting and submaximal exercise metabolic data collection was repeated No group differences were observed at baseline. Likewise, 72 hours after injection, there was no exercise effect or exercise by treatment interaction, but there was a treatment effect between groups for VO2, VCO2 and energy expenditure (EE) (DOX groups, 12%, 20%, and 16% less, respectively). DOX injections resulted in an inability to match aerobic demands while running at 50 cm/s due to altered metabolic processes regardless of whether rats were exercised for 10 weeks prior to injection. Prior exercise did not protect against the DOX-induced metabolic disturbances observed during submaximal exercise.

6.2

A PILOT STUDY: ACUTE EFFECTS OF DOXORUBICIN ON HIND-LIMB GAIT KINEMATICS IN RATS

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The purpose of this study was to determine the effects of doxorubicin (DOX) on rat hindlimb mechanics, with specific focus on the accelerations and spatiotemporal characteristics of gait. Fifteen adult male Sprague-Dawley rats were randomly assigned and injected with saline, 10 mg/kg DOX, 12.5 mg/kg DOX, or 15 mg/kg DOX delivered as a bolus i.p. injection. Sagittal plane video was collected while rats walked on a treadmill at 27 cm/sec prior to injection (PRE) and 72 hours post-injection (POST). Two-factor ANOVAs with repeated measures showed no significant ($p>0.05$) dose effects for any of the kinematic or spatiotemporal variables. However, significant time by group interactions were observed for peak ankle vertical acceleration ($p<0.05$, ES=1.02) and peak vertical foot acceleration ($p<0.05$, ES=0.93). In both variables, the peak accelerations were decreased by ~14% in POST for all DOX groups compared to the saline group. Additionally, although not significant, similar interaction trends were observed for peak ankle angular acceleration (ES = 0.88). Regardless of cumulative DOX dosage, reductions in limb accelerations occurred during swing when compared to a saline treated group. These reduced limb accelerations were consistent with reductions in isolated muscle force production previously reported (Hydock et al., 2011) suggesting muscle dysfunction due to DOX treatments may transfer to activities of daily living. Hydock DS, et al. (2011). Characterization of the effect of in vivo doxorubicin treatment on skeletal muscle function in the rat. Anticancer Res. 2011 Jun;31(6):2023-8.

6.3

EFFECTS OF TREADMILL TRAINING ON DOXORUBICIN AND GOSERELIN ACETATE-INDUCED BONE DEGENERATION

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This study examined the individual and combined effects of the GnRH agonist goserelin acetate (GA) and the anthracycline agent doxorubicin (DOX) on bone and determined if treadmill running provides osteoprotection. Sixty nine twelve-week old female rats were randomly assigned to sedentary (SED) or treadmill (TM) activities. SED received GA, DOX, combined GA and DOX (GA+DOX) treatment, or placebo and maintained normal cage activity. TM received GA, DOX, GA+DOX, or placebo and participated in a progressive motorized treadmill protocol. After 8 weeks, tibiae were removed and scanned using micro computed tomography. Significant drug effects were observed for cancellous bone measures (bone volume/tissue volume, $p<0.0001$; trabecular number, $p<0.0001$; trabecular thickness, $p=0.004$; trabecular spacing, $p<0.0001$). No significant activity effects or interactions were observed in cancellous bone, and there were no significant osteoprotective effects of treadmill running within drug treatment groups. Likewise, significant drug effects were observed in cortical bone (cross-sectional volume, $p=0.0005$; cortical volume, $p=0.0006$; marrow volume, $p=0.02$). No significant activity effect or interaction was observed in cortical bone, and there were no significant osteoprotective effects of treadmill running within drug treatment groups. These results suggest that treadmill running is not protective against GA, DOX, and GA+DOX treatment-induced bone degeneration in female rats.

6.4

TISSUE SPECIFIC EFFECTS OF ACETAMINOPHEN AND TREADMILL EXERCISE ON COLLAGEN CONTENT IN MALE WISTAR RATS

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The purpose of this study was to determine if chronic exercise and/or acetaminophen (APAP) alters collagen content in the gastrocnemius, soleus, heart, femur, or tibia. Male Wistar rats (n=50, 8-week-old) were divided into placebo (P) or APAP groups and into sedentary (S) or exercised (R) groups. APAP (200 $mg \bullet kg^{-1}$) was administered once daily by oral gavage. Exercised groups ran on a treadmill 5 $days \bullet week^{-1}$ for 8 weeks with progression to 60 minutes per day, 20 $m \bullet min^{-1}$, and 8° incline. Tissues were assayed for hydroxyproline content by HPLC. All data was expressed as µg $collagen \bullet mg$ dry $weight^{-1}$. Gastrocnemius ($p<0.05$, S-P: 55±8 vs. R-P: 108±15) and soleus ($p<0.05$, S-P: 52±7 vs. R-P: 104±27) collagen increased with exercise. The increase in collagen was blunted by APAP in the gastrocnemius (S-APAP: 54±8 vs. R-APAP: 65±8) and soleus (S-APAP: 57±8 vs. R-APAP: 57±10). Heart collagen was not influenced by exercise or APAP (S-P: 28±2; R-P: 26±1; S-APAP: 26±1; R-APAP: 27±2). Exercise did not influence femur collagen content (S-P: 223±5 vs. R-P: 226±6) but collagen was greater in S-APAP ($p<0.05$, 235±5) compared to S-P. Exercise nullified the effect of APAP on femur collagen ($p<0.05$, R-APAP: 217±5). Tibia collagen content was not influenced by APAP but was lower ($p<0.05$) in exercised animals (S-P: 284±7; R-P: 262±7; S-APAP: 282±15; R-APAP: 269±8). Our findings suggest that exercise increased collagen content only in skeletal muscle and APAP has tissue specific effects on collagen.

6.5

CHRONIC ORAL -(-)EPICATECHIN DOES NOT AFFECT RAT HINDLIMB SKELETAL MUSCLE VASCULAR FUNCTION DURING EXERCISE

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-(-)epicatechin (EPI) is a naturally occurring dietary compound that promotes beneficial cardiovascular adaptations. Recently, EPI supplementation improved skeletal muscle fatigue resistance and treadmill running endurance in mice (Nogueira et al, J Physiol, 589, 2011). It is unknown if enhanced vascular control during exercise underlies these improvements which would potentially benefit patient populations suffering from vasomotor dysfunction (heart failure, diabetes, etc.). We tested the hypothesis that EPI augments rat hindlimb muscle blood flow (BF) and vascular conductance (VC, BF/mean arterial pressure (MAP)) during exercise. Rats received water (CON, n=5) or 2 mg/kg EPI (n=5) via oral gavage twice daily for 21 days. Subsequently, MAP (arterial catheter) and BF (radiolabelled microsphere infusion) were measured during treadmill exercise (25 m/min, 5% grade). EPI reduced exercising MAP (CON: 140±3, EPI: 128±4 mmHg, $p<0.05$) but had no effects on total hindlimb muscle BF (CON: 175±23, EPI: 167±11 ml/min/100g, $p>0.05$) or VC (CON: 1.25±0.16, EPI: 1.32±0.10 ml/min/100g/mmHg, $p>0.05$).BF and VC were unchanged in all 28 individual hindlimb muscles or muscle parts ($p>0.05$ for all). Despite reducing MAP, chronic EPI treatment (2 mg/kg) does not improve skeletal muscle vascular function during exercise and thus improved vascular control is unlikely to account for any EPI-induced improvements in exercise performance. (Funding: ACSM, AHA Midwest Affiliate 0750090Z, NIH HL-108328).

6.6

INFLUENCE OF CHRONIC ETHANOL INGESTION ON COMPENSATORY MUSCLE HYPERTROPHY IN THE RAT

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Acute ethanol exposure inhibits muscle protein synthesis, while chronic ethanol exposure causes muscle wasting in humans and laboratory animals. In contrast, resistance exercise increases muscle protein synthesis and thus muscle mass, but few studies have addressed the interaction of ethanol and exercise. To assess this interaction, we overloaded the right plantaris in Sprague-Dawley rats by removal of the right gastrocnemius and soleus and then pair-fed the animals for five weeks on a nutritionally complete liquid diet in which ethanol contributed 36% of calories. Rats in the alcohol-treatment group were fed *ad libitum* while rats in the control group were pair-fed equal volumes of an isocaloric diet. Preliminary results (n=9) indicate that surgically overloaded plantaris muscles were significantly and uniformly larger than contralateral, non-overloaded muscles. However, ethanol treatment had no significant effects on body mass, heart mass, or mass of either the overloaded or contralateral plantaris. These results indicate that ethanol consumption is unable to prevent overload-induced hypertrophy in skeletal muscle. This work was sponsored by the Department of the Navy, Office of Naval Research, under Award # N00014-11-1-0359.

6.7

MAC25 PROMOTES MUSCLE HYPERTROPHY BY COORDINATING BOTH IGFII AND TGFBETA PATHWAYS

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Aging has been associated with a gradual decline in muscle mass, function and overall strength. Scientists have attempted to determine the molecular event that ultimately contributes to this inevitable disease currently known as sarcopenia. The only available therapeutic intervention is exercise and this too has limitations in the very elderly (>80 years of age). To further elucidate the molecular changes that are associated with beneficial exercise, an array was performed from a controlled study where vastus lateralis biopsies were taken before and 4 hours after a single bout of leg extensions in untrained human subjects. The same subjects were then resistance trained for a period of 12 weeks and muscle biopsy samples were collected again in the same manner to identify gene transcript changes in a "trained" state. Hundreds of genes were altered and were correlated with either mass or strength gains. A collated list was generated for purposes of screening *in vivo* using an electrotransduction technique to promote over expression of the identified targets. MAC25, also known as IGFBP7 or IGFBP-rP1 has been described as playing multiple roles I n IGF and insulin peptide binding and activity. MAC25 is a chimeric protein that possesses an IGF-binding domain, IgG domain and a Follistatin-like domain. Our data demonstrates the ability of MAC25 to regulate the Smad2/3 translocation by an unknown mechanism and can suppress baseline activity levels in the Smad binding element (SBE)-Luciferase assay. In summary, MAC25 is regulated by resistance exercise in human subjects and this correlates with gain in muscle strength as a result of exercise.

6.8

INFLUENCE OF NRF2 ACTIVATOR SUPPLEMENTATION ON PHYSIOLOGICAL RESPONSES TO SHORT TERM SPRINT INTERVAL TRAINING

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Sprint interval training (SIT) improves endurance performance in adult humans, in part through increased mitochondrial biogenesis. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a putative regulator of mitochondrial biogenesis. Hypothesis: responses to SIT will be augmented with prior/concurrent Nrf2 activator supplementation. Experimental procedures conformed to the Declaration of Helsinki. 38 young healthy adults were randomly assigned to 120 days consumption of either Protandim (Nrf2-A; a known activator of Nrf2) or placebo (PLAC), in a double-blind fashion. 26 participants then completed 9 sessions of SIT, comprising 4-8 x 30-second sprints (track-running) over 3-weeks, while 12 remained sedentary. SIT increased maximal oxygen uptake (Nrf2-A SIT from 43.9±1.7 to 46.2±1.5 & PLAC SIT from 44.9±0.9 to 45.2±1.2 *vs*. Nrf2-A SED from 48.1±1.8 to 45.4±1.7 & PLAC SED from 50.3±3.1 to 49.5±3.0 ml/kg/min; P=0.02; mean±SE), and improved 10 km time-trial performance (Nrf2-A SIT from 64.1±2.5 to 61.4±2.4 & PLAC SIT from 68.6±2.3 to 67.9±2.2 *vs*. Nrf2-A SED from 61.4±2.2 to 65.1±4.8 & PLAC from 59.2±5.9 to 58.6±5.3 min; P=0.06), but there was no difference in the responses to SIT between Nrf2-A and PLAC. Additional benefits of SIT included decreased fat mass and increased lean mass (both P=0.04). These data suggest the physiological responses to SIT are not augmented with Nrf2 activator supplementation.

6.9

EFFECTS OF THE PHOSPHODIESTERASE-5 INHIBITOR TADALAFIL ON PHYSIOLOGICAL RESPONSES DURING SUBMAXIMAL EXERCISE IN NORMOXIA

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The stimulation of the nitric oxide (NO)-3'5'cyclic guanosine monophosphate (cGMP) signaling pathway results in vasorelaxation and increased muscle blood flow. Tadalafil (TAD), a phosphodiesterase-5 inhibitor, reduces cGMP hydrolysis and might, to some extent, influence physiological responses to exercise. The aim of this study was to verify whether the oral administration of TAD influences physiological responses during submaximal exercise in normoxia. Twelve healthy men were randomly assigned to receive either two tablets of placebo (PLC) or TAD (20mg) in a double-blind crossover design. After the administration of either PLC or TAD, the subjects performed a 30-min bout of exercise at anaerobic threshold on a cycle ergometer. Gas exchange measures and heart rate (HR) were recorded throughout test, while blood lactate concentrations (La) and blood pressure responses (BP) were recorded every 5-min period. This study was designed according to the Declaration of Helsinki. Compared to PLC, the TAD condition did not differ for HR (139±13 vs. 142±13 bpm), systolic (145±17 vs. 143.5±26 mmHg) and diastolic blood pressure (58±15 vs. 64±13 mmHg), and La concentration (3.5±0.5 vs. 3.6±0.7, respectively for PLC and TAD). However, oxygen uptake was significantly higher in TAD (2046±276 mL/min) compared with PLC (2216±334 mL/min). In summary, the oral administration of TAD does not substantially influence physiological responses during submaximal exercise in normoxia. However, TAD might affect gas exchanges responses to exercise.

6.10

NITROUS OXIDE NARCOSIS AND HYPERTHERMIA EFFECT THE PATTERN OF BREATHING DURING LIGHT EXERCISE

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HYPOTHESIS: It was hypothesized that breathing of normoxic 30% N_2O during hyperthermic relative to normothermic exercise would give a deeper pattern of breathing. **METHODS**: Six college-aged, healthy male participants volunteered for this SFU Office of Research Ethics approved study. Each participant rode a cycle ergometer at 50 W and ~70 rpm during 2 trials on separate days at ambient temperatures (T_A) of 18°C or 35°C. In each trial the participant breathed air at rest. Subsequently in 3 successive 10 min exercise periods inhalants were air (Air 1), normoxic 30% N_2O and air (Air 2). **RESULTS:** When T_A was 35°C, T_{CORE} was significantly increased ($p<0.0001$) by ~1°C. During hyperthermia pulmonary ventilation (V_E) increased ($p=0.02$) by ~6 L/min, inspiratory flow (V_T/Ti) tended to increase by ~ 25% ($p=0.08$) and expiratory time tended to decrease ($p=0.06$). Irrespective of increases in T_{CORE}, between Air 1 and N_2O breathing, there were increases of V_E by ~ 3 L/min ($p=0.04$), in RER from 0.88 to 0.95 ($p=0.04$) and $P_{ET}O_2$ by ~ 4 mm Hg ($p=0.10$). There were significant T_A x Gas Type inter-actions for $P_{ET}O_2$ ($p=0.04$) and for RER ($p=0.02$). These interactions were explained by smaller responses for these variables during the transitions from Air to N_2O breathing in hyperthermia relative to normothermia. **CONCLUSION**: Irrespective of the inhalant, light exercise with a superimposed hyperthermia elicited hyperventilation whereas normoxic 30% nitrous oxide breathing during hyperthermic exercise gave a deeper pattern of breathing. Supported by Canadian Foundation for Innovation and Natural Sciences and Engineering Research Council of Canada.

7.0: MUSCLE FUNCTION AND ADAPTATION I

7.1

PROLONGED MECHANICAL VENTILATION RESULTS IN DIAPHRAGM HYPOXIA AND A DOWN-REGULATION OF RESISTANCE ARTERY ENOS EXPRESSION

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We have previously demonstrated that prolonged mechanical ventilation (MV) is associated with a severely diminished diaphragm blood flow, microvascular PO_2 (PO_2m), and inability to augment flow with contractions. Whether there is a corresponding tissue hypoxia is unknown. We tested the hypotheses that prolonged MV results in 1) hypoxic regions within the diaphragm, and 2) a reduced expression of endothelial nitric oxide synthase (eNOS) in resistance arteries. **METHODS**: Diaphragm hypoxia (via Hypoxyprobe™) and resistance artery (<150 µm internal diameter) eNOS mRNA expression were measured in female Sprague-Dawley rats (~6 mo old; n = 24). Data were collected during spontaneous breathing (SB) and after prolonged (6 hrs) of MV. **RESULTS**: Prolonged MV resulted in the presence of hypoxia in the diaphragm which was not apparent in the SB animals. Prolonged MV resulted in a significant reduction in eNOS mRNA expression (~50%) versus that measured from the SB group. **DISCUSSION**: Our results demonstrate that prolonged MV is associated with diaphragm tissue hypoxia, which may result in ROS generation within diaphragm mitochondria and activate apoptotic pathways. The reduced expression of eNOS suggests a diminished endothelium-dependent vasodilation after prolonged MV contributes to the blunted hyperemic response during contractions. Both of these novel findings provide additional mechanisms for ventilator-induced diaphragmatic dysfunction (VIDD) associated with MV.

7.2

EFFECTS OF HEAT STRESS ON DIAPHRAGMATIC ATROPHY INDUCED BY 12 H MECHANICAL VENTILATION IN RAT

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This study investigated the effects of heat stress on diaphragmatic atrophy induced by 12 h of mechanical ventilation (MV) in the rat. Adult male Wistar rats (n=40) were assigned randomly to control, heat stress, MV, or heat stress + MV groups. Heat stress consisted of 60 min in a heat chamber set at 41°C, 24 h before MV. MV was performed for 12 h under anesthesia. A strip of diaphragm was used to measure the contractile properties and the rest was frozen and stored for immunohistochemical and Western blotting analyses. All procedures were approved by the animal ethics committee of Juntendo University. MV significantly reduced the mean fiber cross-sectional area ($p<0.05$), whereas this was attenuated by heat treatment ($p<0.05$). Heat stress resulted in a significant induction of heat shock protein 72 ($p<0.01$). MV induced cleaved caspase-3 ($p<0.05$), although this tended to be attenuated by heat stress. MV significantly decreased the force production at each stimulation frequency ($p<0.05$). Our results indicate that heat stress attenuates diaphragmatic atrophy, but cannot attenuate diaphragmatic contractile dysfunction. This work was supported by a Grant-in-Aid for Young Scientists (B) No. 23700781 and JSPS Fellows No. 11J11122 by JSPS.

7.3

THE COMBINED EFFECTS OF INSPIRATORY MUSCLE TRAINING AND CYCLING ON DIAPHRAGM MUSCLE ACTIVITY

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Inspiratory muscle training (IMT) is an intervention employed to improve the strength and performance of ventilatory muscles. The purpose of this study was to investigate whether sub-fatiguing IMT (40% maximal inspiratory pressure) would significantly increase inspiratory muscle activity above resting breathing and whether this effect would be additive to the effects of cycling. We measured DIA (DIA) muscle activity by surface electromyography (sEMG) in ten subjects (7 male, 3 female). Subjects performed IMT at rest or while cycling in either an upright or drops cycling posture. The addition of IMT in the upright posture during resting conditions significantly increased DIA sEMG, but the addition of IMT under other postural conditions did not lead to significant increases in sEMG. The addition of cycling significantly increased DIA sEMG above resting conditions independent of posture. During all cycling interventions, independent of IMT and posture, DIA sEMG was significantly greater than non-cycling conditions that did not incorporate IMT. Cycling in the drops position along with IMT significantly increased DIA sEMG activity above all non-cycling conditions tested. Significant differences in DIA sEMG activity were not observed between the upright and drops cycling postures. In support of our hypothesis, it appears that IMT and cycling have additive effects on DIA sEMG activity. Funding for this study was provided by the Mayo Clinic. The Mayo Clinic IRB approved all methods.

7.4

EFFECT OF INTERMITTENT ACTIVITY DURING CARDIOTHORACIC SURGERY ON HUMAN DIAPHRAGM MITOCHONDRIAL RESPIRATION

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Recent studies have shown that short periods of controlled mechanical ventilation (MV) use leads to ventilation induced diaphragmatic dysfunction. We examined the effect of intermittent diaphragm activity during cardiothoracic surgery on the human diaphragm by measuring mitochondrial respiration (MR) using high- resolution respirometry. In 5 patients (65 ± 6 yrs) undergoing lengthy thoracic surgery, the right or left phrenic nerve was randomly selected for 1 minute of stimulation every hour (30 pulses per minute, 15 msec pulse duration) during the surgery. Shortly before the surgery was completed, full thickness samples of diaphragm muscle were obtained from the anterolateral regions of both hemidiaphragms. The mean duration between the start of controlled MV and tissue harvest was 5.2 ± 1.0 hours. In the stimulated hemidiaphragm, the MR rate (pmol O2/sec/mg wet weight) was 14.63 ± 3.31 during state 3 and 3.79 ± 1.09 during state 4, while in the unstimulated hemidiaphragm the MR rate was 11.78 ± 2.28 during state 3 and 2.48 ± 1.09 during state 4. The stimulated and control samples were different for state 3 and 4 activities, $p < .05$.

7.5

A 28 DAY SOJOURN TO 3454M DIMINISHES SKELETAL MUSCLE RESPIRATORY CAPACITY BUT ENHANCES EFFICIENCY IN HUMANS

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Hypoxia-induced alterations in mitochondrial function are not well understood, and accordingly studies regarding mitochondrial modifications in human skeletal muscle following acclimatization to high altitude are seemingly inconsistent. We previously demonstrated that despite the loss of several mitochondria-specific proteins, 9-11 days of exposure to high altitude did not markedly modify integrated measures of mitochondrial functional capacity in skeletal muscle, though oxidative phosphorylation capacity tended to decrease. The aim of this study was to examine mitochondrial function following a more prolonged exposure to high altitude. Skeletal muscle biopsies were obtained from 8 lowland natives prior to and again after 28 days of exposure to 3454m. High-resolution respirometry was performed on the muscle samples to compare indices of respiratory control and capacity. Respirometric analysis revealed that mitochondrial-specific respiratory capacity decreased the capacity for fat oxidation, complex I-specific respiration, complex II-specific respiration, and oxidative phosphorylation capacity. Some indices of respiratory chain function were also altered, as coupling control improved in response to high altitude exposure. This data suggests that chronic exposure to high altitude reduces respiratory capacity in human skeletal muscle, however the efficiency of electron transport improves.

7.6

ACUTE IN VITRO STATIN EXPOSURE ALTERS MITOCHONDRIAL FUNCTION IN PERMEABILIZED SKELETAL MUSCLE FROM HEALTHY HUMANS

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Statins, widely used in the treatment of cardiovascular disease, are associated with potential adverse side effects in skeletal muscle. Data from cell culture studies suggest statin-induced myopathy may be initiated by altered mitochondrial function. To further examine the potential impact of statins, various aspects of mitochondrial function were assessed in human permeabilized skeletal muscle fiber bundles (PmFB) exposed (30 min) *in vitro* to atorvastatin (ATOR, 10 μM) or simvastatin (SIM, 10 μM), and in PmFB from healthy subjects after acute (2h) and/or chronic (once/d for 7d) treatment with ATOR (80 mg/d) or SIM (40 mg/d). *In vitro* exposure of PmFB to ATOR and SIM decreased both complex I and II supported respiratory capacity (JO_2), whereas only SIM decreased complex I supported mitochondrial calcium retention capacity ($_mCa^{2+}_{RC}$). Neither acute nor chronic *in vivo* treatment with ATOR or SIM altered JO_2 or $_mCa^{2+}_{RC}$. Although mitochondrial H_2O_2 emission potential ($_mE_{H2O2}$) in the presence of complex I or multiple substrates was not altered by *in vitro* or *in vivo* exposure to either statin, both *in vitro* and acute *in vivo* exposure to SIM decreased complex II $_mE_{H2O2}$. These findings in-dicate both ATOR and SIM are capable of directly impacting mitochondrial function in human PmFB exposed *in vitro*. The acute and chronic impact of *in vivo* statin exposure on skeletal muscle mitochondrial function is less clear and will require further study. R01 DK074825.

7.7

ACUTE EXPOSURE TO LOVASTATIN DIMINISHES TENSION DEVELOPMENT IN INTACT ISOLATED MYOFIBERS

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Statins are widely-prescribed cholesterol-lowering drugs shown to cause skeletal muscle myopathy. In particular, the lipophilic statins (e.g. lovastatin, simvastatin, atorvastatin, cerivastatin) can induce skeletal muscle toxicity, which often presents as muscle weakness, fatigue, and pain. The objective of the present study was to determine the effects of acute exposure to lovastatin on muscle contractile function using intact isolated skeletal muscle fibers. All procedures were approved by the UCSD IACUC. Intact muscle fibers were isolated from *Xenopus laevis*, electrically stimulated and tension development recorded. After incubating fibers in 10 μM lovastatin for 1 h, tension development at submaximal and maximal frequencies of stimulation (30-150 Hz) was reduced by 50% and demonstrated slower peak rates of contraction and relaxation compared to preincubation values. The addition of 1 mM caffeine restored the maximal tetanic tension development with lovastatin, but did not restore the slowed relaxation rate. Although the overall time-to-fatigue was not affected by the acute lovastatin treatment, the work performed was smaller in the lovastatin-treated fibers. In conclusion, acute exposure to lovastatin causes a reduction in tension development and slows the rate of muscle contractile activation and relaxation in single myofibers, and our results suggest that this effect is mediated through intracellular calcium handling. Funded by NIH grants NIAMS AR40155 and NHLBI HL91830.

7.8

THREE-DIMENSIONAL DYNAMIC ORGANIZATION OF MITOCHONDRIA IN SKELETAL MUSCLE: EFFECTS OF A SINGLE BOUT OF VOLUNTARY EXERCISE

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Mitochondria undergo fusion and fission events that are frequent and easily observable in proliferating cultured cells, but whether mitochondria undergo morphology transitions in terminally differentiated muscle fibers *in vivo* remains unclear. Furthermore, the acute effect of exercise on mitochondrial dynamics is unknown. Here, using a combination of freeze-fracture scanning EM and transmission EM in both transverse and longitudinal planes, we characterized the morphology of subsarcolemmal (SS) and intermyofibrillar (IMF) mitochondria. High-resolution micrographs were traced and analyzed for mitochondrial size and shape descriptors. In sedentary mice, IMF mitochondria were elongated and branched whereas SS mitochondria were mostly spherical. Electron-dense mitochondrial contact sites consistent with events of outer mitochondrial membrane fusion were also visualized. In exercising mice, a single 3-hour bout of voluntary wheel running decreased blood glucose levels (-38%, $p<0.05$) as well as the amount and size of intramyocellular lipid droplets ($p<0.001$), attesting to an increased in muscular metabolic demand. Although neither mitochondrial size nor morphology significantly differed post-exercise, electron-dense mitochondrial contact sites were more frequent (+130%, $p<0.05$) in exercising animals. We postulate that electron dense contact sites consist in pre-fusion events - a single bout of exercise may prime mitochondria for morphology change, but does not immediately alter mitochondrial size or shape.

7.9

GLYCOLYTIC SKELETAL MYOFIBERS DISPLAY HIGHER P/O RATIOS THAN CARDIAC MYOFIBERS DUE TO ADENYLATE KINASE: PRELIMINARY FINDINGS USING A NOVEL OXI-FLUOROMETER APPARATUS.

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Oxidative tissues such as myocardium rely heavily on fatty acids for mitochondrial ATP production; however, accumulation of fatty acids has been shown to uncouple oxidative phosphorylation through protein-mediated (e.g. UCP3, ANT) and indirect pathways and lead to lower metabolic efficiency (i.e. decreasing P/O ratio). We therefore hypothesized that the efficiency of oxidative phosphorylation (P/O ratio) is: 1) lower in oxidative muscle than in glycolytic muscle and 2) lower during lipid oxidation than carbohydrate oxidation. To test these hypotheses using an enzyme-coupled assay system, we simultaneously measured ATP production (JATP) and oxygen consumption (JO2) in permeabilized mouse left ventricle and white gastrocnemius during state 3 respiration supported by malate and pyruvate or palmitoyl-carnitine over a range (20-500 µM) of ADP concentrations. We observed that P/O ratios were higher in glycolytic than oxidative muscle, but this was ultimately determined to be a result of adenylate kinase activity. No differences in P/O ratios were found between myocardium metabolizing pyruvate or palmitoyl-carnitine at any given ADP concentration. The results of this study demonstrate that: 1) the P/O ratio is highly conserved in muscle mitochondria, 2) adenylate kinase is a major producer of ATP in glycolytic muscle and 3) palmitoyl-carnitine does not promote mitochondrial uncoupling in myocardium under the conditions tested. Funding Sources: R21 HL098780 and R01 DK073488.

7.10

EFFECTS OF AEROBIC TRAINING AND OVERTRAINING ON DNA DAMAGE AND OXIDATIVE STRESS IN SWISS MICE

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We aimed to verify aerobic training and overtraining protocol effects on DNA damage of blood and skeletal muscle cells in mice. To relate possible alterations of these parameters with oxidative stress status, we measured reduced-glutathione (GSH) levels in blood, and GSH levels and lipid peroxidation in gastrocnemius. Rodents were divided into control (C), trained (TR) and overtrained (OTR). All experiments were in accordance with the American Physiological Society “Guiding Principals in the Care and Use of Animals”. Incremental load test (ILT) and exhaustive test (ET) were used to measure performances before (i.e. week 0) and after (i.e. week 8) exercise protocols. 24h after ET, gastrocnemius were removed. While left muscle was minced in 0.9% NaCl and used for comet assay, right muscle was stored at -80oC for determination of GSH and lipid peroxidation - measured by thiobarbituric acid reactive substances (TBARS). Blood was collected, and used for comet assay and determination of GSH. ILT and ET parameters showed intra and inter-groups significant differences. OTR group showed a significant increase in percentage DNA in the tail compared to C and TR groups. GSH levels were significantly lower in OTR group compared to C and TR groups. OTR group showed significantly higher levels of TBARS compared to C and TR groups. In conclusion, overtraining, but not training, is related to DNA damage and oxidative stress. Financial support from FAPESP (2011/02652-0 and 2010/08239-4).

7.11

SARCOLIPIN ABLATION DOES NOT AFFECT EXERCISE TRAINING-INDUCED ADAPTATION OF OXIDATIVE METABOLISM IN SKELETAL MUSCLE

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Ca2+ signaling plays a role in mediating exercise training-induced mitochondrial biogenesis in skeletal muscle. Sarcolipin is a small membrane protein that regulates the activity of sarco (endo)plasmic reticulum Ca2+-ATPases (SERCAs) which serve as vital controllers of intracellular Ca2+ in skeletal muscle. To investigate the potential role of SLN in the adaptive response of skeletal muscle mitochondria to endurance training, mice without (SLNKO) underwent endurance training for 8 weeks (TR) and were compared to their untrained (UT) counterparts. A total of 36 mice (18 SLNKO and 18 wild type (WT)) were randomly assigned to TR and UT groups. Soleus (SOL) and extensor digitorum longus (EDL) muscles were collected from all groups at matching time points following the endurance training to determine the relative abundance of cytochrome-c (cyt-c), adenine nucleotide transporter (ANT) and cytochrome c oxidase IV (COXIV) using Western blotting. TR mice had increased cyt-c content ($p<0.05$) in both SOL and EDL compared to their UT counterparts. ANT and COXIV content were higher ($p<0.05$) in TR EDL compared with UT EDL. A similar trend was observed for the COXIV ($p=0.1$) but not ANT in TR SOL ($p>0.1$). There were no differences ($p>0.1$) between SLNKO and WT for any of the mitochondrial proteins analyzed. Our results show that SLN ablation did not affect the adaptive response of skeletal muscle to increase oxidative capacity with endurance training. This study was funded by CIHR and NSERC.

7.12

NFATC3 REGULATES MUSCLE FIBER-TYPE TRANSITION INDEPENDENTLY FROM THE ACTIVATION OF CALCINEURIN (CAN) DURING LONG-TERM ENDURANCE TRAINING IN RATS

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The purpose of this study was to examine whether the CaN/NFATc3 pathway is required to promote the fiber-type transition during long-term endurance training. *Wistar* male rats (80 days old) were divided into two groups: trained (T, $n = 8$) and control (C, $n = 8$). T group underwent an 8-wk swimming endurance training program (5 days/week). The training protocol was designed to achieve to maximal lactate steady state (5% body weight). After the experiment the animals were euthanized by decapitation and the soleus (SOL) and plantaris (PL) muscles were collected for morphometrical (muscle fiber area), histochemical (fiber-type frequency) and molecular (gene expression) analyses. This experiment was conducted in conformance with the APS “Guiding Principles for the Care and Use of Animals.” Differences were considered significant with $p < 0.05$. Long-term endurance training induced a significant ($p < 0.05$) increase in NFATc3 gene expression in SOL and PL muscles, while the CaN A and B subunits gene expression remained unchanged ($p > 0.05$). In addition, there was a type I-to-IIA fiber transition in SOL and type IIB-to-IIA fiber transition in PL muscle, without any significant ($p > 0.05$) alteration in fiber area of both muscles. The data show that the fiber-type transition induced by long-term endurance training was associated with an increase in NFATc3 expression, but not CaN, indicating that the NFATc3 may mediate the fiber-type transition independently from the activation of CaN.

7.13

PHOSPHOLAMBAN OVEREXPRESSION CAUSES IRREGULAR DISTRIBUTION AND SIZE OF SLOW-TWITCH AND FAST-TWITCH FIBRES IN MOUSE SOLEUS AND DIAPHRAGM

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Regulation of sarco (endo)plasmic reticulum Ca2+-ATPases (SERCAs) occurs in part through physical interaction with sarcolipin (SLN) and phospholamban (PLN). Mouse skeletal muscle only expresses SLN in slow-twitch type I (ST) fibers. To understand the physiological effect induced by dual expression of SLN and PLN, we examined mice with targeted overexpression of PLN in ST fibers. Methods: Soleus, extensor digitorum longus (EDL), and diaphragm were excised from 20 mice (10 wild-type [WT], 10 PLN overexpression [PLN OE]). Immunofluorescent staining was done to characterize fiber types in each muscle. Sub-maximal VO2, VO2 max, and times to exhaustion during treadmill exercise were also recorded. Results: The body weights, EDL weight, and VO2 max between PLN OE and WT mice were not significantly different, whereas soleus weight was significantly lower ($p<0.0001$) in PLN OE (3.6 ± 0.2) vs WT (5.7 ± 0.2). Immunofluorescent staining in soleus and diaphragm reveal elevated proportions of atrophied ST fibers and hypertrophied type IIa fibres. A trend ($p=0.09$) was seen with PLN OE mice having higher sub-maximal VO2 (6716 ± 185.7 ml/kg/hr) than WT (6242 ± 196.1 ml/kg/hr). Time to exhaustion was shorter in PLN OE mice (82.3 ± 7.4 min) vs WT mice (125.9 ± 9.6 min; $p=0.003$). Conclusion: In summary, muscles of mice expressing both SLN and PLN had irregular fiber type distribution, fiber size, and traditional characteristics of myopathy, which likely contributed to reduced exercise capacity.

7.14

PHOSPHOLAMBAN REGULATES BOTH SERCA1A AND SERCA2A IN HUMAN SKELETAL MUSCLE

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Cytosolic Ca2+ in skeletal muscle is maintained via catalytic action of sarco (endo) plasmic reticulum Ca2+-ATPases (SERCAs). SERCAs are regulated by phospholamban (PLN), a 52 amino acid integral membrane protein that can interact with both SERCA1a and SERCA2a when expressed in HEK-293 cells and lower the apparent Ca2+ affinity of both SERCA isoforms. It is well known that PLN and SERCA2a are co-expressed in slow-twitch skeletal muscle; however, no study to date has found evidence of an interaction between PLN and SERCA1a in vivo. Using co-immunoprecipitation and single fiber Western blot analysis on biopsies obtained from the vastus lateralis of five males, we determined the physical interaction and co-expression patterns of PLN with SERCA1a and SERCA2a isoforms in individual fibre types. To define the various fibre types we utilized antibodies directed against slow myosin heavy chain (MHC)-I, fast MHC IIa, and fast MHC IIx. We found PLN to be expressed in all fibres regardless of SERCA or MHC isoform. Furthermore, a significant proportion of type I fibres (21%) and a lower percentage of type II fibres (9%) co-expressed SERCA2a and SERCA1a. Co-immunoprecipitation showed PLN binds to both SERCA1a and SERCA2a. These data indicate that PLN regulates both SERCA1a and SERCA2a in human skeletal muscle. Supported by NSERC.

7.15

ASSESSMENT OF THE INTRACELLULAR CALCIUM TRANSIENT USING HIGH AND LOW AFFINITY FLUORESCENT INDICATORS IN POTENTIATED MOUSE LUMBRICAL MUSCLE

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Fast twitch muscles from knockout mice devoid of skeletal myosin light chain kinase exhibit a potentiation of isometric twitch force that cannot be explained by phosphorylation of the myosin regulatory light chain. We hypothesized that the mechanism for this incomplete negation of elevated twitch force is the influence of repetitive or high frequency stimulation on basal cytosolic or peak intracellular Ca^{2+}levels. Hence, the purpose of this study was to assess changes in basal cytosolic Ca^{2+} levels and in the intracellular Ca^{2+}transient following a potentiating stimulus. Mouse lumbrical muscles were loaded with the Ca^{2+}- sensitive fluorescent indicators to detect changes in peak intracellular Ca^{2+} levels (Mag-fura-2) or basal Ca^{2+} levels (Fura-2 or Indo-1) caused by 2.5 sec of 20 Hz stimulation (37^{o}C). Although this protocol produced an immediate increase in twitch force of 17±3% (n=10) ($P < 0.001$) this potentiation quickly dissipated and was absent 20 - 30 sec after the cessation of stimulation. Fluorescent ratio signals corresponding to basal Ca^{2+} concentrations were increased in muscles loaded with either Indo-1 (5.5 ± 1.5%, n=8; $P<0.01$) or Fura-2 (10.6 ± 1.0%, n=3; $P < 0.01$) compared to pre-stimulus levels; importantly, this increase in basal Ca^{2+}dissipated with the same time course as did PTP. Further, Mag-fura-2 signals showed that neither the amplitude ($P=0.49$) nor the duration ($P=0.68$) of the ICT was altered at any time during PTP. We thus conclude that a normal amplitude and shape of the intracellular Ca^{2+} transient, superimposed on an elevated basal Ca^{2+} level, could contribute to potentiation in mouse lumbrical muscle at physiological temperatures.

7.16

CHANGING MYOGLOBIN'S PARADIGM: A NOVEL LINK BETWEEN LIPIDS AND MYOGLOBIN

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Traditionally, myoglobin (Mb) has been noted for its ability to reversibly bind O2, thus providing a basis for its role as both an O2 reservoir and aid in facilitated diffusion within muscle. Over time, however, research has shown that Mb's high binding affinity for O2 translates into a protein that only releases O2 stores under hypoxic conditions not usually seen in healthy terrestrial species. Yet, levels of myoglobin within the working muscle of elite athletes are high relative to sedentary individuals. If Mb is not largely being utilized for O2 stores, why then do we see more Mb in muscles of terrestrial species? Here, we show a link between lipid availability and Mb, whereby increasing lipid availability in C2C12 mouse skeletal muscle cells causes an increase in Mb. An interesting aspect of this trend is that while hypoxic cells show Mb increasing via functional assays and protein expression, normoxic cells only show an increase in Mb protein expression. The latter data parallel a similar trend in muscle tissue from rats fed high fat diets, suggesting an increase in Mb incapable of binding O2 concomitant with normoxia and high fat. Moreover, normoxic, high fat cells show decreases in calcineurin, suggesting an increase in Mb independent of contraction-associated calcium-signaling. These data allude to a new potential paradigm for functional Mb; could the primary role for Mb in terrestrial animals relate to lipid metabolism rather than solely O2 storage?

8.0: MOLECULAR REGULATORY MECHANISMS

8.1

EFFECT OF EXERCISE AND DIETARY FAT ON GENETIC REGULATORS OF KNEE OSTEOARTHRITIS IN MICE

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Obesity increases the risk of knee osteoarthritis (OA) presumably by increasing local biomechanical factors and systemic inflammatory factors. Although exercise increases joint loading, we have recently shown that it lessens metabolic inflammation and OA in mice. **PURPOSE**: To determine the effect of a high-fat diet and wheel-running exercise on the differential expression of genes in knee cartilage and subchondral bone using whole-genome microarrays. **METHODS**: Male C57BL/6J mice were fed either a 10% or 60% kcal fat diet from 16-20 wks of age. Half of the mice were housed with running wheels (n=5 per group). RNA was isolated from knee femoral and tibial cartilage and subchondral bone and quantified using a whole-genome mouse BeadChip Array (Illumina). Differentially expressed genes ($p<0.005$) were further analyzed using Ingenuity Pathway Analysis in diet-matched sedentary vs. exercised animals. **RESULTS**: 162 genes, including 41 transcriptional regulators, were differentially expressed (>1.25 fold) with exercise in mice fed a high fat diet compared to 35 genes in control diet mice. Pathway analysis predicted that exercise increased nitric oxide signaling and inhibited Myc family target genes in high-fat but not control mice. **CONCLUSION**: Dietary fat content profoundly alters the effect of short-term exercise on genetic regulators of cartilage and bone inflammation and growth, suggesting a role for diet-specific molecular targets in treating OA. Support: Arthritis Foundation & NIH.

8.2

SKELETAL MUSCLE MASS REGULATORS WITH AND WITHOUT CONTRACTILE ACTIVITY IN SPINAL CORD-INJURED VS. ABLE-BODIED INDIVIDUALS

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Spinal cord injury (SCI) is known to induce substantial skeletal muscle atrophy, which progresses rapidly for the first few months and appears to reach a relative plateau approximately 17-18 months post-injury. The mechanisms responsible for the early phase atrophy, as well as this plateau, are incompletely understood. Regardless, it has been shown that SCI muscles even several years post-injury are responsive to hypertrophic stimuli. For example, neuromuscular electrical stimulation (NMES)-induced resistance exercise has been shown to induce muscle regrowth in SCI. However, there is a limited understanding of the mechanisms responsible for NMES myofiber hypertrophy in both SCI and able-bodied (AB) individuals. The two-fold purpose of this project is thus to evaluate muscle mass regulators in the resting, as well as NMES-stimulated, muscles of SCI vs. AB. Recruitment and testing was completed just prior to the abstract submission deadline. Thirteen chronic SCI (ASIA A, B, C; 50 ±11 y), and 13 AB individuals (42±11 y) completed 80 quadriceps NMES isometric contractions (~50% MVC). Muscle samples were collected before, and 10 and 60 min after NMES. Cell signaling and gene expression analyses are ongoing. At the APS IBE we will present findings for both well-established (e.g., atrogenes, myoregulatory factors, anabolic and proteolytic signaling pathways) and novel (e.g., regulatory miRNAs) regulators of muscle mass in SCI and AB before and after the single NMES bout.

8.3

GROWTH HORMONE DEFICIENCY HAS TISSUE-SPECIFIC EFFECTS ON PROTEIN SYNTHESIS

8.4

AICAR INHIBITS CERAMIDE BIOSYNTHESIS IN SKELETAL MUSCLE

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Sarcopenia is associated with a decrease in muscle function and exercise capacity and is associated with a decrease in growth hormone (GH). GH administration has been suggested as a means by which to promote skeletal muscle protein synthesis (PS) and exercise capacity but has shown mixed results. Less is known about anabolic effects of GH in other tissues. Understanding how growth hormone regulates PS in the different cellular compartments in a variety of tissues could provide valuable information about the long-term outcomes of GH therapy. Snell Dwarf (SD, n=10) mice, which are GH deficient, and wild type control mice (CON, n=10) were given 8% D_2O as drinking water for 4 weeks. Gastrocnemius complex (SkM) and heart (Hrt) were collected and fractionated into mixed (Mx), cytosolic (Cyto), and mitochondrial-enriched (Mito) fractions. Fractional synthesis was determined by the D_2 enrichment of alanine incorporated into tissue protein during the labeling period. Protein synthesis was decreased in all fractions within the SkM (Mx: Con=0.73±0.02, SD=0.55±0.02; Cyto: Con=0.81±0.02, SD=0.61±0.02; Mito: Con=0.55±0.03, SD=0.39±0.02). Hrt showed decreased protein synthesis in Mx (Con=0.88±0.03, SD=0.73±0.04) and Cyto (Con=0.98±0.01, SD=0.88±0.04) fractions but Mito synthesis was maintained (Con=0.79±0.02, SD=0.76±0.02). The difference in tissue specific responses illustrates the need to consider tissues beyond skeletal muscle. Further understanding of how

differential protein synthesis is regulated between tissues could improve how exercise adaptations are interpreted and lead to the development of better treatments for sarcopenia and growth-related pathologies.

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The sphingolipid ceramide is increased in hyperlipidemic states and is known to elicit a host of deleterious outcomes. In contrast, AMPK has long been studied for its effects on metabolism and substrate utilization, acting as the critical mediator for several stimuli that induce fatty acid oxidation. We sought to understand the direct effect of AMPK activation on ceramide metabolism in skeletal muscle, a highly active site of both ceramide biosynthesis and fatty acid oxidation. AICAR treatment, known to activate AMPK, induced a significant reduction in ceramide levels in myotubes treated with high levels of palmitate. This observation was further supported by the finding that AICAR treatment, but not AICAR + Compound C, an AMPK inhibitor, significantly reduced expression of serine palmitoyltransferase (SPT) 2, the rate-limiting step in de novo ceramide synthesis. Subsequently, we sought to determine whether the ceramide-specific effects of AMPK were relevant in an in vivo model. Male rats were fed a standard or high-fat diet, with a subset receiving daily AICAR injections. Similar to myotubes, animals receiving AICAR treatments tended to have reduced soleus SPT2 expression and reduced ceramide content. These findings identify ceramide synthesis as a novel therapeutic target of AMPK activation.

8.5

MODULATION OF CARDIAC MITOCHONDRIAL BIOENERGETICS BY ENDURANCE TRAINING AND INTERMITTENT HYPOBARIC HYPOXIA

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Intermittent hypobaric-hypoxia (IHH) and endurance-training (ET) are cardioprotective strategies against several stress-stimuli. Modulation of mitochondrial bioenergetics appears to be an important step of the process. This study aimed to analyse whether a combination of these approaches provide additive or synergistic effects by improving heart-mitochondrial and cardiac-function Wistar male rats were: normoxic-sedentary (NS), normoxic-exercised (NE, 1h/d/5wks treadmill-running), hypoxic-sedentary (HS,6000m,5h/d/5wks) and hypoxic-exercised (HE). In vitro cardiac mitochondrial O2 consumption, membrane potential, ANT and OXPHOS subunits were evaluated. Cardiac function was characterized by echocardiography and hemodynamic parameters Mitochondrial RCR increased in all groups vs. NS. Susceptibility to anoxia/reoxygenation-induced dysfunction decreased in NE, HS and HE vs. NS. HS decreased mitochondrial complex-I and -II subunits; however HE completely reverted the decreased content in complex-II subunits. ANT increased in HE. HE presented normalized ventricular-arterial coupling (Ea) and significantly improved myocardial performance as evaluated by increased cardiac output and normalization of the Tei index vs. HS. Both IHH and ET modulate cardiac mitochondria bioenergetics although without visible addictive effects. It is suggested that the combination of both strategies, although not additive, seem to translate into improved cardiac function. IJUP-71-2009; FCT-PTDC/DES/113580/2009.

8.6

OVARIECTOMY INCREASES HEPATIC MITOCHONDRIAL ROS PRODUCTION IN MICE

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We have previously shown that loss of ovarian function leads to the disruption of lipid metabolism regulators in hepatic tissue, thus increasing the susceptibility for developing hepatic steatosis. **PURPOSE:** To determine if the loss of ovarian function in female mice results in increased triacylclycerol (TAG) storage, impaired hepatic mitochondrial function, and whether any of these changes resulted from altered sirtuin (SIRT) function. **METHODS:** Female C57BL/6 mice were divided into two groups SHAM or bilateral ovariectomy (OVX). Mitochondrial function was assessed by measuring oxygen consumption, reactive oxygen species (ROS) production, and mitochondrial protein content from isolated hepatic mitochondria. In addition, mitochondrial acetylation status and sirtuin 1/3 (SIRT) protein content were assessed. **RESULTS:** Compared to SHAM mice, hepatic mitochondria from OVX mice exhibited no differences in oxygen consumption in either state 3 or 4 conditions, but did exhibit increased ROS production. In addition, no differences in mitochondrial protein content, acetylation status or total SIRT 1/3 content were detected between groups. OVX mice exhibited a non-significant increase in hepatic TAG storage compared to SHAM mice. **CONCLUSION**: The data suggest that ovariectomy contributes to impaired hepatic mitochondrial function by increasing ROS production, which is not a result of altered SIRT function. This work was funded by the Baltimore DRTC (NIH-P60DK079637).

8.7

TREATMENT OF CULTURED MYOTUBES WITH RAPAMYCIN ACTIVATES AMP-ACTIVATED PROTEIN KINASE

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Exercise is one of the best understood and most effective interventions to attenuate chronic diseases associated with aging. Aerobic exercise activates AMP-activated protein kinase (AMPK) while simultaneously downregulating mammalian target of rapamycin (mTOR), both of which have been shown to promote longevity in various human and animal models. While evidence for rapamycin activating AMPK is evident in cancer models, little data exists suggesting the mTOR inhibitor can activate AMPK in post-mitotic tissues such as skeletal muscle. Treatment with rapamycin could stimulate pathways sensitive to energetic stress to elicit cellular effects similar to endurance exercise. The purpose of this study was to determine whether rapamycin can exhibit exercise-like effects through the inhibition of mTOR and activation of AMPK in skeletal muscle cells. Treatment of C2C12 cultured myotubes with 5nM rapamycin for 24 hours significantly activated AMPK, as assessed by phosphorylation of Thr172, while also inhibiting mTOR signaling, as assessed by the hypophosphorylation of ribosomal protein S6 (rpS6). Addition of metformin, a known AMPK agonist, did not enhance the ability of rapamycin to activate AMPK. These results suggest rapamycin could be utilized to understand the mechanisms by which exercise promotes beneficial effects in response to cellular energetic stress to identify potential treatments which mimic the benefits of aerobic exercise. Ongoing experiments are focused on determining the role of autophagy with rapamycin and metformin treatment, and whether the beneficial effects of these pharmaceutical interventions can influence healthspan and longevity.

8.8

SKELETAL MUSCLE ADAPTATION IN RESPONSE TO MECHANICAL STRESS IN P130CAS−/− MICE

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Mammalian skeletal muscles undergo adaptation in response to alteration in functional demands involving mechanical stress-induced cellular signaling called mechanotransduction. We hypothesized that p130Cas which has been reported to act as a mechanosensor, transducing mechanical extension into cellular signaling, plays an important role in maintaining and promoting skeletal muscle adaptation in response to mechanical stress via p38 MAPK signaling pathway. We observed that muscle-specific p130Cas −/− mice have normal expressions of contractile protein in skeletal muscle. Furthermore, muscle-specific p130Cas−/− mice showed normal mechanical stress-induced muscle adaptations including exercise-induced IIb-to-IIa muscle fiber type transformation and hypertrophy as well as disuse-induced muscle atrophy. Finally, we showed evidence that exercise-induced p38 MAPK signaling did not impaired by muscle specific deletion of the p130Cas. We conclude that p130Cas play limited role in mechanical stress-induced skeletal muscle adaptation.

8.9

PHOSPHATIDIC ACID AND MECHANICAL STIMULI ACTIVATE MTOR SIGNALING VIA AN ERK-INDEPENDENT MECHANISM

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Signaling by mTOR is both necessary and sufficient for the induction of hypertrophy in response to mechanical overload. Recently it has been suggested that mechanical stimuli (MS) induce mTOR signaling via a mechanism that requires phosphatidic acid (PA). The mechanism via which PA activates mTOR signaling is not clear, but at least two models have been proposed; 1) direct binding of PA to mTOR, or 2) PA-induced activation of ERK which then stimulates mTOR. In order to define the role of ERK in the regulation of mTOR by PA and MS, we first performed experiments in which C2C12 myoblasts were stimulated with exogenous PA. The results indicated that PA was sufficient to induce signaling through both ERK and mTOR; however, inhibition of ERK with UO126 did not prevent the ability of PA to induce mTOR signaling. Next, we performed experiments in which mouse EDL muscles were subjected to intermittent stretch as a source of MS. The results indicated that MS was sufficient to induce an increase in PA, as well as, signaling through both ERK and mTOR; however, inhibition of ERK did not prevent the ability of MS to induce mTOR signaling. Lastly, we performed in-vitro mTOR kinase activity assays and found that PA could directly activate mTOR signaling. Taken together, these results demonstrate that both exogenous PA and MS induce mTOR signaling through an ERK-independent mechanism that potentially involves a direct interaction of PA with mTOR. Support: NIH grant AR057347 to TAH.

8.10

MTOR PATHWAY ACTIVATION IN THE DESMIN KNOCKOUT MOUSE

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The 52 kDa intermediate filament protein desmin plays an important role in force transmission in skeletal muscle by connecting myofibrils at Z-lines and to the sarcolemma. Desmin content in muscle adapts to contractile activity and may be involved in cellular signaling mechanisms responsible for muscle growth. Purpose: To compare signaling responses of the mTOR pathway in wild type (WT) vs desmin knock out (KO) mice. Methods: WT (n=10) and KO (n=10) mice were exposed to high frequency electric stimulation of the left hindlimb to elicit an acute response of the mTOR pathway. Non-stimulated right hindlimbs were used as a within animal control. Right and left TA and EDL muscles were dissected 30 min post-stimulation and examined for changes in mTOR and p70S6k. Results: Phosphorylated mTOR levels were not different between stimulated and control limbs in either WT or KO, although overall mTOR levels in KO were higher than WT. Stimulated muscles showed an increase in phosphorylated p70S6k in WT and KO. There was no difference in phosphorylated p70S6k levels between WT and KO groups. Conclusion: The absence of desmin does not affect phosphorylation levels of mTOR or p70S6k but KO animals have a higher level of mTOR suggesting an adaptation to the lack of desmin in skeletal muscle.

8.11
WITHDRAWN

8.12
TARGETED INHIBITION OF CALCINEURIN SIGNALING WITH THE CA+2-BUFFERING PROTEIN PARVALBUMIN REDUCES UTROPHIN A EXPRESSION AND EXACERBATES THE DYSTROPHIC PATHOLOGY IN MDX MICE

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We have shown utrophin A, a therapeutically relevant protein that can compensate for the lack of dystrophin in dystrophic mouse muscles, to be regulated by calcineurin (Cn) signaling (*PNAS 2003; Hum Mol Gen 2004 & 2006*). We set out to determine the impact of interfering with Ca^{+2}/Cn-based signaling in targeted dystrophin-deficient myofibers. We thus crossbred mdx mice with transgenic mice expressing the Ca^{+2}-buffering protein parvalbumin (PV), driven by the fiber-specific Troponin I slow promoter. This approach forced expression of this non-native fast Ca^{+2}-regulatory protein in slow fibers thus lowering their Cn activity in the absence of any fiber type conversions. Consistent with impairments in Cn, nuclear localization of NFATc1 was reduced in slow fibers from mdx/PV mice. We also observed significant reductions in utrophin A mRNA and protein in targeted fibers of crossbred mice. In accordance with lower levels of utrophin A, we noted a clear exacerbation of the dystrophic phenotype in mdx/PV slow fibers as exemplified by several pathological indices. These results further establish Ca^{+2}/CaM-based signaling as key to regulating expression of utrophin A in skeletal muscle. Moreover, they illustrate the therapeutic potential of targeting Ca^{+2}/CaM-based signaling intermediates in muscle as well as strategies aimed at promoting the slow oxidative myofiber program as effective countermeasures for Duchenne muscular dystrophy. Funded by CIHR, NSERC and CRC.

8.13
DEPTOR EXPRESSION IS ALTERED BY MECHANICAL LOADING IN SKELETAL MUSCLE OF RATS

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Prior work in our lab has demonstrated that muscle mass can be restored to control levels following multiple bouts of disuse if given adequate recovery time, and chronic resistance training prior to long-duration unloading offered no protective effects. This study determined if a specific modulator of mTOR, called DEPTOR, played a role in the muscle adaptation response to unloading. Male Sprague-Dawley rats (6mo) were either exposed to one or two bouts of 28d hindlimb unloading (1HU, 2HU), or with 56d of re-ambulation following 1HU, with (1HU+EX) or without (1HU+REC) chronic re-sistance exercise during recovery, or with a subsequent HU bout (2HU or 2HU+EX). Gastrocnemius muscle DEPTOR expression and fractional synthesis rates (FSR) were assessed in each group. Results indicated that DEPTOR expression was higher in 1HU animals when compared to normal ambulatory controls. The elevation of DEPTOR, a competitive inhibitor of mTOR, was accompanied by reduced FSR. Reambulation after hindlimb unloading, with or without resistance exercise, reduced DEPTOR expression with a concomitant elevation of FSR, both to control levels. DEPTOR expression was elevated in 2HU, with a similar repression of FSR as 1HU. DEPTOR expression in 2HU+EX was also elevated with a blunted FSR; supporting prior research suggesting that exercise training prior to hindlimb unloading is not protective against losses of muscle mass. These results are the first to associate physiologic changes in DEPTOR expression with alterations of FSR, which may have important implications towards the design of therapeutic targets for the control of muscle mass. *The first and second authors contributed equally on this work.*

8.14
DIFFERENTIAL EXPRESSION OF HDAC GENES DURING SKELETAL MUSCLE ATROPHY

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We are beginning to understand the physiological significance of gene expression changes that accompany skeletal muscle atrophy during catabolic conditions, as well as some of the factors that regulate gene transcription. One important mechanism of gene transcription regulation occurs via histone acetyltransferases (HATs) and histone deacetylases (HDACs). However, our understanding of their changes in expression levels during muscle wasting is limited. Therefore the purpose of the current study was to determine the expression levels of various HATs and HDACs in skeletal muscle during multiple atrophying conditions to determine whether a common transcriptional profile exists. Animals were assigned to control, cast immobilization, nutrient deprivation and denervation groups. Experiments were conducted in accordance with APS Guiding Principals for the care and Use of Animals and the University of Florida IACUC. HDAC4, HDAC6 and SIRT1 were significantly increased in all models. Further, the class I HDACs - HDAC1, HDAC2 and HDAC3 were significantly increased in response to both cast immobilization and denervation. These findings suggest a common increase in specific HDACs during multiple muscle atrophy models, and an increase in class I HDACs during atrophy associated with the loss of muscle tension. This work was by NIH, NIAMS grant R01AR060209-02 (to A.R. Judge). A.W. Beharry is supported by a T32 from the NICHD grant T32-HD-043730.

8.15
EXPLORING RIBOSOMAL REGULATION OF HUMAN SKELETAL MUSCLE HYPERTROPHY

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Increased skeletal muscle protein synthesis is necessary for myofiber hypertrophy following resistance training (RT), and is thought to be regulated primarily by translational efficiency (i.e. increased rate of translation per ribosome). Previously, we clustered 66 human adults as non- (Non), modest (Mod), or extreme (Xtr) responders based on myofiber hypertrophy following 16 wk of RT. Only Xtr increased skeletal muscle total RNA (26%) 24 h after the initial bout of resistance exercise (RE), suggesting enhanced translational capacity as well (i.e. ribosomal biogenesis), since the majority of skeletal muscle RNA is rRNA. Additionally, genomic microarrays identified numerous ribosomal protein transcripts that were robustly upregulated in Xtr when compared to Non (up to 22.4-fold higher) at baseline. Two potential regulators of rRNA and ribosomal protein transcription via chromatin modulation, NAP1L1 and histone H3, also displayed much higher levels of expression in Xtr compared to Non (17.4- and 8.6-fold, respectively). Follow-up immunoblotting revealed no difference in baseline NAP1L1 protein between clusters. On the other hand, Mod and Xtr had higher acetylated histone H3 (K36) protein at baseline than Non ($P = 0.01$), which may lead to enhanced transcriptional activity. Overall, our current data suggest responders, and particularly Xtr, may be poised to more effectively enhance translational capacity in response to RE.

8.16
SKELETAL MUSCLE FIBER TYPE-SPECIFIC TRANSCRIPTIONAL RESPONSE TO AEROBIC EXERCISE

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The purpose of this investigation was to explore the fiber type-specific expression of genes involved in skeletal muscle oxidative capacity at rest and in response to 45 min of non-exhaustive (72±1% VO_2max) cycling in recreationally active men (n=6, 25±1y, 54±3ml·kg^{-1}·min^{-1}). Gene expression was assessed by qPCR in slow (MHC I) and fast (MHC IIa) fiber pools isolated from vastus lateralis muscle biopsy samples obtained at rest and 2h after exercise. Of the 16 genes examined, basal expression of NRF-1 and β-HAD mRNA was higher ($P<0.05$) in MHC I fibers, while UCP3 mRNA was higher ($P<0.05$) in MHC IIa fibers. Due to vast individual variability, only PGC-1α mRNA increased ($P<0.05$) in both fiber types after exercise, while Mfn1 and Mfn2 mRNA decreased ($P<0.05$ and $P=0.06$, respectively) in the MHC IIa fibers. An interaction ($P<0.05$) occurred for β-HAD mRNA, as evidenced by a decrease (26±23%) in MHC I and an increase (20±19%) in MHC IIa fibers following the bout of aerobic exercise. In summary, basal and exercise-induced expression of some oxidative capacity-related genes appears to be fiber-type specific, suggesting the dynamics of mitochondrial turnover may differ between fiber types. These findings highlight the prevalence of individual variability in the fiber type-specific response to aerobic exercise in recreationally active men and provide insight into the well documented heterogeneous response to aerobic exercise training in humans. *Supported by NIH AG032127.*

9.0: AGING

9.1
MARKERS OF "SR STRESS" IN AGING AND EXERCISED MUSCLE

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Purpose: Impaired sarcoplasmic reticulum (SR) function has been associated with reduced muscle force generation and locomotor function. This study was conducted to de-

termine the extent to which aging increased SR stress markers, and the extent to which volitional exercise affected them. Methods: Gastrocnemius muscles were harvested from adult (8 months; n = 8), aging (24 months; n = 8) and F344/BN rats that aged with wheel access for 16 months (24 months; n = 4). SR calcium handling assays and immunoblots (Caspase 12, Dysferlin and LC3) were performed on crude homogenates and SR-enriched microsomal fractions. Results: Aging was associated with increased Caspase 12 and SR dysferlin, as well as a reduced LC3II/I ratio and impaired calcium release. Wheel running partially restored SR calcium release and dysferlin toward younger levels, despite further increases in Caspase 12. Of note, the LC3II/ratio was also partially restored in the running group, suggesting increased autophagy. Discussion: These results suggest that impaired SR function with aging is associated with age-related increases in SR stress, possibly related to reduced autophagy. Long-term volitional exercise improved SR function and markers of autophagy, despite increased Caspase 12, suggesting that running contributed a beneficial stress that differed from the "distress" of sedentary aging. Conclusion: Age-related SR dysfunction may be partially explained by decreased autophagy increasing SR stress.

9.2

IDENTIFICATION OF DIFFERENTIALLY EXPRESSED MRNAS BETWEEN YOUNG AND OLD RATS DURING MUSCLE REGENERATION

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Adult skeletal muscle has a remarkable regenerative capacity. However, skeletal muscle regeneration is markedly impaired with age. We hypothesized that during muscle regeneration the mRNA for regeneration potentiating factor would be present in the damaged muscle of young (3- to 6-mo-old) but reduced in old (30- to 32-mo-old) Fischer 344 x Brown Norway rats. Gene expression levels of >31,000 transcripts were determined by using Affymetrix GeneChip Rat Genome 230 2.0 Array in homogenate samples of tibialis anterior (TA) muscles at 0, 3, and 7 days of muscle regeneration after bupivacaine injection. Each muscle sample was applied to an independent set of arrays. Analysis of microarray data revealed that 301 mRNAs were significantly altered by using two-way ANOVA. Fourteen of the 301 mRNAs were upregulated in young damaged TA muscles (more than 10-fold change) but no increase during regeneration in the old damaged TA muscles (less than 2-fold change), including muscle-specific the bHLH transcription factor myogenin, cyclin-dependent kinase inhibitor 1 (p21), and muscle ankyrin repeat protein family member Ankrd1/CARP. The mRNAs that were differentially expressed between young and old rats could modulate muscle regeneration, and highlight new candidate mechanisms to explain the impaired muscle regenerative capacity with age.

9.3

RAGE AND STAT3 SIGNALING IN CHRONIC AICAR-TREATED YOUNG ADULT AND OLD SKELETAL MUSCLE

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Age-related changes in skeletal muscle are thought to be due in part to increased inflamemation. The receptor for advanced glycation end-products (RAGE) activates intracellular pro-inflammatory pathways and is thought to mediate some of the detrimental effects of aging. AMP-activated protein kinase (AMPK) has anti-inflammatory effects and may be defective in aged skeletal muscle. Our aim here was to determine 1) if RAGE is expressed by aged skeletal muscle fibers and 2) if AMPK activation decreases phosphorylation of the RAGE target STAT3. RAGE protein expression was 218% higher in gastrocnemius muscles from old (O; 30 mo) vs. young adult (YA; 8 mo) Fisher Brown-Norway F1 hybrid rats. Immunohistochemistry showed that RAGE is expressed on the membrane of O but not YA skeletal muscle fibers. To determine the effect of AMPK activation on RAGE signaling, YA (5 mo) and O (22 mo) C57Bl6 mice were injected daily with the AMPK activator AICAR or saline for 4 wks. Although immunodetection of RAGE in mouse skeletal muscle was unsuccessful using our antibody, phosphorylation of STAT3 (downstream of RAGE signaling) was elevated in O vs. YA saline-treated muscle, but was reduced in AICAR-treated O muscles to the level of YA muscles. We conclude that RAGE is expressed in O, but not YA skeletal muscle fibers and that AMPK activation may attenuate RAGE or other pro-inflammatory signaling pathways. Funded by NIAMSD Grant AR-51928 and BYU Gerontology Grant.

9.4

AGE-RELATED DECREMENTS IN HUMAN WHOLE MUSCLE PERFORMANCE CORRELATE WITH SLOWER MYOSIN-ACTIN CROSS-BRIDGE KINETICS

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Age-related skeletal muscle dysfunction may be affected by alterations in myofilament protein quantity and/or function. To evaluate this hypothesis, skeletal muscle structure and function at the whole muscle, single fiber and molecular levels were measured in young (21-35 years) and older (65-75 years) male and female volunteers with similar physical activity levels. After adjusting for muscle size, knee extensor isokinetic torque and power output decreased with age, while isometric torque was maintained. At the molecular level, aging slowed myosin-actin cross-bridge kinetics (longer myosin attachment times and reduced rates of myosin force production) and stiffened the myofilament lattice, especially in females. Decreased whole muscle power output was correlated ($P<0.05$) with these sex-specific molecular changes in myosin heavy chain (MHC) IIA fibers. These sex-specific molecular alterations also lead to higher single fiber isometric tension with age, primarily in females. In conclusion, our results are the first to show that aging alters the contractile function of human skeletal muscle at the molecular level. Reductions in cross-bridge kinetics and/or increased myofilament stiffness with age appear to maintain whole muscle and single fiber isometric contractile function at the expense of dynamic performance. This phenomenon, most notable in females, highlights potential molecular mechanisms underlying the development of physical disability with age. Support: NIH AG-031303.

9.5

AGE-SPECIFIC ADAPTATIONS IN MYOFIBER CONTRACTILE FUNCTION IN RESPONSE TO AEROBIC EXERCISE TRAINING IN YOUNG AND OLDER MEN

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To examine potential age-specific adaptations in skeletal muscle size and myofiber contractile physiology in response to aerobic exercise, seven young (YM; 20±1 yr) and six older (OM; 74±3 yr) men performed 12 weeks of cycle ergometer training. Muscle biopsies were obtained from the vastus lateralis to determine size and contractile properties of isolated slow (MHC I) and fast (MHC IIa) fibers. Aerobic capacity was higher ($P<0.05$) after training in both YM (16±2%) and OM (13±3%). Quadriceps muscle volume was 5±1 and 6±1% greater ($P<0.05$) after training for YM and OM, respectively, which was associated with an increase in MHC I fiber cross-sectional area (CSA), independent of age. MHC I peak power was higher ($P<0.05$) after training for both YM and OM while MHC IIa peak power was increased ($P<0.05$) with training in OM only. MHC I and MHC IIa fiber peak and normalized (P_0/CSA) force were preserved with training in OM while MHC I P_0/CSA and MHC IIa peak force were lower ($P<0.05$) after training in YM. These data suggest improvements in muscle size and aerobic capacity are similar between YM and OM while adaptations in myofiber function showed a general improvement in OM. Training-related increases in MHC I and MHC IIa peak power reveal that skeletal muscle of OM is responsive to aerobic exercise training and further support the use of aerobic exercise for improving cardiovascular and skeletal muscle health in older individuals. *Supported by NIH AG032127 & NASA NNJ06HF59G.*

9.6

CHANGES IN MUSCLE STRENGTH AND BONE MINERAL DENSITY FOLLOWING EXERCISE TRAINING IN OLD ADULTS

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Purpose: To determine effects of 8wks of progressive whole-body training, preceded by 4wks of regional specific (RS) or aerobic exercise training (AE), on bone mineral density (BMD)and muscle strength. Methods: Subjects were >70yrs and randomized to AE or RS for the first 4 wks (Phase 1). AE consisted of 60min of walking/biking at 40-60% of HRR, 3 d/wk. RS consisted of 3-5min of exercise specific to lower and upper body parts, at 40-70% of max strength of the primary muscle group, for 45min, 3 d/wk. After Phase 1, all subjects performed a whole-body program (Phase 2). DXA and strength (Sum of chest/leg press, seated row and handgrip (TOT)) were examined before and after 4 and 12 wks of training. Results: Groups were similar in age and weight. There was a grp*time effect (p=0.006) for TOT (RS: Base: 385, 4wks: 432, 12wks: 502; AE: Base: 385, 4wks: 395, 12wks: 442 kg), and lumbar and thoracic spine BMD ([Lumbar] RS: Base: 1.05, 4wks: 1.09, 12wks: 1.09; AE: Base:1.05, 4wks: 1.06, 12wks: 1.05g/cm2; [Thoracic] RS: Base: 0.98, 4wks: 1.00, 12wks: 1.04; AE: Base: 0.98, 4wks: 1.00, 12wks: 0.98g/cm2). There also was a main effect for pelvis BMD (p=0.003). Conclusion: Progressive whole-body training results in significant gains in strength and BMD. The gains after phase 2 were superior in those who used RS during phase 1. These results suggest RS serves as a primer for musculoskeletal gains in the elderly.

9.7

NOVEL PERIPHERAL TRAINING AS A PRIMER FOR INCREASED GAINS IN FUNCTIONAL CAPACITY IN FRAIL ELDERLY

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The purpose of this study was to determine: (1) differences between 4 weeks of a regionally specific training stimulus (RSTS) versus standard aerobic exercise training (AET) on VO2peak and combined muscle group 1RM strength (C1RM); (2) the effects of subsequent 8 weeks of progressive whole-body training protocol on VO2peak and C1RM. Frail (walked between 218-490yds in 6 min) subjects >70 yrs were randomized to 4wks of AET (60min of walking/biking at 40-60% of HRR, 3d/wk) or RSTS [specific muscle group exercises focused on the calf, thigh, buttocks, arms, shoulders, and torso, performed for 3 to 5 min, at ~40-70% of the MVC (60 min total), 3d/wk] (Phase 1). All subjects then advanced to a well-rounded, whole-body exercise program according to ACSM guidelines (Phase 2). VO2peak and C1RM were examined at baseline and after phases 1 and 2. Both groups included 54 subjects (RSTS=14 men; AET=16 men), age =76±5yrs. After adjustment for baseline (16.9ml/kg/min), there was a group*time effect in favor of RSTS for VO2peak following phase 2 (19.3 vs. 18.4ml/kg/min, $p<0.05$). RSTS also showed greater gains in C1RM following both phase 1 (+47lbs vs. +7lbs, $p<0.01$) and phase 2 (+51lbs vs. +30lbs, $p<0.01$). These results suggest initial RSTS may serve as an effective modality for enhancing strength and aerobic fitness in the elderly. Supported by 1RC1AG035822-01 and Duke Pepper Center OAIC (AG0287) to JDA.

9.8
LONG-TERM CREATINE SUPPLEMENTATION COMBINED WITH RESISTANCE TRAINING IMPROVES FUNCTIONAL CAPACITY BUT NOT MAXIMAL STRENGTH IN OLDER WOMEN

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This study examined the effects of long-term creatine supplementation combined with resistance training (RT) on the one-repetition maximum (1RM) strength, motor functional performance (e.g., 30-s chair stand, arm curl, and getting up from lying on the floor tests) and body composition (using DEXA scans) in older women. Eighteen healthy women (64.9±5.0 yr) were randomly assigned in a double-blind fashion to a creatine (CR, N=9) or placebo (PL, N=9) group. Both groups underwent a 12-wk RT program (3d·wk-1), consuming an equivalent amount of either creatine (5g ·d1) or placebo. This study was conducted in accordance with procedures as set forth in Declaration of Helsinki. After 12 wk, the CR group experienced a greater ($P<0.01$) increase in training volume (Δ%, CR: 294.1 vs. PL: 129.9), fat-free mass (Δ%, CR: 3.2 vs. PL: no change) and muscle mass (Δ%, CR:3.7 vs. PL:0.9) and were more efficient in performing submaximal strength functional tests than the PL group. However, there was a similar increase between the groups for the 1RM bench press, biceps curl and knee extension from pre- to post-test. No changes ($P>0.05$) in body mass or % body fat were observed. The results indicate that long-term creatine supplementation combined with RT improves the ability to perform submaximal-strength functional tasks and promotes a greater increase in fat-free mass and muscle mass in older women. However, creatine supplementation fails to promote additional benefits to maximal strength.

9.9
EFFECT OF INCREASING ESSENTIAL AMINO ACID AVAILABILITY FOLLOWING RESISTANCE EXERCISE ON SKELETAL MUSCLE LET-7 MIRNA EXPRESSION IN OLDER MEN

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We have previously observed that relative to young individuals, older adults have an impaired muscle protein anabolic response to resistance exercise (RE). However, provision of essential amino acids (EAA) postexercise overcomes this impairment. In addition, older adults have a higher basal expression of skeletal muscle Let-7 microRNAs (miRNA), which is indicative of impaired cell growth, proliferation and cell cycle function. We hypothesized that increasing EAA availability following resistance exercise would reduce skeletal muscle Let-7 miRNA expression concomitant with increased expression of genes associated with satellite cell regulation and muscle protein anabolism (Pax7, MyoD) in older adults. Older men performed a bout of high-intensity resistance exercise and at 1h postexercise ingested 10g of EAA. Muscle biopsies (*vastus lateralis*) were obtained at rest and 2, 5 and 24h postexercise to examine miRNA and mRNA expression. Let-7a, -7b, and -7e expression was reduced by ~10% at 2 and 5h and by ~15% at 24h, with Let-7e showing the greatest reduction at all timepoints. MyoD expression was increased at all timepoints and Pax7 expression was increased at 24h. These preliminary data suggest that EAA ingestion following RE may improve satellite cell regulation and muscle protein anabolism by altering Let-7 miRNA expression. NIAMS R01AR049877, NIA P30AG024832, NCRR 1UL1RR029876, NIDRR H133P110012.

9.10
ESSENTIAL AMINO ACID INGESTION FOLLOWING AEROBIC EXERCISE IN OLDER ADULTS ENHANCES SKELETAL MUSCLE AMINO ACID TRANSPORTER EXPRESSION

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Older adults are at an increased risk of frailty and sarcopenia, but exercise and nutritional interventions may prevent or delay these conditions. The objective of this study was to examine the potential of aerobic exercise combined with essential amino acid (EAA) supplementation to enhance amino acid (AA) transporter mRNA expression in skeletal muscle of older adults. Healthy untrained older adults (65-85 y) were recruited for this study. After a resting vastus lateralis muscle biopsy, subjects walked on a treadmill for 45 min at approximately 70% of their heart rate max. Immediately after exercise subjects consumed either a placebo (PLA) or 15 g of a leucine-enriched EAA beverage. Another muscle biopsy was collected three hours post-beverage consumption. Real-time qPCR was used to measure mRNA expression of select AA transporters. Ingestion of EAA post exercise increased CAT1 and SNAT2 mRNA expression ~2 fold and PAT1 mRNA expression ~4 fold; PLA had less than two-fold increases in all measured genes. In conclusion, aerobic exercise combined with EAA supplementation enhances the expression of select AA transporter mRNA in the skeletal muscle of older adults. Future work will identify whether enhanced AA transporter expression is linked to mTOR signaling and muscle growth during aerobic exercise training. NIH/NIA R01 AG030070.

9.11
AEROBIC EXERCISE ATTENUATES THE AGE-ASSOCIATED DETERIORATION OF HUMAN SKIN

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Exercise is associated with a lower risk of cancer, neurological disease and diabetes, suggesting systemic benefits that may oppose the aging process. In order to better understand the underlying mechanism(s) for this reduction in disease incidence, we investigated the effects of long-term (>10 years) and short-term (3 months) aerobic exercise (AE) on the biological aging of human skin. Skin biopsies were acquired from the sun naïve upper buttocks of individuals throughout the lifespan (20-86 y) that regularly exercised (N=51, ACT) as well as those who remained largely sedentary (N=56, SED). A subset of SED older adults (>64 y) underwent 3 months of AE training. Epidermal stratum corneum (SC) thickness increased with age, was higher in SED compared to ACT subjects and short-term AE reduced SC thickness in SED older adults ($P<0.05$). Dermal collagen content was reduced with age, was higher in ACT subjects vs. SED and increased with AE training in elderly, SED subjects ($P<0.05$). Similarly, average skin telomere length was higher in ACT vs. SED ($P<0.05$), decreased with age ($P<0.05$) and tended to increase with AE in older adults ($P=0.08$). Overall, these results demonstrate that aerobic exercise can mitigate the effects of aging on skin when performed habitually as well as partially reverse these alterations in previously inactive older adults. Supported by NSERC.

10:0 PERSONALIZED EXERCISE PRESCRIPTION BASED UPON INTEGRATIVE BIOLOGY

10.2
ADVERSE AND ENHANCED RESPONDERS TO THE SAME EXERCISE EXPOSURE

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The response of VO_2max and cardiometabolic risk factors to exercise training is characterized by a significant genetic component. Transcriptomics and genomics can be used to investigate the molecular basis of this variation. Whole-genome transcriptomics from skeletal muscle yielded a panel of 29 transcripts whose abundance profile accounted for 58% of the variance in VO_2max gains among 24 sedentary men trained for 6 weeks. A genome-wide association study in the HERITAGE Family Study was based on 324,611 single-nucleotide polymorphisms (SNPs). The top 21 SNPs explained 49% of the variance in VO_2max trainability. The sum of favorable alleles was used as a genomic predictor score, with a theoretical range from 0 (no beneficial alleles) to 42 (2 copies of the beneficial alleles at all 21 loci). The difference in VO_2max trainability between those carrying 9 or less of these alleles and those carrying 19 or more represented a 3-fold range. An examination of the response distribution for risk factor traits in HERITAGE yielded suggestive evidence that there were adverse responders. Exploration of adverse responses in 5 other exercise intervention cohorts confirmed that the prevalence reached about 10% for any given risk factor with about 7% experiencing multiple adverse responses. The identification of transcriptomic and genomic predictors of the ability to respond to regular exercise will illuminate the underlying biology and provide screening tools for potentially harmful response patterns. Timmons JA et al, *J Appl Physiol* 108, 1487-96, 2010. Bouchard C et al, *J Appl Physiol* 110, 1160-70, 2011. Bouchard C et al, *PLoS One* 7, e37887, 2012.

10.3
GENE-ACTIVITY/INACTIVITY INTERACTION

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A family history of type 2 diabetes (e.g. first degree relatives, FDR) and low birth weight (LBW) are risk factors of type 2 diabetes and predisposes to type 2 diabetes via genetically and environmental susceptibility, respectively. Providing a careful matching (e.g. age, habitual physical activity, body composition etc) these two groups represents very useful "models" for studying the influence of genes and environmental factors on responses to alterations in the daily physical activity level. Severe physical inactivity could purposely unmask their predisposal and reveal a larger vulnerability to physical inactivity than those without preexisting risk factors. Furthermore, comparisons between FDR and LBW in the response to alterations in the daily physical activity level may exemplify the relative influence of genes and environmental factors. We have studied young men before and after a ten-day bed rest intervention study, which was followed by a four wk retraining program. Thirteen FDR (age: 26 ± 1 yr; body weight 80 ± 3 kg; BMI: 25 ± 1; VO2max: 39 ± 1 ml/min/kg), twenty LBW (age: 26 ± 1 yr; body weight 72 ± 3 kg; BMI: 23 ± 1; VO2max: 44 ± 3 ml/min/kg) and twenty healthy controls (CON) (age: 25 ± 1 yr; body weight 78 ± 2 kg; BMI: 24 ± 1; VO2max: 44 ± 1 ml/min/kg) was included in the study. Insulin secretion and action, endothelial function, inflammation, and muscle transcriptional and translational changes was studied in a comprehensive experimental program. (Sonne MP, Alibegovic AC, Hojbjerre L, Vaag A, Stallknecht B and Dela F. Effect of 10 days of bedrest on metabolic and vascular insulin action: a study in individuals at risk for type 2 diabetes. J Appl Physiol 108: 830-837, 2010.).

10.4
HIGH RESOLUTION PHYSIOLOGICALLY-BASED PHENOTYPING ALONG WITH AN INTEGRATED MEDICAL RECORD SYSTEM TO PROVIDE INSIGHT ABOUT INDIVIDUAL PATIENTS

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It is hoped that genetic information on individual patients will yield insights into pathophysiology and disease risk for both common and uncommon diseases. If successful then so-called "individualized medicine" will emerge. In this context, population based genetic studies on issues related to disease risk sometimes use data gleaned from medical records in an effort to link genetic variants with disease phenotypes. In this talk I will review the types of information available in typical medical records systems and the many limitations with it. I will also discuss issues related to data curation and other challenges associated with using essentially clinical tools for research purposes. These challenges are amplified by the loss of what might generally be described as "clinical physiology" expertise and capabilities at many (most?) medical institutions. Several recent examples of how high resolution phenotyping of humans along with genetic data have yielded insight into disease risk will be discussed.

10.5
LIFESTYLE MEDICOPHARMACOGENETICS

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There are very important interactions between genetic variation, exercise and pharmacologic therapies when considered with respect to therapeutic interventions for a variety of health and disease conditions. The concept that exercise is the best of all medicines has been developing over the past decade, leading to the Exercise is Medicine™ initiative being led by the American College of Sports Medicine. However, as will be discussed in this session, just as is the case with pharmacologic therapy, there is a wide range of responses—not all positive—when exercise is directed at improving a specific medical issue. What is relatively understudied is the variation in responses that are observed when exercise as a lifestyle medicine agent is combined with medical therapy, especially when directed at a specific health condition. As an example of how different exercise intensities and their interactions with medications is of potential import, we have observed that women on combined hormone replacement therapy had a robust improvement in insulin-induced uptake of glucose into skeletal muscle in response to vigorous intensity exercise training, whereas women not on hormone replacement therapy had almost no improvement—on average—in these responses. In contrast, moderate intensity exercise effects were relatively invariant to hormone replacement effects in women. What is known about the three-way interactions of genetic variants, exercise as a therapeutic intervention (lifestyle medicine) and pharmacologic therapy will be discussed. Ref: Huffman KM, Slentz CA, Johnson JL et al., Mediators of exercise training-induced improvements in insulin action for sedentary overweight men and post-menopausal women. Metabolism 57:888-895, 2008.

11.0: ACETYLATION: LINKING CHANGES IN NAD TO METABOLISM AND GROWTH

11.2
PATHOPHYSIOLOGICAL SIGNIFICANCE AND THERAPEUTIC POTENTIAL OF NAMPT-MEDIATED NAD^+ BIOSYNTHESIS IN METABOLIC DISEASES

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Sedentary lifestyles and calorie-rich diets have overwhelmed our adaptive metabolic pathways, contributing to the current epidemic of obesity and type 2 diabetes (T2D). In mammals, one such adaptive metabolic response is mediated by nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting NAD^+ biosynthetic enzyme, and the NAD^+-dependent deacetylase SIRT1. An accumulating body of evidence suggests that NAMPT-mediated NAD^+ biosynthesis and SIRT1 together play a pivotal role in numerous biological processes, such as metabolism, stress response, and inflammation. Previously we discovered that NAMPT and SIRT1 comprise a novel transcriptional-enzymatic feedback loop for the regulation of circadian rhythm, thus demonstrating an interesting connection between metabolism and physiological rhythmicity. We have recently found that NAMPT-mediated NAD^+ biosynthesis is severely compromised in metabolic organs of high-fat diet-induced T2D mice. Remarkably, nicotinamide mononucleotide (NMN), a product of NAMPT reaction, ameliorates glucose intolerance and insulin resistance by restoring NAD^+ levels and SIRT1 activity. Furthermore, NMN improves metabolic complications in age-induced T2D mice. These findings will provide great insights into the development of "nutriceutical" intervention, using key NAD^+ intermediates, against metabolic diseases. REFERENCES: Yoshino J, Mills KF, Yoon M, Imai S. "Nicotinamide mononucleotide, a key NAD^+ intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice". Cell Metab. 2011;14(4):528-36.

11.3
REGULATION OF THE ADAPTIVE RESPONSE TO EXERCISE BY THE ACETYLTRANSFERASE GCN5

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In the last decade, reversible acetylation of protein lysine residues has garnered significant attention as a fundamental means of modulating cellular metabolism. Protein acetylation status represents a balance between the activity of acetyl-transferases (that add acetyl groups to proteins), and deacetylases (that remove acetyl groups). Whilst the majority of work within this field has focused on the sirtuin (SIRT) family of protein deacetylases, little attention has been given to understanding the reciprocal role of aceyltransferases. The acetyltransferase, general control of amino acid synthesis 5 (GCN5), has been implicated in the regulation of mitochondrial metabolism due to its ability to acetylate and suppress the activity of the transcriptional co-activator, PGC-1α. In this talk, the role and regulation of GCN5 will be discussed in the context of mitochondrial metabolism, with particular focus on recent data from our laboratory indicating novel regulation of GCN5 (and hence PGC-1α acetylation) in response to endurance exercise. This talk will also discuss the therapeutic potential of targeting GCN5 in order to modulate mitochondrial function.

11.4
SIRTUINS: REGULATING METABOLISM WITHIN THE MITOCHONDRIA

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Sirtuins are a family of NAD+-dependent protein deacetylases that have been shown to regulate cell survival and longevity, and have important metabolic effects. SIRT3 is localized to the mitochondria and regulates the acetylation status of several proteins. Acetylation is increasingly recognized as an important post-translational protein modification, particularly in metabolic regulation, and over one-third of all proteins in the mitochondria are acetylated. SIRT3 is upregulated during fasting, and plays an important role in nutrient sensing and energy homeostasis under metabolically stressed conditions. During high-fat diet feeding, SIRT3 is down regulated, and hepatic mitochondrial protein acetylation is elevated. Mice lacking SIRT3 (SIRT3KO) placed on a high-fat diet show accelerated obesity, insulin resistance, hyperlipidemia, and steatohepatitis compared to wt mice. We further identify a single nucleotide polymorphism in the human SIRT3 gene that shows a strong genetic association with the metabolic syndrome. New post-translational acyl modification can also regulate metabolism. Our findings show loss of SIRT3 and dysregulation of mitochondrial protein acylation is a crucial metabolic regulatory axis in both mice and in humans. (Work supported by AHA 12SDG8840004 and 12IRG9010008). References: Anderson, K. A. & Hirschey, M. D. Mitochondrial protein acetylation regulates metabolism. Essays Biochem. 52, 23–35 (2012); Hirschey, M. D. Old Enzymes, New Tricks: Sirtuins Are NAD(+)-Dependent De-acylases. Cell Metab (2011) 14, 718–719 (2011); Hirschey, M. D. et al. SIRT3 Deficiency and Mitochondrial Protein Hyperacetylation Accelerate the Development of the Metabolic Syndrome. Mol Cell 44, 177–190 (2011); Hirschey, M. D. et al. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature 464, 121–125 (2010).

11.5
THE HISTONE DEACETYLASE SIRT6, A CRITICAL MODULATOR OF GLUCOSE METABOLISM AND TUMORIGENESIS

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Efficient glucose metabolism is critical for maintaining cellular viability. Under hypoxia or nutrient stress, metabolism is switched to glycolysis, increasing lactate production and reducing mitochondrial respiration, a switch known to play an important role in cancer cells, as defined by Otto Warburg decades ago. Little is known whether chromatin plays a role in carbohydrate flux. We discovered that the mammalian SIRT6 is a chromatin factor that influences glucose metabolism and DNA repair. In mice, SIRT6-deficiency provokes a profound and lethal hypoglycemia which culminates in accelerated death. At the cellular level, SIRT6 inactivation leads to increased cellular glucose uptake, higher lactate production and decreased mitochondrial activity. SIRT6 directly regulates expression of several key glycolytic genes. In this context, SIRT6 functions at chromatin to co-represses Hif1α, acting as a histone H3 lysine9 (H3K9) deacetylase to inhibit expression of Hif1α-target genes (Zhong et al, 2010). Strikingly, our new studies indicate that SIRT6, in contrast to other HDACs, appears to regulate transcriptional elongation, a novel function for histone deacetylases. Furthermore, the "glycolytic switch" observed in the absence of

SIRT6 provides a unique growth advantage in the context of tumorigenesis, suggesting that SIRT6 might play a critical role in modulating the Warburg effect.

12.0: CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM ANIMAL STUDIES

12.2
EXERCISE AND CARDIAC ARRHYTHMIA

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Sudden cardiac death resulting from ventricular tachyarrhythmias remains the leading cause of death in industrially developed countries. Yet, despite the enormity of this problem, both the identification of factors contributing to ventricular fibrillation as well as the development of safe and effective anti-arrhythmic agents remains elusive. Alterations in cardiac autonomic regulation that occur as a consequence of cardiac disease increase the risk for malignant ventricular arrhythmias. In particular, a subnormal cardiac parasympathetic regulation coupled with an elevated cardiac sympathetic activation following myocardial infarction can lead to intracellular calcium dysregulation and arrhythmias (1). As it is well established that exercise training improves cardiac autonomic balance (increasing cardiac parasympathetic regulation and restoring a more normal beta-adrenoceptor balance), this intervention could protect against life-threatening changes in cardiac rhythm (1). Indeed, a growing body of experimental and epidemiological data suggests that aerobic exercise conditioning can dramatically reduce cardiac mortality in both healthy individuals and patients with pre-existing cardiac disease (1). Conversely, a sedentary life-style is strongly associated with an enhanced risk for chronic debilitating diseases (1). Thus, prudently designed exercise training programs may reverse the autonomic neural remodeling induced by cardiac disease and thereby enhance the electrical stability of the heart in individuals shown to be at an increased risk for sudden cardiac death. [Reference: 1. Billman GE, Am J Physiol Heart Circ Physiol 297:H1171-H1193, 2009].

12.4
EXERCISE, SARCOLEMMAL KATP CHANNELS AND CARDIOPROTECTION

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Physical activity is one of the most important determinants of cardiac function. The ability of the heart to increase delivery of oxygen and metabolic fuels relies on an array of adaptive responses necessary to match bodily demand while avoiding exhaustion of cardiac resources. The ATP-sensitive potassium (K_{ATP}) channel has the ability to adjust cardiac membrane excitability in accordance with the metabolic status of the cell, and up-regulation of its expression that occurs in response to exercise could represent a critical element of this adaption. However, the mechanism by which K_{ATP} channel expression changes result in a beneficial effect on cardiac excitability remains to be established. We demonstrate that an exercise-induced rise in K_{ATP} channel expression enhanced the rate and magnitude of action potential shortening in response to heart rate acceleration. This adaptation in membrane excitability promoted significant reduction in cardiac energy consumption. Genetic disruption of normal K_{ATP} channel pore function abolished the exercise-related improvement in action potential duration adjustment and caused increased cardiac energy consumption. Thus, an expression-driven enhancement in the ability of K_{ATP} channels to respond to alterations in cardiac workload represents a previously unrecognized mechanism for adaptation to physical activity and a potential target for cardioprotection. NIH HL093368. Zingman LV, Zhu Z, Sierra A, Stepniak E, Burnett CM-L., Maksymov G, Anderson ME,. Coetzee WA, Hodgson-Zingman DM. Exercise-induced expression of cardiac K_{ATP} channels promotes action potential shortening and energy conservation. *J Mol Cell Cardiol.* 51:72-91, 2011.

12.5
CARDIAC KATP CHANNELS AND EXERCISE CARDIOPROTECTION

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Ischemic heart disease is a leading cause of morbidity and mortality in industrialized nations, while exercise is an important countermeasure against ischemic heart injury. Exercise induced cardioprotection research reveals that multiple cellular mechanisms mediate protection against ischemia-reperfusion (IR) injury. Within exercised hearts, protective mechanisms appear to be unique to major clinical benchmarks of IR injury in that different mechanisms protect against IR-induced ventricular arrhythmias, contractile dysfunction, and tissue death. Among recently studied cardioprotective mechanisms are the ATP-sensitive potassium channels (KATP) located on the sarcolemma and inner membrane of the mitochondria. Mitochondrial KATP channels appear to mediate protection against ventricular arrhythmias experienced during IR, while sarcolemmal KATP channels are responsible for partially preventing tissue death in exercised hearts. Observed tissue sparing effects following experimental IR challenges prevent myocardial tissue necrosis, but not apoptosis. Preliminary evidence also suggests that both mitochondrial and sarcolemmal KATP channel activity within exercised hearts may improve cardiac tissue viability through preservation of autophagy in the hours immediately following IR.

13.0: FIT, FAT AND LEAN LIVER: EXERCISE ADAPTATIONS IN NON-TRADITIONAL TISSUES

13.3
INTRINSIC FITNESS AND EXERCISE PREVENT HEPATIC LIPOTOXICITY

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Hepatic steatosis, the excessive storage of lipids in the liver, increases risk for liver injury (steatohepatitis and cirrhosis), and is also linked to hepatic insulin resistance and the metabolic syndrome. Both physical inactivity and low aerobic fitness are linked to increased prevalence of steatosis, while exercise is an effective treatment, however, liver specific mechanism(s) for these associations remain poorly understood. We have shown that daily physical activity (voluntary wheel running) both effectively prevents and treats hepatic steatosis in a hyperphagic, obese rat model. We have also shown that sedentary rats bred to have reduced fitness (low capacity runners (LCR)) display increased susceptibility to hepatic steatosis and aging induced liver injury compared to sedentary rats bred for high fitness (high capacity runners (HCR)). In both cases, daily physical activity or high aerobic fitness is associated with higher hepatic mitochondrial content and complete fatty acid oxidation, suggesting that these factors play a role in susceptibility for steatosis. Current studies are testing if there are differential responses in lipid metabolism between low fit-LCR and high fit-HCR rats with acute and chronic high fat diets known to induce steatosis and if genetically altering mitochondrial content and function modifies these responses.

13.4
EXERCISE, IL-6 AND ADIPOSE TISSUE METABOLISM

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Interleukin 6 (IL-6) has been extensively studied over the past decade with a particular emphasis being placed on its role as a muscle-derived signaling factor during exercise. By virtue of its essential role in locomotion and the fact that it accounts for the vast majority of systemic glucose disposal and fatty acid (FA) oxidation, the regulation and function of IL-6 in the context of exercise has been examined primarily in skeletal muscle. However, adipose tissue (i.e. fat) is increasingly being recognized as a critical player in systemic fuel metabolism. In this regard our laboratory has been investigating the effects of IL-6 on adipose tissue metabolism both during, and in the recovery from, exercise. In our hands we have not been able to demonstrate a direct role for IL-6 in modulating the effects of exercise on adipose tissue lipolysis or gene expression. However, in the post-exericse period it would appear that adipose tissue derived IL-6 may play a unique and important role in the control of adipose tissue metabolism. We now have evidence to suggest that adipose tissue IL-6 may increase fatty acid efflux through an impairment of insulin action and through an indirect modulation of the lipolytic signalling pathway.

13.5
ENERGETIC REGULATION OF WHITE ADIPOSE TISSUE METABOLISM

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Obesity is a dysfunctional metabolic alteration characterized by the excessive expansion of the white adipose tissue (WAT) that develops as a result of prolonged positive energy balance. Therefore, strategies aimed at depleting the fat content of the WAT are of great relevance for the treatment of obesity and its co-morbidities. In this context, several studies have demonstrated that metabolism of the WAT can be remodeled to increase its ability to dissipate energy within itself and reduce lipid storage. Studies in rodents show that this can be achieved through chronic pharmacological activation of the cellular energy sensor AMP-activated protein kinase. This approach up-regulates the oxidative machinery of the WAT, increases spontaneous physical activity and whole-body energy expenditure, and reduces adiposity. More recently, it was also demonstrated that chronic endurance exercise induces the expression of thermogenic genes in the WAT conferring to it a phenotype typical of brown adipose tissue. Interestingly, these effects seem specific to subcutaneous fat depots, since visceral fat depots show very limited ability to acquire a “brown-like” phenotype under chronic endurance training conditions. Unraveling the mechanisms by which pharmacological agents and endurance exercise remodel WAT metabolism may lead to the development of new strategies to improve the long-term success rate in the treatment of obesity and its co-morbidities. Reference: Gaidhu MP, Frontini A, Hung S, Pistor K, Cinti S, Ceddia RB (2011). Chronic AMP-kinase activation with AICAR reduces adiposity by remodeling adipocyte metabolism and increasing leptin sensitivity. J Lipid Res. 52(9):1702-11.

15.0: CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM HUMAN STUDIES

15.5
EXERCISE ATTENUATES THE PREMATURE CARDIOVASCULAR AGING EFFECTS OF TYPE 2 DIABETES MELLITUS

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Type 2 diabetes mellitus (T2D) is an example of a disease process that results in decrements in function additional to those imposed by the inexorable 'primary aging' process.

These decrements due to disease, rather than primary aging, can be termed 'secondary aging', and include the premature development (as early as adolescence) of asymptomatic preclinical cardiovascular abnormalities (e.g. endothelial dysfunction, arterial stiffness, diastolic dysfunction), as well as impaired exercise performance. These abnormalities are important, as they are associated with greater cardiovascular morbidity and mortality in people with and without T2D. A better understanding of the pathophysiology of secondary cardiovascular aging in people with T2D is warranted, and an evaluation of the benefits of existing treatments for these abnormalities is useful (e.g. exercise training). The focus of this review is to discuss the data relevant to the following key postulates: (a) T2D causes premature cardiovascular aging; (b) in contrast to primary cardiovascular aging, the premature cardiovascular aging of T2D may be modifiable with exercise. The exercise-focused perspective for this review is appropriate because impairments in exercise performance are markers of premature cardiovascular aging in T2D, and also because exercise training shows promise to attenuate some aspects of cardiovascular aging during the preclinical stage. Support: NIH/NCRR Colorado CTSI Grant Number KL2 TR000156, and institutional support from the Center for Women's Health Research and Division of General Internal Medicine. Reference: Huebschmann AG, Kohrt WM, Regensteiner JG, Exercise attenuates the premature cardiovascular aging effects of type 2 diabetes mellitus, Vasc Med 16(5):378-90, 2011.

16.0: SKELETAL MUSCLE LIPID DROPLET BIOLOGY IN EXERCISE AND DISEASE

16.3
EXERCISE-INDUCED REGULATION OF LIPID DROPLET PROTEINS IN HUMANS

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Excessive skeletal muscle fat (intramyocellular lipids, IMCL) accumulation is linked with the development of muscle insulin resistance and mitochondrial lipotoxicity. Paradoxically, IMCL is also increased in highly insulin sensitive and healthy endurance trained athletes, suggesting that IMCL per se are not detrimental to muscle function. Rather, lipid-droplet dynamics appear to determine the relationship between muscle fat accumulation and cellular function. Lack of ATGL, the main lipase in skeletal muscle responsible for hydrolysis of IMCL results in massive fat accumulation in skeletal and cardiac muscle, and cardiac failure. On the other hand, overexpression of PLIN2 and PLIN5, the main lipid-droplet coat proteins in muscle also result in massive fat accumulation, but protect muscle against lipid-induced insulin resistance. Interestingly, endurance trained athletes are also protected against lipid-induced insulin resistance and are characterized by elevated expression of lipid droplet coating genes as well as gene expression of the major lipases. Furthermore, an endurance and resistance training program in type 2 diabetic patients improves muscle insulin sensitivity in parallel with increases in LD-coat protein content. Together, these data suggest that for a metabolic healthy skeletal muscle a proper balance between muscle fat content, oxidative capacity and lipolytic action is required. Reference: Bosma, M., Kersten, S., Hesselink, M.K.C., Schrauwen, P. Re-evaluating lipotoxic triggers in skeletal muscle: relating intramyocellular lipid metabolism to insulin sensitivity. Prog Lipid Res, 51 (1), 36-49, 2012.

16.4
CARDIAC COORDINATION OF LIPID STORAGE AND UTILIZATION

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Excess accumulation of lipids in oxidative tissues in obesity and diabetes can cause cellular dysfunction, particularly in the heart. Growing evidence indicate that packaging and location of lipid stores in cardiomyocytes determine the impact of excess fat on cardiac function and structure. Previous work by us and others established that lipid droplets (LDs) are metabolically associated with mitochondria and that they protect mitochondria from lipotoxicity during fasting and exercise, but cease to be protective when their number and size increase and reach extremely high levels. Hence, it is clear that development of tissue lipotoxicity and dysfunction is not simply due to the presence of LDs in cardiac muscle but due at least in part to alterations in LD function. To directly examine the function of cardiac LDs by overexpressing perilipin 5, a lipid droplet associated protein and member of the perilipin protein family. To investigate perilipin 5 function in vivo, we obtained transgenic mice with heart-specific plin5 over-expression (MHC-Plin5). These mice have a strong cardiac LD phenotype. Hearts from MHC-plin5 mice expressed at least 20-fold higher levels of plin5 and exhibit a 3.5- fold increase in triglyceride content versus non-transgenic littermate. Chronic cardiac excess of LDs was found to result in mild heart dysfunction with decreased expression of a subset of PPARα target genes, decreased mitochondria function and left ventricular concentric hypertrophia. Lack of more severe heart function complications may have been prevented by a strong increased expression of oxidative induced genes via NF-E2-related factor 2 pathway. Our results suggest that perilipin 5 plays an important role in stabilizing cardiac LDs and promote cardiac steatosis without major heart function impairment. NIH/NIDDK RO1 DK 075017, AHA Grant in Aid 11GRNT7600027, P30 DK072488-01, VA GRECC.

18.0: MICROCIRCULATION

18.1
CHRONIC -(-)EPICATECHIN ADMINISTRATION DOES NOT AFFECT CONTRACTING SKELETAL MUSCLE MICROVASCULAR OXYGENATION

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The flavanol **-(-)**epicatechin (EPI) is a naturally occurring component of cocoa, consumption of which is associated with numerous cardiovascular health benefits. Chronic EPI reportedly augments mouse skeletal muscle capillarity and mitochondrial density (Nogueira et al, J Physiol, 589, 2011). These effects may translate to improved skeletal muscle O_2 delivery-utilization matching (i.e. ↑ microvascular O_2 pressure (PO_2mv)) during contractions. We tested the hypothesis that EPI would elevate PO_2mv at rest and contractions. Rats were administered EPI (2mg/kg , n=5) or water (CON; n=5) via oral gavage twice daily for 21 days. PO_2mv was measured via phosphorescence quenching in the spinotrapezius muscle at rest and during 180 s of 1 Hz twitch contractions. EPI did not change resting baseline PO_2mv (EPI=29±4; C=30±2 mmHg; p>0.05). Following the onset of contractions the time delay (EPI=9±1; C=8±2 s; p>0.05) and time constant (time to 63% of transient response, EPI=16 ±4; C=23±3 s; p>0.05) of the PO_2mv fall were not altered by EPI nor was contracting steady-state PO_2mv (EPI=18±4; C=19±2 mmHg; p>0.05). Despite previous reports of the efficacy of EPI to improve the O_2 transport pathway, the present data indicate that chronic EPI treatment (2mg/kg) does not improve skeletal muscle microvascular oxygenation at rest or during contractions. (Funding: ACSM, AHA Midwest Affiliate 0750090Z, NIH HL-108328).

18.2
RELATION OF ARTERIO-VENOUS DIFFERENCES IN NITRATE AND NITRITE TO OXYGEN CONTENT AND ACID BASE STATUS

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We had two aims with the study 1) To evaluate the influence of acid base state and the oxygenation of the blood on the Nitrate and Nitrite concentration 2) To test whether NO3 and NO2 in arterialized blood of an superficial hand vein differs from arterial blood. **METHODS:** 5 subjects (3 males and 2 females) took part in the study. No prescription related to food intake was given. Blood was sampled from the arteria radialis, a cubital vein and a superficial hand vein. The hand was warmed by a heating pad. Acid base status was measured by an ABL 520 and plasma NO2 and NO3 by mass-spectroscopy. **RESULTS:** Oxygen saturation was 98 % (art), 58 % (cub), and 90% (hand). The respective [NO3] were 51.53, 47.14, and 50.35 µmol/l. Cub was significantly lower than art ($p<0.02$). The differences between hand and art were not significant ($p<0.76$). [NO2] were 0.98 (art), 0.98 (cub), and 0.95 nmol/l (hand). None of the differences between the sampling sites was significant. No meaningful correlation between NO3 and HBO2, PCO2, and pH could be found. The same holds true for [NO2]. There was no significant correlation between [NO3] and [NO2]. **CONCLUSION:** 1) Under resting conditions there seems to be no influence of the acid base status and the oxygenation on the concentrations of NO3 and NO2. 2) In terms of [NO3] and [NO2] blood from an arterialized hand vein corresponds to arterial blood.

18.3
FOXO1 AND FOXO3A ARE INVOLVED IN THE REGULATION OF EXERCISE INDUCED ANGIOGENESIS

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The Forkhead Box “O” (FoxO) family of transcription factors are known to be anti-angiogenic. We hypothesized that downregulation of FoxO1 and FoxO3a in capillaries in response to repeated aerobic exercise contributes to the typically observed angiogenic response. In mice exercised on a treadmill, both FoxO1 and FoxO3a protein in plantaris muscle significantly increased after an acute exercise bout, then decreased after 5 days of training. Conditional deletion of FoxO1,3,4 (MxCre:FoxO1,3,4$^{fl/fl}$) in mice resullted in reduced vascular endothelial expression of FoxO1 and 3a, and promoted an earlier increase in capillary number, which was detectable after 7 days of training compared to 14 days in wildtype littermates. We assessed FoxO protein levels in humans in response to prolonged (6 weeks) training. These subjects were classified retrospectively as high or low responders, based on their % increase in VO_2max. Following training, FoxO1 and FoxO3a levels were elevated in the high but not the low responder group. Our results demonstrate that FoxO1 and FoxO3a are down-regulated in response to short term training, and that further reduction in FoxO proteins accelerates the angiogenic response. In contrast, an increase in FoxO proteins following prolonged training, as seen in the human high responder group, correlates with markers of matrix synthesis and may indicate a role for FoxO proteins in stabilizing the newly expanded vascular network. Funded by CIHR.

18.4
MYOCYTE-DERIVED VEGF REGULATES ADAPTATIONS TO INCREASED BLOOD FLOW IN SKELETAL MUSCLE

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Vascular endothelial growth factor (VEGF) is a key regulator of vascular remodeling, and can be produced by both mesenchymal and endothelial cells. Skeletal muscle angiogenesis can be initiated by either metabolic or hemodynamic stimuli. Skeletal myocyte VEGF is required for exercise-induced angiogenesis. We hypothesized that muscle-derived VEGF is not required for vascular adaptations to increased blood flow. Myocyte-specific VEGF deleted ($mVEGF^{-/-}$) mice or wildtype littermates were treated with prazosin for 14 days to induce a sustained increase in blood flow. The baseline capillary to fiber ratio, vascular area and number of small smooth muscle actin positive vessels were reduced in the EDL muscles of $mVEGF^{-/-}$ vs. WT littermates ($p<0.01$, n=3-7 per group). Prazosin treatment resulted in an increase in vascular area in the EDL of WT but not $mVEGF^{-/-}$ mice, suggesting that angiogenesis was inhibited by the muscle VEGF deletion ($p<0.05$, n=3 per group). Preliminary evidence also indicates that arteriolar remodeling may not occur in the $mVEGF^{-/-}$ mice treated with prazosin, as the number of large smooth muscle actin positive vessels tended to increase in the WT but not $mVEGF^{-/-}$ mice (n=3 per group). Our results show that lack of myocyte-derived VEGF impairs development of an appropriate microvascular network and prevents vascular adaptations to increased blood flow within skeletal muscle. Funded by NSERC and the Heart and Stroke Foundation of Canada.

18.5
THE IMPACT OF NEURONAL NITRIC OXIDE SYNTHASE (NNOS) EXPRESSION ON RUNNING PERFORMANCE AND THE CAPILLARY SYSTEM IN SKELETAL MUSCLE OF MICE

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Given the sarcolemmal localization of neuronal nitric oxide synthase (nNOS), we hypothesized that nNOS-generated NO might be involved in the communication between muscle fibers and the capillaries important for performance. We therefore subjected male wild type (WT) mice and nNOS-knockout (KO) littermates (n= 8 in both strains) at the age of 12 weeks to an incremental and a run-to-exhaustion (conducted at 70% of maximal velocity) exercise test on a treadmill. Peak power (+8.3%) as well as running time (+27.8%) and distance (+16.9%) were non-significantly higher in the nNOS-KO mice than WT mice. Both the C/F-ratio (-12.1%; $p\leq0.05$) and the mean cross-sectional fiber area (-25.9%; $p\leq0.05$) were significantly lower in the extensor digitorum longus muscle (EDL) of nNOS-KO mice than in that of their WT counterparts. Not surprisingly therefore, the numerical density of capillaries was higher in the EDL of the nNOS-KO mice than in that of the WT mice (+15.9%; ns). Finally, the capillaries in the EDL of both mouse strains subjected to a morphometric analysis at transmission electron microscopy level. Mean cross-sectional capillary area, volumen densities and the surface-to-volume-ratios of the capillary fractions (lumen, endothelial cells, pericytes, basement membrane) differed only non-significantly between the nNOS-KO mice and the WT mice. In summary, we conclude that EDL muscle fibers from mice lacking nNOS are smaller and more richly supplied with capillaries than those of WT mice.

18.6
AMELIORATIVE EFFECTS OF ANTIOXIDANT ASTAXANTHIN ON CAPILLARY REGRESSION IN HINDLIMB UNLOADING-INDUCED ATROPHIED MUSCLE

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PURPOSE: Oxidative stress is proposed as the initial pathologic step of skeletal muscle and endothelial injuries during unloading. The purpose of the present study was to investigate the ameliorative effects of astaxanthin (ASX), an antioxdent, on capillary regression in the soleus muscle during hindlimb unloading (HU) and to elucidate the regulations of pro- and anti-angiogenic factors. METHODS: Twenty-four adult male Wistar rats were assigned randomly either to a control, control treated with ASX, HU, or HU treated with ASX group. RESULTS: HU for 7 days resulted in a decrease in muscle weight, capillary number and volume in the atrophied muscle. In addition, the accumulation of reactive oxygen species, the overexpression of SOD-1, a decrease in the level of VEGF and its receptors and angiopoietins, and an increase in the level of thrombospondin-1 (TSP-1), as an anti-angiogenic factor, were observed in the atrophied muscle. Administration of ASX attenuated the changes in SOD-1, VEGF, TSP-1, and other angiogenic factors and prevented the capillary regression in the atrophied muscle. Furthermore, the VEGF-to-TSP-1 ratio was higher in the ASX treated groups than in the control and HU groups. CONCLUSIONS: These results suggest that ASX may be an effective treatment to counter a chronic decrease in the capillary network in skeletal muscles and associated with angiogenic factors. *Supported by Grants-in-Aid for Science Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology*.

18.7
CHRONIC HEART FAILURE AND MUSCLE MICROVASCULAR OXYGENATION: EFFECTS OF EXERCISE TRAINING

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Exercise training promotes multiple adaptations within skeletal muscle that enhance local O_2 delivery-utilization matching (i.e., microvascular O_2 pressure; PO_2mv) in healthy indi-viduals. We tested the hypothesis that exercise training would ameliorate muscle micro-vascular oxygenation deficits in rats with chronic heart failure (CHF) during metabolic transitions. CHF rats (LVEDP=18±2mmHg) were assigned to sedentary (S; n=9) or treadmill exercise trained (ET; n=10; 60 min/d, 5 d/wk, ~8 wks, 35 m/min; -14% grade) groups. PO_2mv was measured via phosphorescence quenching in the spinotrapezius muscle at rest and during 1 Hz twitch contractions. ET rats had ~8% greater whole-body VO_2peak than S rats ($p<0.05$). Despite similar resting PO_2mv (S=25±2; ET=22±2mmHg; $p>0.05$), ET rats had slower PO_2mv fall throughout contractions as assessed by the primary time constant (S=12±2; ET=19±2s) and mean response time (S=22±2; ET=31±2s) than S rats ($p<0.05$ for both). Contracting steady-state PO_2mv was not differ-ent between groups (S=17±2; ET=14±1mmHg; $p>0.05$). Exercise training leads to greater muscle microvascular oxygenation (and thus enhanced driving force for transcapillary O_2 flux) following contractions onset in rats with CHF. Elevation of micro-vascular O_2 pressures, especially during metabolic transients, after exercise training in CHF likely constitutes an important mechanism for training-induced metabolic adaptations in this population. (ACSM, AHA Midwest Affiliate 0750090Z, NIH HL-108328).

18.8
THE EFFECTS OF ACUTE DIETARY NITRATE SUPPLEMENTATION ON MUSCLE MICROVASCULAR OXYGENATION IN CONTRACTING RAT MUSCLE

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Nitric oxide (NO) bioavailability modulates the O_2 supply/utilization matching (PO_{2mv}) within the muscle microvasculature. Recently, increased NO via dietary nitrate supplementation has been shown to reduce the O_2 cost of submaximal exercise in humans. However, the effects of nitrate supplementation on the PO_{2mv} remain uncertain. We tested the hypothesis that acute dietary nitrate supplementation via beetroot juice (BR) would improve muscle microvascular oxygenation during metabolic transitions. Young male Sprague-Dawley rats were randomized into control or nitrate-supplemented groups. Either untreated (control, n=11) or nitrate supplemented (1 mmol/kg/d BR, n=8) distilled water was available ad libitum for 5 days and consumption monitored. PO_{2mv} was measured in the spinotrapezius muscle using phosphorescence quenching at rest and during 1-Hz twitch contractions. The time delay preceding the fall in PO_{2mv} at contractions onset was longer in BR (Control: 7±1; BR: 13±2s;$P<0.05$). BR also had a slower rate of PO_{2mv} fall (mean response time; Control: 17±2; BR: 26 ±3s;$P<0.05$) and lower PO_{2mv} amplitude (Control: 17±1; BR: 11±1mmHg;$P<0.05$). Dietary nitrate improves microvascular oxygenation throughout contractions suggesting that BR elevates muscle O_2 delivery relative to O_2 demand. The BR induced enhanced driving pressure for transcapillary O_2 flux constitutes a potential mechanism for improved metabolic control and exercise tolerance. *NIH HL-108328, AHA Midwest Affiliate 0750090Z.*

19.0: BLOOD FLOW REGULATION

19.1
CENTRAL COMMAND CONTRIBUTES TO INCREASING BLOOD FLOW TO NON-CONTRACTING MUSCLE DURING MOTOR IMAGERY AND VOLUNTARY ONE-LEGGED EXERCISE

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Whether neurogenic vasodilatation contributes to exercise hyperemia in humans is still controversial. Blood flow to non-contracting muscle, however, is regulated by a neural mechanism. Although vasodilatation in non-exercising limb has been observed at the onset of voluntary exercise, it was unclear whether central command or muscle mechanoreflex accounts for the vasodilatation. To clarify this, we measured the change in concentration of oxygenated-hemoglobin (Oxy-Hb) of the non-contracting left vastus lateralis (VL) muscle with near-infrared spectroscopy, as index of tissue blood flow, and femoral blood flow to the non-exercising leg during voluntary or passive one-legged cycling with the contralateral right leg. In addition, to examine the pure influence of central command without any feedback from contracting muscle, the Oxy-Hb and femoral blood flow were measured during motor imagery of the voluntary one-legged cycling. Oxy-Hb in the non-contracting VL and femoral blood flow increased ($P<0.05$) at the start period of the voluntary cycling without a rise in arterial blood pressure. In contrast, no increases in Oxy-Hb and femoral blood flow were detected at the start period of passive one-legged cycling. Motor imagery increased both Oxy-Hb of the left VL muscle and femoral blood flow. Taken together, it is concluded that centrally-induced vasodilator signal is transmitted to the non-contracting VL muscle at the start period of voluntary exercise and during motor imagery.

19.2

ALTERATIONS IN CEREBRAL BLOOD FLOW DURING EXERCISE AT HIGH ALTITUDE

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We examined changes in regional cerebral blood flow (CBF) and arterial blood gases at rest and during supine incremental cycling exercise to exhaustion at sea level (SL) and high altitude (HA; 5050 m). Blood flow in the internal carotid (QICA) and vertebral (QVA) artery (vascular ultrasound) and velocity (transcranial Doppler) was monitored in distal cerebral arteries (middle [MCAv] and posterior [PCAv]). Intra-arterial blood pressure, arterial PO2 (PaO2) and arterial PaO2 (PaCO2) were sampled during steady state changes at 20, 40, 60, 80 and 100% of the maximum achieved wattage (% Wmax) at each condition. Regional cerebral oxygen delivery (DO2) was calculated as the product of arterial O2 content (CaO2) and QICA and QVA, separately. At HA %Wmax was reduced by ∼50%. PaO2 (42± 3 vs. 92 ± 7 mmHg), PaCO2 (24 ± 4 vs. 38 ± 3 mmHg) and CaO2 (18 ± 2 [HA] vs. 21 ± 2 [SL] ml.dl-1) were reduced at rest compared with SL. At rest, blood flow (QICA, QVA) and velocities (MCAv and PCAv) were unchanged at HA. During maximal exercise, PaO2 (37 ± 3 vs. 84 ± 12 mmHg) and PaCO2 (22 ± 2 vs. 35 ± 3 mmHg) were markedly reduced at HA compared to SL. CaO2 was 15 ± 4 % lower (P<0.05) at maximum exercise at HA compared with SL. During exercise at HA, compared with SL, there were greater (range, 2 % to 23 %; P<0.05) elevations in QICA and MCAv (at 40 %Wmax), and both MCAv and PCAv (at 80% Wmax). Regional DO2 was maintained at HA and SL in both the ICA and VA during exercise. The hypoxemia during exercise at HA resulted in general elevations in CBF which likely helped to maintain effective cerebral O2 delivery.

19.3

EFFECT OF PCO2 CLAMPING ON BRAIN BLOOD FLOW, OXYGENATION AND PERFORMANCE DURING 15 KM TIME TRIAL CYCLING IN SEVERE HYPOXIA

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During exercise in hypoxia, hyperventilation-induced hypocapnia leads to cerebral vasoconstriction and a reduction in cerebral blood flow (CBF). This impairs cerebral O_2 delivery and could account for the reduced exercise performance in hypoxia. We measured end-tidal PCO_2 ($PETCO_2$), ventilation (V'E), middle cerebral artery velocity (MCAv; index of CBF), brain and muscle oxygenation ([O_2Hb]) and perceived effort of exertion (RPE) in ten healthy men during 15 km time trial cycling in normoxia and hypoxia (FIO_2=0.10) with and without CO_2 clamping ($PETCO_2$ ~45 mmHg). Hypoxia elevated MCAv, V'E and RPE throughout exercise, while $PETCO_2$, $PETO_2$, muscle [O_2Hb] and cerebral [O_2Hb] were lowered throughout exercise with hypoxia (P<0.05). CO_2 clamping elevated MCAv during the last 3 km of the time trial in normoxia, whilst MCAv was only elevated between 2nd and 4th km in hypoxia (P<0.05). CO_2 clamping did not affect muscle and cerebral [O_2Hb] or RPE (P>0.05). Exercise performance was impaired by 19±7% with hypoxia (P<0.05), whilst no effect was observed with CO_2 clamping in either normoxia or hypoxia (P>0.05). Our data indicates that the 'normal' CBF response to CO_2 is impaired during exercise in hypoxia, presumably due to a greater vasodilatory effect of the hypoxic stimuli. These findings refute the hypothesis that hyperventilation-induced hypocapnia limits exercise performance in hypoxia. This study was supported by the Swiss National Science Foundation and the Fondation de Reuter.

19.4

CONTRIBUTION OF NITRIC OXIDE TO EXERCISE HYPEREMIA IN OBESE ADULTS

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INTRO: Previous research indicates obese adults exhibit impaired endothelial dependent dilation due, in part, to reduced nitric oxide (NO) bioavailability in resting skeletal muscle. The contribution of NO to exercise hyperemia in young obese adults is currently unknown. We hypothesized the relative contribution of NO to exercise hyperemia would be lower in young obese adults when compared to lean adults. METHODS: Three healthy lean (23±2yrs,BMI=24±1) and 3 obese adults (25±3yrs,BMI=39±6) performed 10 minutes of dynamic forearm exercise (20 contractions/minute) at 15% of maximal voluntary contraction. A brachial artery catheter was used for continuous blood pressure (BP) measurements and local infusion of the NO synthase inhibitor, L-NMMA (10 mg/min) during the final 5 minutes of exercise. Forearm blood flow (FBF) was measured using Doppler ultrasound, and forearm vascular conductance (FVC) was calculated (FBF÷BP=FVC). RESULTS: Steady state FVC was similar between lean and obese adults (201 vs. 183 ml/min*100mmHg). With infusion of L-NMMA, lean subjects' FVC decreased by 29 ml/min*100mmHg, whereas obese subjects' FVC decreased by 28 ml/min*mmHg. The relative decrease in FVC was also similar between groups (~26 vs 24% respectively). CONCLUSION: The effect of NO Synthase inhibition on exercise hyperemia appears to be similar between groups, suggesting the contribution of NO to exercise hyperemia remains intact in young obese adults. Support: NIH R01 grant #HL105820.

19.5

EFFECT OF β-ADRENERGIC BLOCKADE ON EXERCISE HYPEREMIA IN METABOLIC SYNDROME

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In younger healthy adults, β-adrenergic mediated vasodilation does not contribute to moderate intensity exercise hyperemia. Adults with metabolic syndrome (MetSyn) exhibit greater sympathetic nerve activity which may activate this vasodilator system during exercise. We hypothesized MetSyn adults would demonstrate a significant reduction in steady state exercise hyperemia after β-adrenergic blockade. We studied 14 adults with metabolic syndrome (31±3 yr) and 16 healthy controls (35±3 yr). Forearm blood flow (FBF, Doppler ultrasound) and blood pressure (MABP) were measured during 4 minutes of dynamic forearm exercise at 15% maximal voluntary contraction under control conditions and after non-specific β-adrenergic receptor inhibition (propranolol). Propranolol was infused via brachial artery catheter. Due to higher MABP in MetSyn, FBF was normalized for perfusion pressure by calculating forearm vascular conductance (FVC = FBF ÷ MABP). Changes in steady-state exercise FVC with propranolol infusion were assessed. The rise in FVC with exercise was greater in adults with MetSyn when compared with healthy controls. There was no significant effect of propranolol infusion on FVC in either group. β-adrenergic receptor-mediated vasodilation is not obligatory to moderate intensity exercise hyperemia in metabolic syndrome adults. Funding: AHA 10PRE3870000, NIH 1R01HL105820.

19.6

EFFECT OF ENDURANCE TRAINING ON SPLANCHNIC CIRCULATION DURING HEAD-UP TILT

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Endurance training (ET) has been reported to increase orthostatic intolerance. The splanchnic circulation contains up to ~30% of blood volume and receives ~25% of cardiac output at rest. Moreover, upon standing vasoconstriction of the splanchnic bed contributes to increased peripheral resistance. The aim of this study was to determine the effect of ET on superior mesenteric (SM) vascular responses to orthostatic stress. It was hypothesized that SM vasoconstrictor responses to head-up tilt (HUT) would be attenuated after ET. Arterial blood pressure, heart rate, and SM blood flow velocity (SMBFV; Doppler ultrasound) were measured during 25 min of an 80 ° HUT test before and after 8 wk of ET (N=8; 24±1 yr). Training elicited a 19±2% increase in VO_{2peak}. Mean arterial pressure during HUT progressively increased 6±3 mmHg (P=0.01) before ET, but did not increase during HUT after ET (1±2 mmHg). SMBFV (Δ38±6 cm/s) and SM vascular conductance (Δ55±4%) were decreased during HUT. However, ET did not alter the decline in SMBFV (Δ31±7 cm/s) during HUT, but the decrease in SM vascular conductance was less (Δ41±9%; P=0.03). In summary, 8 wk of ET resulted in less vaso constriction in the SM vasculature during HUT, which was associated with an attenuated blood pressure reflex response to HUT. Therefore, alterations in splanchnic circulation with ET might contribute to the increased incidence of orthostatic intolerance observed in endurance-trained athletes. Support by NIH HL109952.

19.7

VASOCONSTRICTOR RESPONSIVENESS DURING HYPERBARIC HYPEROXIA IN CONTRACTING HUMAN MUSCLE

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We tested the hypothesis that functional sympatholysis (blunting of α-adrenergic vasoconstriction) is attenuated during hyperoxic exercise. Nine male subjects (28±1 years) performed forearm exercise (20% of maximum; 7-min) in a hyperbaric chamber under normoxic (at 1 ATA while breathing 21% O_2) and hyperoxic (at 2.82 ATA while breathing 100% O_2) conditions. Forearm blood flow (FBF; ml/min) was measured using Doppler ultrasound. Forearm vascular conductance (FVC) was calculated from FBF and blood pressure (mmHg; brachial arterial catheter). Vasoconstrictor responsiveness was de-termined with intra-arterial tyramine during the final 3 min of rest and each exercise bout. FBF and FVC were ~20-25%; (P<0.01) lower during hyperoxic exercise compared to normoxia. At rest, vasoconstriction to tyramine (% decrease from pretyramine values) did not differ between normoxia and hyperoxia (-34±3 vs. -37±5%; P=0.83). During exercise vasoconstrictor responsiveness was greater during hyperoxia compared to normoxia (-22±3 vs. -17±2%; P<0.05). Although the vasoconstrictor responsiveness during hyperoxic exercise was slightly, yet significantly greater, it likely does not explain the ~25% lower FVC during hyperoxic exercise. Therefore, an attenuated functional sympatholysis is not a major contributor to the relative increase in vascular resistance and large reductions in blood flow seen during hyperbaric hyperoxic exercise. NIH HL46493 (MJJ), HL105467 (DPC) and RR-024150.

19.8

ALTERATIONS IN ENDOTHELIAL FUNCTION WITH PHYSICAL INACTIVITY: A PRELIMINARY REPORT

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Previous bed rest studies have reported impaired endothelial function. However, the early effects of a transition from high (>10,000 steps/day) to low ambulatory activity (<5,000 steps/day) on endothelial function are unknown. Thus, we sought to examine the time course of change in endothelial function following 5 days of inactivity, and after 1 day return to activity (RA) in young, healthy men. Four recreationally active men (26±3 yrs, 20.4±1.8% body fat) performing > 10,000 steps/day underwent 5 days of reduced ambulatory activity (<5,000 steps/day), followed immediately by RA (>10,000 steps/day). Endothelial function was assessed in the arm (brachial) and leg (popliteal) using flow-mediated dilation (FMD) at baseline, 1, 3, and 5 days following inactivity, and RA. Subjects consumed a standardized diet throughout. Brachial FMD normalized to shear stimulus was not significantly altered over 5 days of inactivity or following a 1 day RA. However, popliteal FMD normalized to shear appeared lower following inactivity and was maintained with RA (baseline: 0.52±0.25, inactivity 1: 0.46±0.22, inactivity 3: 0.21±0.09, inactivity 5: 0.10±0.05, RA: 0.17±0.08, p=0.05). These preliminary findings suggest that short term reductions in daily ambulatory activity impairs leg but not arm endothelial function. Furthermore, a 1 day RA did not appear to be sufficient to return endothelial function to pre inactivity values. Funded by HL-093167 (PJF) & 5 T32 AR048523 (LJB).

20.0: CARDIOVASCULAR

20.1
REGULAR EXERCISE REVERSES SUPPRESSIONS OF SERCA ACTIVITY AND A-MHC EXPRESSION IN THE HEART OF ORCHIDECTOMIZED RAT

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A high incidence of heart disease in hypogonadal man indicates a crucial role of male sex hormones in cardiac function. Suppressions of both cardiac systolic and diastolic functions have been reported in orchidectomized (ORX) rat. We have also found decreases in SERCA activity and α-MHC expression in ORX rat heart which could be reversed by testosterone supplement. Unfortunately, the use of testosterone is precluded in some patients. We then tested whether regular exercise could prevent the systolic and diastolic dysfunction in ORX rat. With the protocol approval by Experimental Animal Committee, Faculty of Science, Mahidol University, in accordance with guidelines of Guiding Principles for the Care and Use of Animals, adult male rats were divided into SHAM and ORX rats with/without regular exercise. One week after sham-operation or orchidectomy, exercised rats were subjected to a nine-week treadmill running program with moderate intensity. Results showed an induction of cardiac hypertrophy in both SHAM and ORX rats after regular exercise. Using triple enzyme assay, the suppressed maximum SERCA activity detected in the heart of sedentary ORX rat was disappeared in exercised ORX rat. Regular exercise also completely normalized the enhanced Ca^{2+} sensitivity of SERCA observed in OVX rat heart. Moreover, the shift of α-MHC toward β-MHC observed in the heart of ORX rat was also abolished by regular exercise. This study was granted by Mahidol University.

20.2
REGULAR EXERCISE PREVENTS THE CARDIAC MYOFILAMENT CA2+ HYPERSENSITIVITYIN ANGIOTENSIN II-INFUSED OVARIECTOMIZED RAT

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The myofilament Ca2+ hypersensitivity detected in ovariectomized (OVX) rat heart was further enhanced after chronic AII infusion. We therefore tested in this study whether the preventive effect of regular exercise on changes in cardiac myofilament activity observed in OVX rat also extends to the heart of AII-infused OVX rat. With the protocol approval by Experimental Animal Committee, Faculty of Science, Mahidol University, in accordance with guidelines of Guiding Principles for the Care and Use of Animals, adult female rats were divided into two main groups, exercise and sedentary, with four subgroups, sham and OVX rats with/without AII infusion, in each main group. One week after sham-operation or ovariectomy, exercised rats were subjected to a nine-week treadmill running program with moderate intensity. AII was infused using mini-osmotic pump throughout the last four weeks of 10-week study duration. As expected, the cardiac myofilament Ca2+ hypersensitivity detected in OVX, AII-infused, and AII-infused OVX rats was all disappeared after regular exercise. An increased tropomyosin phosphorylation in OVX rat hearts but a decreased regulatory light chain phosphorylation in AII-OVX rat hearts was also completely normalized by regular exercise. Surprisingly, exercise only reversed the shift of MHC in the heart of OVX but not AII-OVX rats. This work was granted by Faculty of Science, Mahidol University.

20.3
SARCOLIPIN (SLN) AND PHOPHOLAMBAN (PLN) PROTECT SARCO(ENDO)PLASMIC RETICULUM CA2+-ATPASE (SERCA) FUNCTION DURING HEAT SHOCK

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SERCA is responsible for initiating muscle relaxation and maintaining low resting cytosolic [Ca^{2+}]. SLN and PLN are homologous proteins that regulate SERCA activity through physical interactions with it. In culture, we have shown that SLN and PLN protect SERCA function during heat stress. Here, we hypothesized SERCA function would be reduced following heat shock in mice lacking SLN ($SLN^{-/-}$) or PLN ($PLN^{-/-}$). Diaphragms of $SLN^{-/-}$ (n = 6) and WT counterparts (n = 6), along with left ventricles of $PLN^{-/-}$ (n = 10) and WT controls (n = 14) were homogenized and subjected to heat shock (37°C) for 0, 30 and 60 min, after which Ca^{2+}-dependent ATPase activity was measured. At 0 min, maximal SERCA activity (V_{Max}) of diaphragm homogenates was similar between WT and $SLN^{-/-}$ mice. Following 60 min of heat stress, V_{Max} was reduced in both genotypes ($P < 0.05$), but was ~16% lower ($P < 0.001$) in $SLN^{-/-}$ animals. Within ventricular homogenates of WT and $PLN^{-/-}$ mice, heat stress progressively reduced ($P < 0.05$) V_{Max}, however, activity was greater ($P < 0.05$) in $PLN^{-/-}$ mice at all time points. Despite this, $PLN^{-/-}$ animals displayed a greater ($P < 0.05$) percent reduction of V_{Max} with heat shock relative to WT mice (46.4 ± 2.6 vs. 37.0 ± 2.0). These data indicate endogenous expression of SLN and PLN protect SERCA function during heat shock. In addition to regulating activity, SLN and PLN likely have roles in maintaining SERCA function during cellular stress. This work was funded by NSERC and CIHR.

20.4
SYNERGISTIC IMPACT OF ENDURANCE TRAINING AND INTERMITTENT HYPOBARIC HYPOXIA ON HEART MITOCHONDRIAL SUSCEPTIBILITY TO PERMEABILITY TRANSITION PORE OPENING AND APOPTOTIC SIGNALING

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Mitochondrial permeability transition pore (MPTP) opening is an important triggering event for inducing apoptotic cell death. This study aimed to analyse whether a combination of intermittent hypobaric-hypoxia (IHH) and endurance-training (ET), two effective non-pharmacological cardioprotective strategies, afford synergistic effects to a more resistant phenotype against heart mitochondrial-driven apoptosis. Wistar rats were: normoxic-sedentary (NS), normoxic-exercised (NE, 1h/d/5wks treadmill-running), hypoxic-sedentary(HS,6000m,5h/d/5wks) and hypoxic-exercised (HE). In vitro susceptibility to calcium-induced MPTP, CypD, ANT, Bax, Bcl2, MDA, –SH contents, caspase 3, 8, 9, aconitase, MnSOD activities, and HIF-1a gene expression were determined. The susceptibility to MPTP decreased in NE, HS and HE vs. NS and even further in HE. ANT increased in HE. Bcl-2/Bax ratio increased in NE and HS. Decreased caspase 3 activity in HE vs. NS and HS and caspase 9 in HE vs. NS and NE were observed. Aconitase activity increased in HE and HS vs. others. No significant differences between groups were observed regarding MnSOD and caspase 8 activities, MDA and –SH contents. IHH and ET synergistically modulate heart mitochondria into a more resistant phenotype against calcium-induced MPTP opening and apoptotic signalling although without visible addictive effects. IJUP-71-2009; FCT-PTDC/DES/113580/2009.

20.5
ENDURANCE-TRAINING IN EARLY LIFE RESULTS IN LONG-TERM PROGRAMMING OF CARDIAC HYPERTROPHY IN RATS

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This study examined the impact of short-term endurance-training early in life on cardiac hypertrophy in adulthood. Male WKY rats were allocated to sedentary (SED) or exercise groups, either early in life (Early Ex) or later in life (Late Ex) (N=10/ group). The rats ran on a motorised treadmill 1hr/d, 5d/wk for 4 wks. The Early Ex group trained at 5-9 wks, the Late Ex trained at 20-24 wks, with all rats killed at age 24 wks. 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. Compared to SED rats, there was a significant ($P<0.05$) ~10% increase in relative heart mass (heart/body mass) in Early Ex and Late Ex at 24 wks. Consistent with exercise-induced cardiac hypertrophy, whole-genome gene expression (Illumina Inc.) in the heart found, compared to SED, both Early Ex and Late Ex rats had significantly increased (~20-40%) expression of many genes involved in protein transcription and translation (ribosomal proteins, elongation/initiation factors, mitochondrial ribosomal proteins), contraction (myosin, troponin and actin), energy production (ATP synthase, cytochrome oxidase, creatine kinase) and antioxidant defences (superoxide dismutase 3, glutathione-S-transferase). These findings suggest long-term and perhaps permanent cardiac programming by endurance-training during juvenile cardiac development. This study was funded by the Australian NHMRC, HF and The University of Melbourne.

20.6
HIGH FAT DIET-INDUCED HYPERINSULINEMIA INDUCES EARLY CARDIAC ADAPTION TO INSULIN RESISTANCE

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Reduced cardiac glucose uptake and mitochondrial dysfunction are thought to promote cardiac dysfunction in diabetes. However, changes in heart metabolism during insulin resistance (IR) remain unclear. We investigated early cardiac metabolic changes in middle-aged (12mo) male LDLR$^{-/-}$ mice fed chow or high fat diet (HFD) for 3 months. HFD induced systemic IR and hyperinsulinemia, but dramatically increased positron emission tomography-assessed cardiac glucose uptake (2.9 fold). HFD also increased mitochondrial respiration and ATP/O ratios in isolated mitochondria measured with respirometry. Shift to glucose utilization is thought to be associated with cardiac dysfunction; however echocardiography showed no contractile impairment. Insulin signaling (p-AKT, p-IRS-1 and p-GSK3b) measured by Western blotting was increased in HFD-fed mice, even under fasting conditions. To test whether the hyperinsulinemia drives glucose uptake in the insulin-sensitive hearts of these mice, we induced insulin deficiency with Streptozotocin (STZ). STZ reduced cardiac glucose uptake and mitochondrial function, but was rescued by treatment with exogenous insulin, indicating that hyperinsulinemia drove the HFD-induced changes. In conclusion, the heart remains insulin-sensitive during systemic IR and increases its glucose uptake due to IR-induced hyperinsulinemia, resulting in an early adaptive change that may preserve mitochondrial and cardiac function in the face of obesity-related stress.

20.7

APOCYNIN PREVENTS EXERCISE-INDUCED CARDIAC DYSFUNCTION AND CA^{2+} LEAK FROM THE SARCOPLASMIC RETICULUM OF RAT MYOCARDIUM

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This study examined the effects of *in vivo* NADPH Oxidase (NOX) inhibition on isolated perfused heart function and sarcoplasmic reticulum (SR) Ca^{2+} handling following acute exhaustive exercise. Male Sprague-Dawley rats (20-23 wks) were given tap water or tap water supplemented with 1.5 mM apocynin (APO), a NOX inhibitor, for 3 days prior to random group assignment. The control groups (CTL & CTL-APO) only participated in treadmill acclimation and the exercise groups (EX & EX-APO) performed a single running bout (5° grade, 20 m/min) to exhaustion. In animals that were given tap water, left ventricular developed pressure (LVDP) was reduced immediately after exercise (CTL 137±4 vs EX 118±5 mmHg). APO did not alter LVDP under control conditions (CTL-APO 135±3 mmHg). Interestingly, NOX inhibition preserved LVDP in the EX-APO group (EX 118±5 vs EX-APO 135±4 mmHg).Rates of maximal Ca^{2+}-ATPase activity was assessed *in vitro* from LV homogenate and was not different between groups. Similarly, oxalate-supported SR Ca^{2+} uptake was not affected by exercise in the absence or presence of NOX inhibition. However, the rate of Ca^{2+} leak from the SR was 44% greater in the EX group, an effect that was not observed in the EX-APO group. These results suggest that NOX generation of superoxide radical during exhaustive exercise caused greater SR Ca^{2+} leak, which may reduce SR Ca^{2+} load and depress left ventricular contractility. Supported by NSERC.

20.8

POST-EXERCISE FLOW-MEDIATED DILATION IS INFLUENCED BY RETROGRADE AND OSCILLATORY SHEAR

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We tested the hypothesis that elevated doses of retrograde shear rate (SR) in the brachial artery during lower body supine cycle exercise would attenuate post-exercise flow-mediated dilation (FMD) in a dose-dependent manner. Twelve men completed 3 exercise sessions (90 W, 20 min). One brachial artery was exposed to augmented oscillatory and retrograde SR using different forearm cuff pressures (20, 40, 60mmHg) (contralateral arm=control) during exercise. Retrograde, antegrade, and oscillatory shear index (OSI=|retrograde SR|/(|retrograde SR|+|antegrade SR|)) increased in both arms and in all exercise sessions (P<0.05). Retrograde SR and OSI were greater in the cuffed arm vs the control arm during all exercise sessions (P<0.01). The 60mmHg cuff pressure elicited the greatest retrograde SR during exercise (P<0.05). OSI was not different in the cuffed arm between sessions during exercise (P=0.20). Antegrade SR during exercise was similar in all arms and conditions. Post-exercise FMD were lower in the cuffed arm vs the control arm (P<0.05) and without differences between cuff pressures (20mmHg: 5.7±2.2%; 40mmHg: 4.7±1.3%; 60mmHg: 5.4±2.4%) (P>0.05).These results indicate that augmented oscillatory and retrograde SR in non-working limbs during lower body exercise attenuates post-exercise FMD without an evident dose-response in the range of cuff pressures tested.

20.9

DIFFERENTIAL VASODILATOR EFFECTS OF INSULIN BETWEEN GASTROCNEMIUS AND SOLEUS MUSCLE FEED ARTERIES: ROLE OF ENDOTHELIN-1

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The vascular actions of insulin are complex as it can stimulate both nitric oxide (NO)-mediated dilation and endothelin-1(ET1)-mediated constriction. The ET1 pathway predominates in insulin-resistant states, owing to selective down-regulation of the NO pathway. We examined vasoreactivity to insulin in feed arteries (FA) of the gastrocnemius (GFA) and soleus (SFA) muscles of sedentary Long Evans Tokushima Otsuka (LETO, n = 8) and Otsuka Long Evans Tokushima Fatty (OLETF, n = 7) rats, an established model of obesity/insulin resistance. There were no differences between LETO (healthy) and OLETF (obese/insulin resistant/type 2 diabetic) rats in insulin vasoreactivity in either vessel. SFA dilated more than GFA in LETO at 1000 μIU/mL (15% vs. 2%; P < 0.05 for between-vessel difference) and in OLETF at 10, 100, and 1000 μIU/mL (13% vs. 3%, 20% vs. 1%, and 27% vs. 3%, respectively; all P < 0.05). In the presence of 3 μM tezosentan, a non-specific ET1 receptor blocker, insulin-induced dilation of the GFA was enhanced such that differences between vessels were abolished at all insulin doses in both groups. We conclude that the insulin/ET1 vasoconstrictor pathway is more active in GFA than in SFA, independent of obesity/diabetes status in the OLETF rat model. We speculate that this phenomenon is related, in part, to between-muscle differences in resting recruitment patterns and the associated between-vessel differences in blood flow and vascular wall shear stress.

20.10

EFFECTS OF FLEXIBILITY LEVELS ON STRETCHING EXERCISE- INDUCED REDUCTION IN ARTERIAL STIFFNESS

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PURPOSE: Poor flexibility is associated with arterial stiffening. Currently, it is unknown whether arterial stiffness is reduced after one bout of stretching exercise, and moreover whether the effects of stretching exercise is affected by flexibility levels. The purpose of this study was to determine the effects of flexibility levels on changes in arterial stiffness induced by stretching exercise. Methods: Twenty four healthy adults (age 24 +/- 1 yrs, 11 men and 13 women) participated in this study. Subjects were divided into either poor- or high-flexibility groups on the basis of a sit-and-reach test. Arterial stiffness (baPWV; brachial-ankle pulse wave velocity), systolic blood pressure and heart rate were measured before and immediately after the stretching exercise as well as 15, 30, 45, and 60 minutes after the stretching exercise. Results: The baPWV significantly decreased at 45 minutes after stretching exercise (P<0.05). Although systolic blood pressure increased and heart rate decreased after stretching exercise in both groups, changed these parameters to baseline levels within 30 min after stretching exercise (P<0.05 in both). The trends of changed parameter in both groups responded in a similar fashion to stretching exercise (no group - by -time interaction was detected). CONCLUSION: These results suggest that stretching exercise acutely decreases arterial stiffness regardless of flexibility levels.

20.11

LONG-TERM AEROBIC AND RESISTANCE TRAINING DIFFERENTIALLY IMPACT CONDUIT ARTERY STRUCTURAL PROPERTIES

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The purpose of this study was to determine the impact of long-term aerobic (AT) or resistance exercise training (RT) on conduit artery characteristics in previously sedentary adults with the metabolic syndrome. After obtaining written informed consent, participants from the Studies of Targeted Risk Reduction Interventions through Defined Exercise II (N=23; age, 49±2 y; BMI, 31±1 kg/m^2; blood pressure, 120±3/78±2 mmHg; VO_2peak, 27±1 ml/kg/min) were randomized to 8 months of AT (14 kcals/kg/wk, 65-80% of VO_2peak) or RT (3 sets, 8-12 repetitions, 4 upper and 4 lower body exercises, 3d/wk). Doppler ultrasound and DICOM-based software were used to measure brachial (BA) and femoral artery (FA) diameter, wall thickness, and wall:lumen ratio prior to and 48h post-intervention. Resting BA and FA lumen diameter increased by 6±2% (P=0.01 vs. baseline) and 7±3% (P=0.05) in AT and by 4±3% (P=0.26) and 5±3% (P=0.19) in RT, respectively. Wall thickness decreased by 1±3% (P=0.56) and 13±8% (P=0.11) in AT and by 5±5% (P=0.25) and 11±6% in RT (P=0.12) in the BA and FA. The BA and FA wall:lumen ratio decreased by 6±3% (P=0.05) and 21±7% (P=0.03) in AT and by 2±5% (P=0.94) and 14±7% (P=0.10) in RT. In conclusion, only AT resulted in significant changes in BA and FA lumen diameter and wall:lumen ratio, suggesting that long-term AT and RT differentially effect conduit artery structural properties in previously sedentary adults with the metabolic syndrome. Support: AHA 11POST440017, NIH HL-57354.

20.12

ACUTE EXERCISE AND ACTIVATION OF NITRIC OXIDE SYNTHASE IN AORTA OF RATS: ROLE OF REACTIVE OXYGEN SPECIES, AKT AND AMP-ACTIVATED PROTEIN KINASE

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The objective of present study was designed to evaluate *ex vivo* eNOS phosphorylation in rat aortas incubated with H_2O_2 and to test this hypothesis *in vivo* in the aortas of rats submitted to acute exercise. For *ex vivo* studies, six groups of aortic tissue were formed: control, H_2O_2, N-acetylcysteine (NAC), LY294002, compound C, and LY294002 plus compound C. While incubation with H_2O_2 increased Akt, AMPK and eNOS phosphorylation, pre-incubation with NAC strongly reduced the phosphorylation of these enzymes. For *in vivo* studies, male Wistar rats were divided into four groups: control, cont+NAC, exer-cise, and exer+NAC. After a 3 h swimming session, animals were decapitated and aortas were excised for biochemical and immunoblotting analysis. All experiments were con-ducted following Guiding Principals in the care and Use of Animals. Acute exercise in-creased superoxide levels and dichlorofluorescein (DCF) concentrations, and this in-crease was related to phosphorylation of Akt, AMPK and eNOS. On the other hand, use of NAC reduced superoxide levels and DCF concentration. Reduced superoxide levels and DCF in the exer+NAC group were associated with decreased Akt, AMPK and eNOS phosphorylation. Our results indicate that ROS induced by acute exercise play the im-portant role of activating eNOS, a process apparently mediated by Akt and AMPK. Support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

20.13
EFFECTS OF VOLUNTARY WHEEL RUNNING ON AORTIC DOXORUBICIN ACCUMULATION AND DYSFUNCTION

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Doxorubicin (DOX) is a highly effective anthracycline antibiotic used to treat a wide array of cancers. However, its use is limited due to dose-dependent cardiovascular toxicity. While it is known that exercise preconditioning reduces the severity of DOX-induced cardiotoxicity, it is unknown as to whether it can help mitigate DOX-induced vasculotoxicity. The purpose of this study was to determine if exercise reduces the degree of DOX-induced dysfunction and its accumulation within vascular tissue. Ten week old male Sprague-Dawley rats were randomly assigned to undergo 14-weeks of voluntary wheel running (WR) or remain sedentary (SED) and further randomized to receive 15 mg DOX/kg of body mass or equivalent saline (SAL) i.p. injection. Animals were sacrificed 24 hours post injection and isolated aortic rings were used to examine vascular function. Aortic DOX accumulation was quantified using high performance liquid chromatography (HPLC). Significant differences were found between WR-DOX and SED-DOX groups ($p<0.05$) with vasoconstriction and endothelium-independent vasodilation, however no differences ($p>0.05$) were found with endothelium-dependent vasodilation. There were also no differences in accumulation (WR-DOX 189±31 ng DOX/g aorta; SED-DOX 216±46 ng DOX/g aorta). These data suggest that exercise can help reduce the severity of vascular smooth muscle dysfunction but not endothelial dysfunction associated with DOX treatment and is independent of its accumulation.

20.14
THE TEMPORAL NATURE OF CARDIOPROTECTION IN VOLUNTARY WHEEL RUNNING MICE

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Preservation of exercise-induced cardioprotection requires exercise levels be maintained. By determining the time course of transcription/translation of key protective adaptations, the relative importance of certain molecular pathways will be determined. We analysed our established phenotype of voluntary wheel-running and cardiac ischaemia-reperfusion injury in various time points of brief (2-days; 2EX), moderate (7-days; 7EX) to extended periods (28-days; 28EX). Gene and protein signalling mechanisms were determined to ascertain which pathways were activated in a time-dependent manner. Both 7EX and 28EX groups (both n=7) recovered with greater contractile function, 13% and 16% more than matched sedentary groups, respectively (p-value= <0.05). Hearts did not exhibit signs of physiological hypertrophy, however gene expression showed upregulation of beneficial contractile proteins such as Titin and reduction of opposing matrix metalloproteinase 2 that degrade them. PGC1a, an instigator of mitochondrial biogenesis, and Caveolin-3 (Cav3) implicated in important GPCR signalling were modestly upregulated in exercised groups. 7- and 28- day exercised groups showed improved contractile function and decreased levels of diastolic dysfunction compared to sedentary groups. Voluntary exercise initiates transcriptional regulation of genes with prolonged activity, and is therefore required for establishment of translational pathways of cardiovascular physiological adaptation.

20.15
THE TRANSIENT CARDIOPROTECTIVE EFFECTS OF TRAINING, DE-TRAINING AND RE-TRAINING OF ACUTE VOLUNTARY WHEEL-RUNNING MICE

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We have shown that 7 days of voluntary wheel running in untrained mice can produce significant cardioprotection from ischemia/reperfusion (I/R) injury. Timecourse and de-training/re-training studies were performed to understand the temporal nature of this protection. We hypothesized that exercise exerts cardioprotection via pro-survival signaling pathways (Akt, Erk1/2) and attenuation of pro-death (GSK3b) kinase expression. Functional responses of isolated mouse hearts (8-10 wks old) subjected to I/R (25 min ischaemia/45 min reperfusion) via Langendorff perfusion showed that 14-days of wheel running improved left ventricular developed pressure recovery from 48% to 58% (21% increase). Detraining occurred rapidly, returning to baseline levels after 7-days. 3 days of re-training returned protection back to 56%. Whole genome microarray and subsequent qRT-PCR showed an upregulation of metabolic function and an attenuation of inflammatory markers. Preliminary protein expression studies (total and phosphorylated) performed via Western Immunoblotting showed modest activation of protective mechanisms via Akt and Erk1/2, and attenuation of GSK3b. The protective effects of 14-days wheel running are diminished with 7-days of detraining (wheel-locked), but are returned after 3 days suggesting that prior exercise has preconditioned the heart via protective pathways. This study confirms the need for regular activity to maintain protective signaling in the heart.

20.16
CHRONIC LOW-INTENSITY INTERVAL EXERCISE TRAINING INCREASES CARDIAC TORSION AND IS ASSOCIATED WITH ENHANCED SYSTOLIC AND EARLY DIASTOLIC STRAIN RATE IN MINI-SWINE WITH COMPENSATED HEART FAILURE

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Increased or preserved left ventricular (LV) torsion and strain at rest is a defining clinical feature of heart failure with preserved ejection fraction (HFpEF). We have shown chronic low-intensity exercise conserves normal diastolic function and contractile reserve in aortic-banded (AB) miniature swine. Alterations to the magnitude or rate of mechanical deformation during the cardiac cycle may underlie exercise-dependent improvements in LV function. The purpose of this study was to measure LV torsion, strain, and strain rate in AB sedentary (AB-S, n=5), AB exercise trained (AB-TR, n=5) and control sedentary (CON, n=4) male Yucatan mini-swine using 2D speckle-tracking echocardiography. Torsion was increased in AB vs. CON regardless of training status and positively correlated with ejection fraction and tau Glantz. Elevated torsion in AB-TR was associated with increased systolic transverse strain and displacement, increased apical systolic radial and circumferential strain rate, and increased early diastolic apical radial and circumferential strain rate. In contrast, late diastolic longitudinal and mitral valve radial strain rate was increased in AB-S. In conclusion, chronic exercise alters mechanical properties of the LV that may benefit systolic emptying and diastolic filling. Our data suggest 2D speckle tracking echocardiography may reveal a novel set of diagnostic criteria that can differentiate between pathologically and physiologically elevated cardiac torsion in HFpEF.

20.17
EFFECTS OF DEPLOYMENT-RELATED EXPOSURES ON CARDIOPULMONARY FUNCTION

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High-levels of particulate matter that exceed environmental exposure guidelines have been reported in the deployment environments of Afghanistan and Iraq (OEF/OIF). Post-deployment, veterans endorse respiratory symptoms and limitations to exercise that may be the result of these exposures. However, the extent and severity of respiratory problems are not well understood. 20 male veterans who self-reported exposure to airborne particulates and were deployed to OEF/OIF for a period of 1 – 5 months (n = 6; 34.6 ± 8.7 yrs; Low-Exposed) or 6+ months (n = 14; 35.4 ± 7.7 yrs; High-Exposed) volunteered for this study. All veterans participated in a standard treadmill-based exercise challenge with spirometry before and after exercise. We observed no differences in spirometry obtained at rest, but 31% of the High-Exposed group exhibited exercise-induced bronchoconstriction (i.e. greater than 15% drop in FEV1 at 10 minutes post-exercise) as compared to 0% of the Low-Exposed group. Further, 38% of the High-Exposed group exhibited ventilatory limitation to exercise (i.e. Ve/MVV > 85%), but no limitations were observed in the Low-Exposed group. Although we observed airflow restriction in High- but not Low-Exposed veterans, we emphasize cautious interpretation as sample size was low and groups were of unequal size. Future studies on cardiorespiratory function in deployed veterans are warranted.

20.18
MODERATE-INTENSITY RESISTANCE TRAINING IMPROVES VASCULAR FUNCTION IN OBESE WOMEN

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Obesity contributes to impaired vascular function (VF), a precursor to cardiovascular disease. Resistance training (RT) is recommended for obesity management and is associated with favorable effects on VF; however, previous studies show that acute resistance exercise impairs VF in sedentary lean adults. Therefore, we sought to determine if acute resistance exercise impairs VF in obese adults and if 8 wks of RT is vasculoprotective.

Ten obese young women were evaluated at four time points before (wks 0 and 4), during (wk 8), and after (wk 12) participation in an 8-wk moderate-intensity RT intervention. Vascular function was assessed using brachial artery flow-mediated dilation (FMD) determined by ultrasound at each time point before and after a single bout of weightlifting (SWL). Fasting blood lipids, glucose, blood pressure (BP), waist circumference (WC), body composition, and muscular strength were also assessed. Brachial artery FMD was reduced after SWL at wk 0 ($p=0.002$) and wk 4 ($p=0.006$). At wk 8 (after 4 wks of RT) and wk 12 (after 8 wks of RT) FMD was significantly greater compared to wks 0 and 4 ($p<0.001$). Subjects also demonstrated significant improvements in WC, lean body mass, and muscular strength after RT. There were no training-associated changes in fasting blood lipids, glucose, or BP. The major result of this study is the initial demonstration that acute resistance exercise-associated impairment in VF among obese adults is reversible with 4 to 8 wks of RT.

20.19
EFFECTS OF HIGH INTENSITY INTERMITTENT TRAINING ON AEROBIC CAPACITY, ENDURANCE CAPACITY AND SHORT TERM RECOVERY

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To investigate the above mentioned relations we used a 6s/24s exercise to pause ratio with 250% of the maximal power (WLmax) reached in an incremental test (IT). Training intervention consisted of three training sessions per week with 90 intervals. A warm up and a cool down per session. Before and after the training intervention an incremental test, endurance capacity test (constant load to fatigue, ET) and double Wingate-Test (WT) were completed by every subject (n = 8). The ratio of WT2/WT1 was used as the indicator for the short term recovery (STR). After the training intervention performances were significantly better in IT 6.1% (±4.8; $p<0.01$) and in ET 39.1% (±16.5;$p<0.01$). In WT the increase in mean power reached significance level in WT1 with 3.2% (±4.4; $p<0.05$) and in WT2 with 8.4% (±7.9%; $p<0.05$). The max power in WT2 was higher (12.8% ± 8.8; $p<0.01$) than before the training intervention. In IT VO2max did not change whereas the ratio of VO2/Watt was significantly ($p<0.01$) lower after the training intervention. Neither there was a correlation between the improvement in the ET, nor between the aerobic capacity and the significant improvement in STR. Conclusion: Since the improvement of short term recovery did not correlate to the improvements in endurance properties, such as endurance capacity and VO2max, there have to be different limiting factors. This is supported by the fact that there was no increase in VO2max in this study.

20.20
FACTORS LIMITING AEROBIC CAPACITY: CARDIO-PULMONARY OR PERIPHERAL?

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To test the hypothesis that peripheral tissue diffusion contributes to limiting aerobic capacity ($\dot{V}O_2max$), we ran six goats on a treadmill at speeds eliciting $\dot{V}O_2max$ with com-binations of 0.09-0.50 inspired O_2 fraction, 0.00 or 0.05 inspired CO_2 fraction, and suf-ficient CO to maintain carboxyhemoglobin fraction from 0.02-0.45. Specific $\dot{V}O_2max$ of goats breathing different gases varied by as much as 5.5×, specific total cardiopulmonary O_2 delivery ($\dot{T}O_2max$) by 5.7×, arterial O_2 partial pressure (P_aO_2) by 9.8× and mixed-venous O_2 partial pressure ($P_\bar{v}O_2$) by 3.0×. We calculated for each goat its specific pe-ripheral tissue O_2 diffusing capacity (D_TO_2) as the slope of $\dot{V}O_2max$ *vs.* $P_\bar{v}O_2$ and its O_2 extraction fraction (EO_2) as the slope of $\dot{V}O_2max$ *vs.* $\dot{T}O_2max$ for all gas combinations it breathed. These relationships were identical over a large range of P_aO_2, regardless if $\dot{T}O_2max$ were altered by pulmonary diffusive or circulatory convective mechanisms. Goats varied almost three-fold in D_TO_2 and goats with greater D_TO_2 had higher EO_2 ($R^2 = 0.797$, $P < 0.001$) and $\dot{V}O_2max$ ($R^2 = 0.742$, $P = 0.028$). Forward stepwise linear re-gression indicated that D_TO_2 and $\dot{T}O_2max$ are significant predictors of $\dot{V}O_2max$ for all goats breathing all gases and that D_TO_2 accounted for 11% of the limitation to $\dot{V}O_2max$. These data suggest that peripheral tissue diffusion contributes to limiting $\dot{V}O_2max$ in goats. Supported by the U.S. Army Medical Research and Material Command (Contract No. W81XWH-06-C-0051) through L-3/Jaycor.

21.0: CHO/LIPID METABOLISM

21.1
IDENTIFICATION OF CIRCULATING BIOMARKERS OF MUSCLE FATTY ACID OXIDATION

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Uncoupling protein 3 (UCP3) was shown to facilitate muscle fatty acid oxidation (FAO) and it is well known that endurance training increases muscle FAO. The aim of this study was to identify metabolite biomarkers of “efficient” vs. “inefficient” muscle FAO. We compared metabolomics signatures between untrained or endurance trained wild-type (WT) and UCP3 transgenic (Tg) mice. To increase muscle FAO immediately prior to the collection of samples, half of the studied mice were subjected to a moderate intensity exercise-bout (EB). Plasma samples were analyzed using unbiased metabolite analysis platforms. Our study was approved by the Animal Care Committee of the University of Ottawa. EB increased circulating levels of some metabolites independently of the genotype (e.g. some tricarboxylic acid (TCA) cycle intermediates). Interestingly, the increased circulating free fatty acid levels following EB in WT mice was absent in UCP3 Tg mice, suggesting decreased adipose tissue lipolysis or increased muscle fatty acid uptake in UCP3 Tg mice. Furthermore, some anaplerotic metabolites (e.g. serine, phenylalanine, methionine, isoleucine, glycine, and glutamine) were decreased only in UCP3 Tg mice following the EB, suggesting that UCP3 Tg mitochondria had a better TCA cycle replenishment. Ongoing analysis will identify other metabolites that were affected by the different interventions.

21.2
INSULIN SIGNALING IN MYOTUBES DERIVED FROM OBESE ADULTS WAS NOT IMPAIRED IN RESPONSE TO A MIXTURE OF FATTY ACIDS RESEMBLING THAT FOUND IN HUMAN PLASMA

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The primary aim of this study was to examine alterations in insulin signaling in myotubes derived from muscle of obese adults in response to 12h incubations in lipid mixtures containing the most abundant fatty acids in human plasma (i.e., oleate, palmitate, linoleate, stearate, palmitoleate). We compared: 1) a "normal" physiologic mixture of these fatty acids (NORM; 40% saturated), 2) a mixture very high in saturated fatty acids (HSFA; 60% saturated), and 3) 100% palmitate (PALM). At 0.4mM, PALM markedly suppressed insulin-stimulated phosphorylation of Akt ($pAkt^{Thr308}$) and AS160 ($pAS160^{Thr642}$) (both $P<0.001$), but impairments in insulin signaling were not found with NORM at this concentration. Doubling the concentration of NORM to 0.8mM still did not impair insulin signaling. In contrast, 0.8mM HSFA reduced $pAkt^{Thr308}$ and $pAS160^{Thr642}$ (both $P<0.004$), suggesting the “saturation-state” of available fatty acids may impair insulin signaling in primary human skeletal muscle cells. However, because the proportion of saturated fatty acids in our HSFA solution was far greater than that ever observed *in vivo*, further study is needed to examine the effects of a more physiologic elevation in saturated fatty acids. The main findings from this study indicate that the robust impairment in insulin signaling with palmitate incubation was not found when myotubes were exposed to a mixture of fatty acids resembling that commonly found in human plasma.

21.3
SKELETAL MUSCLE FATTY ACID SYNTHASE MODULATES SARCOPLASMIC RETICULUM PHOSPHOLIPID COMPOSITION TO REGULATE INSULIN SENSITIVITY AND MUSCLE STRENGTH

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Abnormal lipid metabolism is implicated in the pathogenesis of skeletal muscle insulin resistance. Endogenous fat production is not thought to impact muscle insulin resistance, but we recently reported (*Diabetes* 61: Suppl 1, 102-OR, 2012) that the lipogenic enzyme fatty acid synthase (FAS) was increased in skeletal muscle of mice with diet-induced obesity. Moreover, FAS knockout in skeletal muscle (FASKOS) mice were protected from diet-induced insulin resistance. Dogma holds that FAS is cytoplasmic, but we discovered a pool of sarcoplasmic reticulum (SR) resident FAS that modulates sarco/endoplasmic reticulum calcium ATPase (SERCA) activity. In muscles deficient in FAS, decreased SR phosphatidylethanolamine and increased SR phosphatidylcholine was associated with lower SERCA activity. The reduction in SERCA activity in FAS deleted muscles led to calcium-mediated activation of AMP-activated protein kinase (AMPK) signaling that was abolished with overexpression of SERCA1. Elevated AMPK likely explains the increased insulin sensitivity phenotype of FASKOS mice, but decreased SERCA activity also led to muscle weakness. Thus, inhibition of skeletal muscle FAS prevents obesity-associated diabetes in mice, but comes at the expense of decreased muscle strength, suggesting that mammals have retained the capacity for lipogenesis in muscle to preserve physical performance in the setting of disrupted metabolic homeostasis. Funding sources: NIDDK, AHA and ADA.

21.4
POST-EXERCISE VALUES FOR MUSCLE AS160 PHOSPHORYLATION AND INSULIN-STIMULATED GLUCOSE UPTAKE ARE GREATER FOR CHOW-FED VS. HIGH FAT FED RATS

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Previous studies demonstrated that acute exercise can cause increased insulin-stimulated glucose uptake (ISGU) concomitant with increased T642-phosphorylation of Akt Substrate of 160 kDa (pAS160) in muscles of rats with normal insulin sensitivity prior to exercise. Because little is known about mechanisms for exercise effects on ISGU in insulin-resistant muscle, our goal was to assess exercise effects on ISGU and pAS160 in muscles from rats fed normal rodent chow (14% kcal fat, low fat diet, LFD) or a high fat diet (60% kcal fat, HFD, for 2wk to induce insulin resistance). Half of the rats from each

diet group were sedentary (LFD-SED & HFD-SED), and the others performed 2h of exercise (LFD-EX & HFD-EX). At 3h post-exercise (3hPEX), both epitrochlearis muscles from each rat were isolated. Paired muscles were incubated with [3H]-2-deoxyglucose ±100μU/mL insulin. Insulin-stimulated muscles from HFD-SED vs. LFD-SED rats had lower values for ISGU and pAS160. At 3hPEX, ISGU in muscles from HFD-EX rats was increased sufficiently to attain values that were similar to the LFD-SED group even though exercise did not elevate pAS160 in HFD-EX rats. For muscles from LFD-EX rats, ISGU and pAS160 were elevated to attain values that were greater than both the LFD-SED and HFD-EX groups. These results indicate that exercise can enhance muscle ISGU of both LFD and HFD rats, and suggest the greater ISGU in LFD-EX rats may be related to this group attaining greater pAS160 at 3hPEX.

21.5

PERILIPIN 2 AND 5 ARE NOT MODULATED BY PHYSIOLOGICAL STRESSORS AFFECTING TRIACYLGLYCEROL STORAGE OR UTILISATION IN SKELETAL MUSCLE

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Background: Recent studies using forced protein expression in cell lines indicate that recently identified proteins of the Perilipin (PLIN) family are important for the regulation of triacylglycerol (TG) storage and mobilisation. This study tested the hypothesis that physiological stressors known to affect TG storage or lipolysis would modulate PLIN2 and 5 gene expression, protein content and localization in skeletal muscle. Methods: Murine studies: C57Bl/6J mice were subjected to acute fasting/refeeding, 6 weeks high-fat diet, and 6 weeks endurance exercise training, as well as two genetic models of dys-regulated TG metabolism. Skeletal muscle was collected to determine mRNA and protein content. Human studies: Nine males completed 1 h of cycle exercise at 60% VO2 max. Skeletal muscle biopsies determined PLIN5 and ATGL distribution and colocalization with lipid droplets (LD) through immunohistochemistry. Results: Murine studies: There was no difference in the protein content of PLIN2 and 5, ATGL or its co-activator CGI-58. There was no difference in gene expression of Plin 2 and 5 in any of the models. Human studies: There was no difference in PLIN5-LD colocalization following exercise whereas ATGL-LD colocalization increased following 60 min of exercise. Conclusions: These results demonstrate that skeletal muscle PLIN2 and PLIN5 expression are not regulated by prolonged fasting, high-fat feeding or endurance exercise training, nor are they altered in models of lipolytic dysregulation. Furthermore, PLIN5 is not recruited to the LD following acute exercise, questioning the role of this protein in TG metabolism. These studies were funded by research grants from the Australian Research Council and Monash University.

21.6

DIVERGENT EFFECTS OF L-CARNITINE ON PYRUVATE-SUPPORTED O_2 CONSUMPTION AND H_2O_2 EMISSION WITHIN PERMEABILIZED MYOFIBERS

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Pyruvate dehydrogenase (PDH) is one of the seven potential sites for $O_2^{\bullet-}$ generation within mammalian mitochondria. PDH flux is linked to metabolic balance via the NADH/NAD^+ and acetyl-CoA/CoA ratios, which along with pyruvate exert allosteric regulation on the complex. To determine if PDH supported H_2O_2 emission is sensitive to matrix levels of acetyl-CoA, saponin permeabilized fibers were prepared from red gastrocnemius muscle of rats and energized with pyruvate [1mM] as the sole substrate. Under these conditions acetyl-CoA rapidly accumulates within the matrix and PDH flux is minimal. Addition of L-carnitine removes accumulated acetyl-CoA via the activation of carnitine acetyltransferase (CrAT) and formation/export of acetyl-carnitine. Following the addition of 5mM L-carnitine, pyruvate supported NADH production increased ~3 fold (-Carnitine 37.75 ± 2.54, +Carnitine 113.20 ± 8.22 pmol/sec/mg dw; $P<0.001$, N=6) oxygen consumption increased ~ 8 fold (-Carnitine 25.92 ± 2.43, +Carnitine 222.70 ± 19.03 pmol/s/mg dw; $P<0.001$, N=6), and H_2O_2 emission decreased by ~50% (-Carnitine 1.82 ± 0.47, +Carnitine 0.90 ± 0.28 pmol/min/mg dw; $P<0.05$, N=6). These data demon-strate the divergent relationship between PDH catalytic flux and H_2O_2 emission and suggest that PDH-supported H_2O_2 emission *in vivo* may be maximal under conditions of elevated acetyl-CoA/CoA in conjunction with low metabolic demand (i.e., positive meta-bolic balance combined with low activity level). RO1 DK073488.

21.7

REDUCED RESPIRATION IN SKELETAL MUSCLE MITOCHONDRIA FROM OBESE MICE IS ASSOCIATED WITH DECREASED SIRT3 EXPRESSION AND HYPERACETYLATION OF MITOCHONDRIAL PROTEINS

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Reversible lysine acetylation has emerged as a critical regulator of the activity of several metabolic enzymes. Here we investigated if mitochondrial lysine acetylation is altered in skeletal muscle of obese mice. Mitochondria were isolated from hindlimb muscles of wild-type and *ob/ob* mice and acetylated proteins were immunoprecipitated and analysed by mass spectrometry. We identified ~150 proteins that were acetylated in muscle mitochondria. Of these proteins, 15 were acetylated only in wild-type mitochondria, while interestingly, 93 mitochondrial proteins were acetylated only in *ob/ob* muscle. The markedly higher acetylation levels in *ob/ob* mitochondria was associated with decreased mitochondrial function, with significantly ($P<0.05$) reduced rates of ADP-stimulated respiration observed with multiple substrates. *Ob/ob* muscle also exhibited reduced expression of the NAD^+-dependant deacetylase enzyme Sirt3 (2.44 vs. 1.83 AU, $P<0.05$). To investigate whether changes in Sirt3 expression could directly affect mitochondrial function, we overexpressed Sirt3 in skeletal muscle of adult rats using adeno-associated virus. Overexpressing Sirt3 increased mitochondrial respiration, indicating that specific upregulation of this enzyme can enhance mitochondrial function. Our findings suggest that reduced respiratory capacity of *ob/ob* mitochondria may be partly due to reduced Sirt3 expression and a subsequent hyperacetylation of mitochondrial proteins. Supported by the NHMRC of Australia.

21.8

ACUTE HEAT TREATMENT ALTERS ADIPOSE TISSUE FATTY ACID HANDLING

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We have previously shown that chronic heat treatment improves whole-body and skeletal muscle insulin resistance and results in a decrease in epididymal adipose tissue (AT) mass. The purpose of the present study was to examine the effects of an acute heat treatment on lipolysis in multiple AT depots. Male Wistar rats consumed a high-fat (HF) or chow diet for 6 weeks. After 6 weeks, rats received either sham (20 min, 37 °C) or heat (20 min, 42 °C) treatment via lower body water immersion. 24 h following treatment, AT explants from the subcutaneous, epididymal, and retroperitoneal depots (SCAT, eWAT, and rpWAT, respectively) were removed for *ex vivo* experiments. Explants were incubated with water (basal) or epinephrine (Epi) for 2 h and glycerol and non-esterified fatty acids (NEFA) released into the media were assayed. Protein expression was measured from frozen AT using standard Western blotting procedures. Heat treatment increased basal fatty acid re-esterification in SCAT. Heat treatment reduced Epi-stimulated fatty acid re-esterification in rpWAT in chow-fed animals. HF diet altered lipolysis in a depot specific fashion. Heat treatment increased heat shock protein 72 (Hsp72) expression in all AT depots and increased citrate synthase and total AMPK expression in rpWAT. In conclusion, acute heat treatment altered fatty acid re-esterification and lipid handling in AT in a manner that may decrease lipogenesis, while increasing the ability to oxidize fatty acids. NIH AG031575.

21.9

THE UPREGULATION OF GENES INVOLVED IN FATTY ACID OXIDATION IS DEPRESSED WITH SEVERE OBESITY

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PURPOSE: Severely obese individuals are unable to increase fatty acid oxidation (FAO) in response to dietary lipid, which may contribute to positive lipid balance and weight gain. The purpose of the present study was to determine whether fatty acids differentially regulate genes that play a role in FAO in human skeletal muscle cell cultures (HSkMC) from lean and severely obese women. **METHODS:** mRNA content was measured using real-time PCR in HSkMC from 9 lean (BMI= 22.8 kg/m^2 ±2.2; Age= 23.4yrs ±4.6) and 10 severely obese (BMI= 41.3 kg/m^2 ±4.9; Age= 30.2yrs±8.3) Caucasian women following a 48hr incubation in 1) lipid (250μM oleate:palmitate) or 2) 5% BSA (control). **RESULTS:** The lipid-induced responses of critical genes that play a role in FAO were signifycantly (obese vs. lean, all at $p<0.05$) dampened with obesity: PPARα obese 0.85- vs. lean 1.30-fold increase; PPARδ obese 0.83- vs. lean 1.52-fold increase (in response to lipid); NRF-1 obese 0.90- vs. lean 1.59-fold increase; and NRF-2 (GABPA) obese 0.91- vs. lean 1.56-fold change. **CONCLUSIONS:** The induction of broad transcriptional regulators such as the PPARs and NRF-1 and -2 was reduced in HSkMC from severely obese individuals. The inability to activate these critical genes during periods of increased lipid presence, such during an overnight fast or the dietary consumption of lipid, could contribute to the depressed FAO evident with severe obesity. Funding support provided by NIH Grant AG025205.

21.10

POSTPRANDIAL HEPATIC TRIACYLGLYCEROL SECRETION AND FATTY ACID OXIDATION ARE NOT ALTERED BY PRIOR AEROBIC EXERCISE IN OBESE-SUSCEPTIBLE SPRAGUE-DAWLEY RATS

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Postprandial triacylglycerol (TAG) concentrations are reduced in humans when prior aerobic exercise is performed, but the mechanisms are unknown. We hypothesized aerobic exercise would shift hepatic fatty acid partitioning away from TAG synthesis and secretion and toward fatty acid oxidation (FAO) in obese-susceptible Sprague-Dawley rats fed a normal chow (NC) or high fat (HF) diet. Thirty rats were randomized into one of four groups including 1) NC, 2) NC-acute exercise (NC+Ex), 3) HF, and 4) HF-acute exercise (HF+Ex). Rats in the Ex groups performed 1-hr of treadmill exercise (12.6 $m \cdot min^{-1}$) without electric shock at 2200-2300 h. At 0800 hr the next morning, the rats

were intravenously injected with Tyloxapol (lipoprotein lipase inhibitor) 30 min prior to oral gavage with a 20 calorie meal (40% fat, 45% carbohydrate, and 15% protein) to assess postprandial hepatic TAG secretion in-vivo. Blood was taken via tail vein at baseline and every hr for 4 hr to assess TAG secretion. A week later, the same rats performed the acute exercise bout again, and hepatic FAO was measured with ^{14}C palmitate. Acute aerobic exercise did not alter postprandial hepatic TAG secretion or FAO in either diet group, however, secretion rates were higher in NC compared to HF fed rats, regardless of acute exercise ($P<0.05$). Reduced postprandial hepatic TAG secretion is not a mechanism by which acute exercise reduces postprandial TAG levels.

21.11
ACTIVATION OF THE FAT METABOLISM BY HIGH-INTENSITY SPRINT EXERCISE

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INTRODUCTION: To investigate the behaviour of the fat metabolism after short exercise with maximal intensity we performed 2 repeated Wingate tests (WT) series, one on a cycle ergometer and the other with a forearm ergometer. **METHODS:** *Series 1)* 13 subjects performed two WT separated by a break of 60 s. The WT were followed by the rest period of 30 min. In arterialized blood [Lac] and [Gluc] and in cubital venous blood acid base status, [Lac], [Gluc], and fat metabolites were determined. *Series 2)* 9 subjects performed the WT with handgrip exercise. Arterialized blood was sampled from a heated hand vein. Blood draining the working muscle was collected from the cubital vein to determine PCO_2, [Lac], [Gluc], [fGlyc], [FFA], pH, Hb, HCT. Blood flow was determined plethysmographically. **RESULTS:** *Cycling*: [Lac] increased to 13.6±2.6 ($p<0.001$), pH in venous blood decreased to 7.119±0.094 ($p<0.001$). [fGlyc] rose from 0.06±0.04 to 0.25±0.08 mmol/l ($p<0.001$) and [FFA] from 0.36±0.331 to 0.50±0.0401 mmol/l ($p<0.003$). *Hand grip:* Immediately after the second WT pH in venous blood decreased to 7.110±0.032, and PCO_2 increased to 103.3±12.9 Torr (both $p<0.001$). After terminating of the WT, there was a significant uptake of glucose ($p<0.03$). During the recovery phase a significant release of fGlyc from the forearm occurred ($p<0.001$). Simultaneously there was an increase in FFA uptake ($p<0.003$). **CONCLUSION:** Both series show that short exercise of maximal intensity activates the fat metabolism.

21.12
ERYTHROPOIETIN INCREASES MITOCHONDRIAL CAPACITY IN WHITE ADIPOSE TISSUE IN MICE

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Erythropoietin (Epo) has been shown to exert effects beyond just the regulation of red blood cell production. In humans, Epo treatment has been demonstrated to increase resting energy expenditure and mitochondrial capacity in skeletal muscle. These effects have been related to increased fat oxidation and mitochondrial biogenesis in animals. More recently, the Epo receptor (EpoR) has been identified in white adipose tissue (WAT), and disruption of Epo-EpoR signaling leads to the development of obesity. We hypothesize that one of the contributors explaining the protective effects of Epo against high-fat diet induced obesity is an increased metabolic potential of WAT. Therefore, we investigated mitochondrial capacity in Wt mice (n=4), mice receiving 65 U/kg of Epo every other day during 3 weeks (Wt-Epo, n=4) and mice constitutively overexpressing Epo (Tg6, n=4). After euthanasia, WAT was harvested and mitochondrial capacity was measured ex vivo using fresh tissue via high-resolution respirometry. Acute Epo treatment and chronic overexpression of Epo enhanced mitochondrial respiration (normalized to wet weight) through complex I, complex II and OXPHOS, as well as electron transport system capacity when compared to Wt mice. Our preliminary results suggest that Epo increases mitochondrial capacity in WAT, although further investigations are needed to elucidate the relevance and importance hereof.

21.13
RESVERATROL SUPPLEMENTATION IMPROVES GLUCOSE HOMEOSTASIS AND WHITE ADIPOSE TISSUE METABOLISM IN A DEPOT-SPECIFIC MANNER IN ZUCKER DIABETIC FATTY (ZDF) RATS

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Resveratrol (RSV) is a polyphenol suggested to have anti-diabetic properties. This study examined the effects of RSV on whole-body and white adipose tissue (WAT) metabolism. Five-week old ZDF rats were fed a chow diet with (ZDF RSV) or without (ZDF chow) resveratrol (200 mg/kg body weight). After 6 weeks, rats were sacrificed, blood collected, and WAT explants from subcutaneous (scAT) and visceral depots were incubated to quantify glyceroneogenesis and adipokine release. ZDF RSV showed lower fasting glucose ($p<0.05$) and higher adiponectin ($p<0.05$), as well as lower glucose area under the curve during I.P. glucose and insulin tolerance tests ($p<0.05$). Insulin-mediated glucose uptake in soleus strips was higher in RSV-fed rats ($p<0.05$). Taken together, these data indicate that glucose tolerance and insulin sensitivity are improved with RSV in type 2 diabetes (T2D). Mechanistically, ^{14}C-pyruvate incorporation into triglycerides ($p<0.05$) and state III respiration ($p<0.05$) were higher in scAT of ZDF RSV compared to ZDF chow and this was associated with increased COX4 protein ($p<0.05$). Adiponectin secretion was elevated in scAT from RSV-fed rats. *In vitro* treatment of scAT with RSV (50 μmol/L) also tended to increase PDK4 ($p=0.08$) and PEPCK ($p=0.06$) mRNA expression at 6 h. Overall, this study suggests that RSV may modulate glucose homeostasis in T2D, through, at least in part, increases in glyceroneogenesis, respiration and adiponectin release in scAT. Funded by NSERC and OGS.

21.14
HEMOLYSIS DUE TO LACTATE INFUSION: IS PH OR OSMOLARITY THE CULPRIT?

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Prolonged hyperlactatemia is of interest as a potential therapy and is relatively easy to achieve; however, maintaining normal acid-base balance is a challenge. Infusion of neutral sodium lactate (NaLa) leads to alkalosis whereas lactic acid (HLa) infusion can cause acidosis and severe hemolysis. Literature is limited on the relation of osmolarity and pH of aqueous NaLa/HLa infusates to hemolysis. **PURPOSE:** Examine the effect of aqueous NaLa/HLa solutions of varying pH and osmolarity on hemolysis of whole blood *in vitro*. **METHODS:** *Osmolarity.* To 1.0 mL of freshly drawn whole dog blood, Na^+La^- solutions ($pH = 7.40 \pm 0.01$) with varying concentrations were added to achieve a $[La^-]$ of 20 mM. *pH.* To 1.0 mL of freshly drawn whole dog blood, an iso-osmolar lactate/lactic acid solution with varying pH was added, resulting in $[La^-]$ of 20 mM. *Combined osmolarity and pH.* Based on the above, the osmolarity experiment was repeated, but with non-physiological pH. **RESULTS:** Addition of an iso-osmolar Na^+La^-solution with low pH to whole dog blood induced more hemolysis than adding a high tonicity Na^+La^- solution at physiologic pH. Higher osmolarity (range 650 to 2000 mM) Na^+La^-solutions resulted in significantly more hemolysis with lower pH. **CONCLUSION:** Low pH is a more significant factor than osmolarity in causing hemolysis. In whole blood the hemolysis caused by addition of a 2000 mM Na^+La^- solution was only a fraction of the hemolysis caused by adding a low pH iso-osmolar solution.

21.15
VERIFICATION OF AN INTRACELLULAR LACTATE SHUTTLE IN HUMAN SKELETAL MUSCLE

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Lactate is recognized as an important intermediate metabolite for different tissues. It is debated whether lactate can be taken up and oxidized directly by skeletal muscle mitochondria. Controversies persist because of the uncertainty regarding mitochondrial purity obtained with isolation procedures. The aim of this study was to analyze the ability of skeletal muscle to oxidize lactate using a mitochondrial preparation that leaves the native tubular reticulum and subcellular interactions of the organelle unaltered. Biopsies were obtained from the m. vastus lateralis in 16 human subjects. Samples were chemically permeabilized with saponin, selectively perforating the sarcolemma while leaving the mitochondrial membranes intact. Cytosolic lactate dehydrogenase (LDH) is lost during this procedure. Respirometric analysis was performed on the mitochondrial preparations using 4 separate and specific substrate titration protocols. We show that mitochondria are capable of oxidizing lactate in the absence of cytosolic LDH and the addition of exogenous LDH fails to further stimulate respiration. These results demonstrate that human skeletal muscle mitochondria are capable of oxidizing lactate independent of extramitochondrial conversion to pyruvate and verify the existence of an intracellular lactate shuttle and a functional lactate oxidation complex in human skeletal muscle mitochondria.

21.16
EFFECTS OF DIETARY INDUCED OBESITY AND EXERCISE TRAINING ON HEPATIC CIDE EXPRESSION

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The cell death-inducing DFF45-like effector (CIDE) family of proteins plays an important role in lipid droplet formation and triglyceride storage in both adipocytes and hepatocytes. The purpose of the present study was to determine the effects of dietary-induced obesity and voluntary wheel running (WR) on the expression of CIDEA and CIDEC in liver. C57B6 male mice were assigned to the following groups: low fat diet sedentary (LFDSED), LFDWR, high fat diet sedentary (HFDSED), and HFDWR. Following 10 weeks of the respective treatments, insulin sensitivity, adiposity, and hepatic CIDEA and CIDEC expression were assessed. Blood glucose values during an insulin-assisted glucose tolerance test were significantly higher in HFDSED compared to LFDSED mice and this effect was prevented by WR. As expected, the changes in insulin sensitivity due to a HFD and WR were associated with changes in body weight and adipose tissue mass. The expression of CIDEA and CIDEB mRNA increased significantly in livers of HFDSED compared to LFDSED mice and this effect was also prevented by WR. The expression of PPARγ and RIP140, nuclear receptors that regulate CIDEs, were significantly elevated in livers of HFDSED compared to LFDSED mice, a

response that was not altered by WR. These results indicate that CIDEs are important for storing excess triglycerides in the liver during dietary-induced obesity, but how CIDEs are regulated by exercise remains to be established.

22.0: MUSCLE INJURY

22.1

ROLE OF LKB1 IN SKELETAL MUSCLE REGENERATION AFTER INJURY

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During skeletal muscle regeneration satellite cells are activated and proliferate before differentiating into myotubes and/or fusing with existing myofibers. Liver kinase B1 (LKB1) plays an important role in skeletal muscle differentiation in culture. Our purpose was to determine the role LKB1 plays in 1) myogenic regulatory factor expression in skeletal muscle and 2) muscle regeneration after cardiotoxin (CTX)-induced damage. We found that protein content for Myf-5, Myf-6 and MyoD were 47%, 45% and 29% lower, respectively, in gastrocnemius muscles from skeletal muscle-specific LKB1 knockout (KO) vs. control (C) mice (n=6/group). To induce muscle damage, C and KO mice (n=4/group) were injected with CTX into the right tibialis anterior (TA) muscle. The left TA served as a control. The mice recovered for 7 days after which both TAs were harvested and prepared for immunohistochemistry. Hemotoxylin and eosin staining showed that the percentage of muscle fibers with centralized nuclei in un-injured muscles was similar between C (2.9%) and KO (2.3%), but after CTX injection was lower in KO (9.0%) vs. C (23.7%) muscles, suggesting a defect in muscle regeneration in the absence of skeletal muscle LKB1. Our findings demonstrate the importance of LKB1 in normal muscle regeneration after acute muscle injury. Funded by NIAMSD Grant AR-51928 and BYU Mentoring Environment Grants.

22.2

MESENCHYMAL STEM CELLS CONTRIBUTE TO EXERCISE-INDUCED SKELETAL MUSCLE HYPERTROPHY AND STRENGTH

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We have demonstrated that mesenchymal stem cells (mMSCs) accumulate in skeletal muscle overexpressing the □7 integrin (□7Tg) and □7Tg mice exhibit increased muscle growth following exercise. **PURPOSE:** The purpose of this study was to determine whether mMSCs isolated from α7Tg muscle contribute to exercise-induced growth. **METHOD**: Sca-1$^+$CD45$^-$ cells were isolated from α7Tg gastrocnemius (GAS), and labeled with DiD. Recipient C57BL/6 mice were exposed to 30 min downhill running 1 hour before cell injection (4×10^4) or saline into both GAS. Animals were then assigned to either sedentary (SED) or exercise trained (EX) group. EX mice were exposed to downhill running 3 times/wk for 4 wk. **RESULTS:** Mean fiber cross sectional area, percentage of larger caliber fibers (>2000 μm^2) and number of nuclei per fiber were significantly increased in Cell/EX compared to Saline/SED and Cell/SED ($P<0.05$). In addition, hindlimb muscle grip strength was significantly increased in mice receiving stem cell transplanttation following exercise. **CONCLUSIONS:** This study demonstrates that the α7 integrin-mediated growth may occur as a result of mMSC accumulation in skeletal muscle following eccentric exercise.

22.3

PROLIFERATION OF HUMAN MYOBLASTS CULTURED IN SERUM OBTAINED AFTER SPRINT EXERCISE

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Maintenance and repair of skeletal muscle is strongly related to the function of satellite cells (SaCs). Systemic and local environmental factors seem to be important for proliferation and differentiation of SaCs. However, the function of the human SaCs and the influence of environmental factors are largely unknown. It has previously been shown that sprint exercise increases growth factors such as growth hormone and insulin. Hence the aim of the present study was to determine the cell proliferation of cultured SaCs in medium supplemented with serum from subjects performing sprint exercise. Method: 18 subjects (8 F and 8 M) at the age of 20 – 30 yrs performed three 30s all out cycle sprints with 20 min rest in between each sprint. Sera were withdrawn from forearm vein at rest, 9 min after second and third sprint and one and two hours after third sprint. SaCs were extracted from vastus lateralis biopsies from one healthy male subject aged 25 years. Cells were cultured in medium containing 20% sera at different cell concentrations in triplicate and cell proliferation was measured with BrdU-ELISA kit. Result: A significant decline was seen in cell proliferation rate in cells grown with sera obtained up to two hours following the three bouts of sprint exercise. Conclusion: There was no improved proliferation among satellite cells cultivated in sera obtained up to two hours after sprint exercise, despite the earlier observed increase in growth factors as a result of such exercise.

23.0: MUSCLE FUNCTION AND ADAPTATION II

23.1

SPACE RADIATION ENVIRONMENT CREATES ION-SPECIFIC INCREASES IN MUSCLE MASS IN SIMULATED LUNAR GRAVITY

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The impact of galactic cosmic radiation (GCR) exposure during long duration spaceflight on skeletal muscle is relatively under-studied. Even less is known about any concurrent effects that may occur in conjunction with partial weight-bearing, as one might encounter in the Lunar and Martian environments. The focus of this study was to examine the effects of simulated GCR, using either ^{28}Si or ^{56}Fe in conjunction with partial loading similar to that experienced on the Lunar surface. Female BalbC/ByJ mice were separated into weight bearing or partial suspension. Groups were further divided by radiation species, receiving 50cGy of either 300 MeV ^{28}Si or 1 GeV ^{56}Fe, or a sham exposure. A single, whole body irradiation was carried out on Day 0, and gastrocnemius muscles (GAST) were weighed after 21d of full or partial loading. Results are as follows: all muscle masses were significantly ($p<0.05$) reduced following 21d of simulated Lunar gravity in non-irradiated controls. In the presence of ^{28}Si, GAST mass increased with unaltered protein concentrations, suggesting an increase in muscle tissue. Animals subjected to ^{56}Fe had an increase in GAST mass in the Lunar group but exhibited a decreased protein concentration, indicating non-muscle protein additives in the tissue. This work may be the first to demonstrate an ion-specific increase in muscle mass, with varying effects resulting.

23.2

SHORT-TERM INTENSE EXERCISE TRAINING REDUCES MARKERS OF CELLULAR STRESS IN HUMAN SKELETAL MUSCLE

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The purpose of this study was to examine the influence of short-term intense exercise training on molecular factors related to skeletal muscle stress, oxidative damage and protein turnover. Ten recreationally active subjects (47±2 ml·kg·min^{-1}, 25±2 yr, 79±3 kg) completed a 12-day study protocol, during which subjects performed steady state (45-60 min/session at ~78% VO_2max) and interval (6x5 min bouts at ~91% VO_2max) cycling sessions on alternating days, for 11 consecutive days. Skeletal muscle biopsies were obtained from the vastus lateralis at rest on days 1 (D1) and 12 (D12) to measure protein content and mRNA expression. SAPK/JNK phosphorylation was 23±11% lower ($P<0.05$) on D12 compared to D1, suggesting a reduction in skeletal muscle cellular stress. Muscle protein oxidation, measured using the Oxyblot technique, was unaltered following the cycling protocol. Training tended ($P \leq 0.08$) to increase protein content for markers of cell protection (MnSOD, 63±30% and HSP70, 14±7%). MuRF-1 mRNA was 75±24% higher ($P<0.05$) and myostatin mRNA transcripts were 55±22% lower ($P<0.05$) on D12, which is consistent with increased muscle protein turnover. Collectively, these data provide a molecular basis for the increase in skeletal muscle protein turnover following exercise training and suggest that short-term intense training reduces basal cellular stress and creates a cellular environment that may be conducive for adaptation. *Supported by NIH AG032127.*

23.3

EFFECTS OF 12-WKS OF AEROBIC EXERCISE TRAINING ON SKELETAL MUSCLE INSULIN SENSITIVITY, MITOCHONDRIAL BIOENERGETICS, SUBSTRATE UTILIZATION, AND ENERGY EXPENDITURE IN PREMENOPAUSAL WOMEN

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Background: Aerobic exercise can improve skeletal muscle insulin sensitivity (SI), mitochondrial function, and increases energy expenditure (EE); however whether improvements in SI and mitochondrial function are due to negative energy balance (EB) induced by the exercise training remains to be determined. Purpose: To assess SI, mitochondrial bioenergetics, substrate utilization, and EE under rigorously controlled EB conditions pre- and 12-weeks post aerobic exercise training (AET) in premenopausal women. Methods: Eight women (age = 32±4; weight = 75±11kg; BMI = 28kg/m2) were assessed at baseline and 12-wks post- AET. Room calorimetry was used for 24-hrs to determine EE, and to insure EB prior to euglycemic hyperinsulinemic clamp measures for SI. Muscle biopsies were obtained, and in situ mitochondrial function was determined in permeabilized muscle fibers using high-resolution respirometry. Results: Mitochondrial bioenergetic analyses are ongoing. A significant improvement in SI occurred following AET (baseline SI clamp = 7.9 ± 3.1; 12wks-post = 11.2 ± 5.1; $P < 0.05$). The 24- respiratory quotient significantly decreased following AET (0.92 ± 0.03 to 0.87 ± 0.03; $P < 0.05$). Importantly there were no significant differences between 24-hr energy intake and EE at baseline compared to 12-wks post AET. No significant changes in EE occurred following training. Conclusion: These preliminary data suggest that increases in SI following 12-weeks of AET occur when changes in EB do not occur.

23.4

SKELETAL MUSCLE OF EXTREMELY OBESE WOMEN IS INSENSITIVE TO ATROPHIC STIMULI

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Obesity is characterized by impairments in carbohydrate and lipid metabolism. Surprisingly, the regulation of protein metabolism, which is essential to the control of skeletal muscle mass and whole body metabolism, is largely unknown. **GOALS:** To determine the effects of obesity on protein turnover and metabolism. **METHODS AND RESULTS:** Body composition assessment using DXA of 79 women (BMI 20-70) revealed that arm, leg, and total lean body mass (LBM) was significantly higher in the obese (BMI>30). Furthermore, LBM correlated positively with fat mass in a logarithmic fashion, suggesting a diminished hypertrophic response in the extremely obese. To assess protein metabolism directly, cultured skeletal muscle myotubes were pooled from four lean (BMI 23 ± 2) and extremely obese (BMI 41 ± 4) women. Basal rates of protein synthesis (^{3}H-Tyrosine incorporation) and degradation (^{3}H-Tyrosine pulse-chase) were similar between pools despite increased mRNA (RT-PCR) for the atrophy-related genes myostatin (2.0 fold), FoxO3 (2.1 fold), and MuRF-1 (4.3 fold) in the obese. Induction of atrophy by serum and amino acid deprivation increased protein degradation rate and decreased synthesis rate to a lesser extent in obese myotubes, despite a greater increase in Atrogin-1 and MuRF-1 mRNA. **CONCLUSIONS:** Protein metabolism, especially protein turnover, is markedly impaired in skeletal muscle of extremely obese women, which may contribute to the whole-body metabolic deficiencies of obesity.

23.5
ACETAMINOPHEN HAS NO EFFECT ON INTEGRIN SIGNALLING FOLLOWING 5-WEEKS OF TREADMILL EXERCISE IN RAT SOLEUS MUSCLE

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Acetaminophen (APAP) has been shown to increase muscle mass following chronic exercise. Exercise, through mechanotransduction, has been shown to be necessary for skeletal muscle hypertrophy by increasing proteins necessary for protein synthesis. In skeletal muscle, the alpha7beta1 integrin detects stretch and coordinates protein signaling through focal adhesion kinase (FAK). FAK signals through the downstream proteins c-Src and extracellular signal-regulated kinase 1/2 (ERK). Exercise, as well as surgical overloading, has been shown to increase integrin signaling in rats and mice. No study has looked at the role of acetaminophen and the integrin pathway following aerobic exercise. PURPOSE: The purpose of this study was to determine if 5 weeks of aerobic exercise would effect expression of alpha7beta1 integrin, FAK, c-Src and ERK in the soleus of control or acetaminophen-treated rats. METHODS: 10 week old male Wistar rats were randomly assigned to either an exercise group (EX; n=5) or an exercise group + APAP (AP; n=4). Rats ran in progressive volumes (up to 60min/day) at 20m/min with an 8˚ grade for 5 weeks. Rats assigned to the EX+APAP received 200mg/kg/day of APAP via oral gavage while saline was administered to CON daily. Protein expression was determined using Western immunoblotting and spot densiometry. RESULTS: There were no differences in the concentration of the beta1 subunit between CON and AP (p=.466), focal adhesion kinase (p=.117), c-Src (p=.753) or ERK(p=.606). CONCLUSION: Consuming acetaminophen has no effect on the alpha7beta1 integrin, FAK, c-Src or ERK1/2 following 5 weeks of aerobic exercise training.

23.6
SIRT1 AND AMPK ACTIVATORS PROMOTE PHENOTYPIC ADAPTATIONS IN DYSTROPHIC SKELETAL MUSCLE AND REPRESENT PRE-CLINICAL THERAPEUTICS FOR DMD

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We have shown recently that chronic pharmacological activation of PPARδ and AMPK stimulates a shift towards a slower, more oxidative fiber type, increases utrophin expression, and ameliorates the dystrophic pathology in mdx mice (Miura et al. Hum Mol Genet. 18:2640-49, 2009; Ljubicic et al. Hum Mol Genet. 20:3478-93, 2011; Ljubicic et al. Am J Physiol Cell Physiol. 302:C110-21, 2012). Resveratrol (RSV) activates SIRT1, while metformin (MET) exerts its anti-diabetic effect, in part, by activating AMPK in skeletal muscle. Here, our goal was to assess whether RSV and MET could evoke beneficial phenotypic plasticity in skeletal muscle. C_2C_{12} muscle cells treated with 50 μM RSV or 2 mM MET increased utrophin, SIRT1, PGC-1α, and PPARδ expression, concomitant with reductions in RIP140. Next, mdx mice were treated with RSV (100 mg/kg/day for 6 wk) and skeletal muscle phenotypic plasticity and function were assessed. SIRT1 content, activity and PGC-1α deacetylation were all increased with RSV, in the absence of any change in PGC-1α content. RSV increased markers of the slow, oxidative myogenic program, including COX IV mRNA and slower MHC isoforms. Peak force was augmented with RSV, while contraction-induced procion orange infiltration was reduced. Thus, MET and RSV administration evokes alterations in the activation and expression of phenotypic modifiers that favor beneficial adaptations in dystrophic muscle. Supported by MDA (USA), CIHR, and Jesse's Journey.

23.7
MIR-23A TARGETS PGC-1A AND REGULATES MITOCHONDRIAL CONTENT IN SKELETAL MUSCLE

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Skeletal muscles contain several subtypes of myofibers that differ in contractile and metabolic properties. Transcriptional control of fiber type specification has been intensively investigated over the past several decades. Recently, microRNA (miRNA) mediated post-transcriptional gene regulation attracts increasing attention. We determined in the present study whether miRNAs could regulate contractile or metabolic properties in skeletal muscle. Microarray analysis revealed that miR-23a was highly expressed in slow muscle compared to fast muscle. We analyzed muscle phenotype of miR-23a transgenic (miR-23a-Tg) mice. The muscle fiber composition was not altered in miR-23a-Tg mice. On the other hand, the amount of mitochondria and PGC-1α expression were significantly decreased in miR-23a-Tg mice. An online database predicted several binding sites for miR-23a on the 3' UTR of PGC-1α. We then subcloned the 3' UTR into down-stream of luciferase reporter vectors. Luciferase activity was markedly reduced when the miR-23a expression vector was co-transfected. In contrast, luciferase activity was markedly increased when the miR-23a expression was knocked down. We next assessed exercise-induced muscle adaptation of miR-23a-Tg mice. Unexpectedly, muscle adaptation of miR-23a-Tg mice was comparable to that of WT mice. These results suggest that miR-23a targets PGC-1α and regulates a basal metabolic property of skeletal muscles.

23.8
PGC-1A IS REQUIRED FOR EXERCISE TRAINING AND RESVERATROL INDUCED EFFECTS ON OXIDATIVE CAPACITY OF MICE SKELETAL MUSCLE

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Aim: The aim was to test the hypothesis that beneficial effects of Resveratrol are mediated through peroxisome proliferator-activated receptor-γ co-activator (PGC)-1α. Methods: Old (15 month of age) whole body PGC-1α knockout (KO) and wildtype (WT) littermates were either exercise trained in running wheels from 3 month of age or sedentary and given either resveratrol supplementation or standard chow. Young (3 month of age) sedentary mice on standard chow served as controls. Skeletal muscles were obtained at respective ages. Results: Capillary/fiber (C/F) ratio of triceps was increased with training and resveratrol supplementation in WT but not in KO mice and the C/F ratio was on average 27% lower in KO than in WT mice in all groups. There was no significant effect of training and/or resveratrol on quadriceps cytochrome (Cyt) C protein content but Cyt C was significantly lower in old KO than in old WT mice. Citrate synthase (CS) activity and protein content of pyruvate dehydrogenase (PDH)-E1α and hexokinase (HK) II was increased with training in WT but not in KO mice. Conclusion: The combination of training and resveratrol supplementation increased capillarization of triceps muscle in a PGC-1α-dependent manner. While resveratrol had no effect, PGC-1α was required for lifelong exercise training increased content/activity of CS, PDH-E1α and HKII.

23.9
THROMBOSPONDIN-1 INFLUENCES SKELETAL MUSCLE MITOCHONDRIAL RESPIRATORY ENZYME ACTIVITY

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Meeting the metabolic demands of skeletal muscle during exercise is critical for healthy muscle function. The multi-domain, multifunctional, protein thrombospondin-1 (TSP-1) has been implicated to be vital in regulating pathological and exercise induced skeletal muscle angiogenesis. Recently, it has also been shown that TSP-1 KO mice have increased mitochondrial density and biogenesis. With this new evidence, we hypothesized that TSP-1 KO mice would have increased mitochondrial enzyme activity, while those given a chronic dosage of the potent TSP-1 mimetic ABT-510 would have decreased enzyme activity. We studied 2.5 month old male WT mice (WT), TSP-1 KO's (KO), and WT mice given a chronic dose of TSP-1 mimetic ABT-510 (30mg/Kg/day) via mini osmotic pump for 14 days (ABT). In the gastrocnemius, we found that under basal conditions KO mice had a 46% increase, while ABT mice had a 24% decrease, in Complex I activity compared to WT. We also found that KO mice had a 36% increase and ABT had a 118% decrease in Complex IV activity compared to WT. Complex III was unchanged between groups. These support the notion that TSP-1 may influence mitochondrial function, adding to its importance in regulating skeletal muscle adaptive response to stress, such as exercise.

23.10
LACK OF ALPHA-ACTININ-3 ATTENUATES M-TOR SIGNALING IN HUMAN SKELETAL MUSCLE AFTER SPRINT EXERCISE

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Polymorphism (R577X) in the ACTN3 gene causes a complete loss of α-actinin-3 protein in homozygous individuals (XX-genotype). α-Actinin-3 is a structural component of the Z-disks in type II skeletal muscle fibers and loss of α-actinin-3 has been shown to alter the elastic properties of the sarcomeres. Lack of α-actinin-3 has also been shown to be associated with smaller muscle mass. It is possible that mechanical sensing, important for hypertrophy signaling during muscle contraction, is affected by the altered properties

of the Z-disks which may have implication for muscle growth. The aim of the study was therefore to elucidate if altered signaling via the AKT/mTOR pathway can contribute to explain the ACTN3 associated differences in muscle mass. 18 healthy subjects with different ACTN3 genotype (4 RR, 7 RX and 7 XX) performed three bouts of 30-s sprint exercise with 20 min of rest in between. Muscle biopsy samples were obtained at rest and 140 min after the last sprint. Phosphorylation of Akt, mTOR, p70S6k, rpS6 and AMPK was analyzed by Western Blot. The exercise-induced increase in phosphorylation of mTOR and p70S6k was smaller in XX than in RR/RX ($p=0.06$ and $p=0.031$ respectively) while there was no difference in increase of Akt, rpS6 and AMPK across genotypes. Results of the present study suggest that differences in the regulation of mTOR by mechanically induced signaling events, may contribute to explain the ACTN3 associated differences in muscle mass.

23.11
RESISTANCE EXERCISE ACUTELY INDUCES THE UNFOLDED PROTEIN RESPONSE IN SKELETAL MUSCLE

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The unfolded protein response (UPR) acts to sequester recently synthesized proteins that are misfolded or unfolded to minimize cellular stress. Resistance exercise (RE) stimulates protein synthesis and the accumulation of unfolded proteins may activate the UPR. Aging may impair protein folding, altering the post-exercise UPR that could partially contribute to anabolic resistance and muscle wasting in elderly muscle. 19 young (n=10; 21±3 yrs) and old (n=9; 70±4 yrs) males were recruited to determine if an acute RE bout influences the UPR. Participants completed unilateral RE for the knee extensors (4 sets of 10RM leg press, leg extension) and muscle biopsies were taken from the non-exercised and exercised vastus lateralis at 3, 24 and 48 hours post-exercise. Protein levels of the three UPR effectors increased following exercise. GRP78 and PERK increased at 48hrs post-exercise (458±117%, $p<0.001$ and 138±23% $p<0.01$ respectively) while IRE1α was elevated at 24 and 48hrs (126±18%, $p<0.05$ and 147±20%, $p<0.001$ respectively). Despite elevated protein, GRP78 and PERK mRNA were unchanged however IRE1α increased at 24hrs (151±28%, $p<0.05$). ATF6 mRNA increased at 24 and 48hrs (142±13% and 145±13%, $p<0.01$ respectively), while ATF4 and CHOP were unchanged. In conclusion, acute RE results in UPR activation irrespective of age. Further work is required to clarify whether downstream components of the UPR pathway are stimulated by resistance exercise. Supported by NSERC and CIHR.

23.12
EFFECTS OF AICAR AND/OR EXERCISE ON MUSCLE FUNCTION AND HSP25 AND 70 EXPRESSION IN MICE.

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AMPK agonists, such as AICAR, can be used in the treatment of diabetes since they mimic several effects of exercise such as stimulating muscle glucose uptake. Exercise training can increase muscle levels of heat shock proteins (Hsps), which are associated with improvements in muscle function and insulin-stimulated glucose uptake. These experiments tested the hypothesis that AICAR treatment is associated with increased muscle Hsp70 and 25 levels and reduced fatigability and these effects are potentiated when combined with exercise. Adult mice received daily AICAR (12.5 mg/day) or saline for 7d, with/without voluntary wheel running (RW). Changes in plantarflexor force and fatigability, and Hsp70 and 25 protein were measured with a lever system and Western blot, respectively. AICAR significantly reduced average daily RW distance vs. saline, 1099±133 and 1923±103 m/day, respectively. There were no significant differences in isometric force or fatigability among all treatments. In sedentary mice, AICAR was associated with 3.6- and 1.7-fold increases in muscle Hsp70 and Hsp25 protein levels, respectively, vs. saline. Similar increases in Hsp70 and 25 were associated with exercise vs. sedentary, but the combined effects of AICAR and RW was not greater than saline and RW. These findings suggest that AICAR treatment mimics exercise induced Hsp upregulation in sedentary muscle and may be one mechanism whereby AICAR and/or exercise improves blood glucose regulation.

23.13
EFFECTS OF UNLOADING ON MYOSIN HEAVY CHAIN PHENOTYPES OF SOLEUS MUSCLE IN HEAT SHOCK TRANSCRIPTION FACTOR 1-NULL MICE

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Heat shock proteins (HSPs) and/or stress response may play an important role in the plasticity of skeletal muscle. However, a role of HSPs and/or stress response, which are regulated by heat shock transcription factor 1 (HSF1), in myosin heavy chain (MHC) phenotypes of skeletal muscle is unknown. We examined the effects of HSF1-deficiency on MHC phenotypes of soleus muscles by using HSF1-null mice. Unloading and reloading were applied by 2-week-hindlimb suspension (HS) and reloading following the HS. Slow-to-fast transition of the fiber type composition was not observed in HSF1-null mice. The expression of myosin heavy chains in skeletal muscle may be regulated by HSF1. This study was supported, in part, by KAKENHI (22240071, 24650411, 24650407) from the JSPS, and Mutual Aid Corporation for Private Schools of Japan.

23.14
EFFECTS OF AGING AND ENDURANCE TRAINING ON THE MUSCLE–TENDON COMPLEX BEHAVIOR

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The purpose of this study was to investigate whether or not behavior of the gastrocnemius medialis muscle–tendon complex (MTC) during maximum plantar flexion contraction (MVC) is influenced by age or endurance training. Subjects comprised 14 boys, 22 adult males (11 with regular endurance training; 11 without); 18 older males (5 with endurance training; 13 without); and 7 male middle-distance (MD) runners seated on a dynamometer with the knee joint fully extended and the tibio-tarsal joint angle fixed at 90 degrees. Subjects were asked to exert MVC force for 5 s to negate the effect of the reaction force at the beginning of the contraction. During MVC, behavior of the muscle–tendon junction (MTJ) was measured by ultrasonography. Stiffness of the Achilles tendon (SAT) and the angle at the MTJ between the superficial and deep aponeurosis (MTJ angle) were calculated. MVC force and SAT were significantly smaller in boys than in other subjects. The largest MVC force was observed in the MD runners. Older males with regular endurance training showed a significantly larger MVC force and smaller SAT than adult and older males without regular endurance training. Runners contracted the muscle with a smaller MTJ angle than non-runners. In conclusion, the tendon was more compliant in boys than in adult and older males. MTC of older males was characterized by low muscle force and a stiff tendon. However, endurance training likely contributes to increasing the force and tendon compliance.

23.15
ICAM-1 PROMOTES SKELETAL MUSCLE HYPERTROPHY

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We previously reported that β2 integrins, adhesion molecules expressed exclusively by inflammatory cells such as neutrophils, contribute to the hypertrophic response to muscle overload. A potential mechanism for β2 integrin-mediated skeletal muscle hypertrophy involves its ligation to intercellular adhesion molecule-1 (ICAM-1), a major ligand for the β2 integrin CD11b/CD18. We recently found that ICAM-1 is expressed by both satellite cells and myofibers in hypertrophying muscles, which suggests a role for ICAM-1 in skeletal muscle hypertrophy. The current study tested the hypothesis that ICAM-1 mediates the hypertrophic response to muscle overload. Plantaris muscles of wild-type and ICAM-$1^{-/-}$ mice were exposed to a control condition or muscle overload using the synergistic ablation model. Expression of ICAM-1 after muscle overload resulted in greater elevations in all markers of skeletal muscle hypertrophy (total protein content, rate of protein synthesis, cross-section area of myofibers, muscle mass), and regenerating fibers in wild-type vs. ICAM-$1^{-/-}$ mice. In particular, ICAM-$1^{-/-}$ mice showed minimal signs of hypertrophy after muscle overload. Furthermore, neutrophil accumulation in overloaded muscles was higher in wild-type mice. Taken together, our findings demonstrated that ICAM-1 expression on skeletal muscle contributes to the hypertrophic response to muscle overload by providing a potential mechanism for communication between inflammatory and skeletal muscle cells.

23.16
CHANGES IN MUSCLE ATROPHY AND PRO-INFLAMMATORY CYTOKINES IN PATIENTS UNDERGOING ACL RECONSTRUCTION AND REHABILITATION

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Anterior cruciate ligament (ACL) tears are among the most common knee injuries sustained in sports. Even after successful reconstruction of the ACL (ACL-R), patients often suffer persistent quadriceps atrophy and weakness, and are at higher risk of developing osteoarthritis (OA) later on in life. There is limited information on the biology of regeneration following ACL-R. To gain a greater understanding of the biology muscle atrophy and cartilage degeneration following ACL-R, we measured plasma levels of the pro-atrophy/pro-inflammatory cytokines myostatin, TGF-β, TNF-α, IL-1β, IL-6, CRP, and the cartilage degradation biomarker COMP over the course of ACL reconstruction and rehabilitation. We hypothesized that there would be an increase in the levels of pro-atrophy/pro-inflammatory cytokines and COMP after reconstruction, and that values would return to normal levels by the time patients were released to full activities. Compared with the pre-operative measurement, 3 days following surgery there was a dramatic increase in CRP and myostatin levels. CRP levels returned to normal 2 weeks later, but myostatin remained elevated until 5 weeks after surgery. TGF-β levels were elevated 2 weeks following surgery but returned to normal 5 weeks after surgery. Surprisingly, COMP levels were lower 3 days after surgery but returned to pre-operative levels two weeks later. No differences in TNF-α, IL-1β or IL-6 were observed over the study. Combined, these results suggest that the initial muscle atrophy that occurs following ACL reconstruction may be due to increases in myostatin and TGF-β, and pharmacological inhibitors that block myostatin or TGF-β may be useful for preventing quadriceps weakness following ACL-R.

24.0: EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE

24.1
LOW-INTENSITY INTERVAL TRAINING ATTENUATES INCREASED MRNA EXPRESSION OF EXTRACELLULAR MATRIX REGULATING BIOMARKERS IN MINI-SWINE WITH COMPENSATED HEART FAILURE

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Left ventricular (LV) hypertrophy caused by pressure overload is correlated with extracellular matrix (ECM) remodeling, characterized in part by increased fibrosis, and plays a significant role in the development of diastolic dysfunction in heart failure (HF). Our laboratory has previously shown that low-intensity interval treadmill training attenuates increased fibrosis following aortic-banding in miniature swine. The purpose of this study was to measure the expression of several regulatory biomarkers (matrix metalloproteinases and their tissue inhibitors; MMP/TIMP's) and ECM components in aortic-banded (AB) sedentary (AB-S, n=8), AB exercise trained (AB-TR, n=8) and sedentary control (CON, n=8) male Yucatan miniature swine. Increased LV fibrosis was associated with augmented mRNA expression of MMP-2, MMP-9, TIMP-1, and TIMP-4 in AB-S compared to CON animals. Enhanced expression of these biomarkers was attenuated by exercise. There were no group differences in total LV collagen content. However, analysis of collagen isoforms demonstrated a training-induced increase in Type III mRNA expression and a concurrent increase in fibronectin. In conclusion, our results suggest exercise attenuates fibrotic LV remodeling via two potential mechanisms: 1) maintenance of normal MMP/TIMP expression; and 2) altering collagen isoform composition. Exercise may attenuate diastolic impairment in HF by promoting more compliant ECM fibrotic components and preserving ECM regulatory mechanisms.

24.2
MECHANICAL LOADING AND TGF-B REGULATE THE EXPRESSION OF MULTIPLE MIRNAS IN TENDON FIBROBLASTS

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Tendons link skeletal muscles to bones and are important components of the musculoskeletal system. There has been much interest in the role of miRNA in the regulation of musculoskeletal tissues to mechanical loading, inactivity and disease, but it was unknown whether miRNA is involved in the adaptation of tendons to mechanical loading. We hypothesized that mechanical loading and TGF-β treatment would regulate the expression of several miRNA molecules with known roles in cell proliferation and extracellular matrix synthesis. To test our hypothesis, we subjected untrained adult rats to a single session of mechanical loading and measured the expression of several miRNA transcripts in Achilles tendons. Additionally, as TGF-β is known to be a central regulator of tendon growth and adaptation, we treated primary tendon fibroblasts with TGF-β and measured miRNA expression. Both mechanical loading and TGF-β treatment modulated the expression of several miRNAs that regulate cell proliferation and extracellular matrix synthesis. We also identified mechanosensitive miRNAs, miR-338 and miR-381, that may bind to the 3'UTR of the bHLH transcription factor scleraxis, which is a master regulator of limb tendon development. The results from this study provide novel insight into the mechanobiology of tendons, and indicate that miRNA could play an important role in the adaptation of tendons to growth stimuli.

25.0: FATIGUE

25.1
BEHAVIOR OF THE TIBIALIS ANTERIOR MUSCLE-TENDON COMPLEX DURING REPEATED MAXIMUM ISOMETRIC DORSIFLEXION

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The present study was designed to examine how behavior of the tibialis anterior (TA) muscle–tendon complex is influenced by repeated isometric maximum voluntary dorsiflexion contractions (MVC). Subjects were 20 males seated on a dynamometer chair with the knee joint fully extended and the tibio-tarsal joint angle fixed on the platform at 90 degrees. A task consisting of 5 s MVC followed by 5 s relaxation was repeated 50 times (8 min 20 s), without giving feedback on the number of repetitions to the subjects. Average electromyography (EMG) and frequency power spectrum were calculated from EMG signals. Length (LT) and elongation (ET) of the tendon structures, as well as the pennation angle (PA) at the point where a fascicle arose from the deep aponeurosis, were measured by ultrasonography. Stiffness of the tendon (ST) was also calculated. After the task, blood lactate concentration was significantly increased, and MVC force, ET, and LT were decreased. PA and ST remained unchanged. Similar changes were observed during the task. MVC per average EMG increased significantly, while mean power frequency decreased. Interestingly, the plantar flexion force increased during TA relaxation with the progress of the task as if it stretched TA that got into the dull movement. These findings imply that fatigue induced by repeated MVC influences muscle function but not tendon structure. In conclusion, fatigue lengthened muscle fibers with incomplete shortening but without changes in PA.

25.2
WHAT DETERMINES THE TIME-COURSE OF PERFORMANCE LOSS AND MUSCLE FATIGUE IN DIFFERENT MODES OF DYNAMIC EXERCISE?

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For nearly a century, investigators have noted the exponential loss in performance that occurs as the duration of an all-out effort increases from seconds to minutes. Our lab group has previously found that the exponents describing the decrements in performance for sprint cycling and sprint running are similar between individuals, but differ between modes of exercise. Here, we tested the hypothesis that these different rates of loss are set by the relative duration of muscle activity in the specific modes. We used a custom ergometer and all-out knee-extension exercise to maintain constant muscle contraction durations, and altered the portion of inactivity; resulting in cycles with muscle activity that were either 25 or 75% of the total. Subjects completed a minimum of 10 all-out trials in each condition at force requirements selected to elicit failure between 3 and 300 s. In support of our hypothesis, the exponential rate of force loss was greatest at the 75% duty cycle($k_{0.75}$=0.018 [sem= ±0.001]s^{-1} vs $k_{0.25}$=0.009 [±0.001]s^{-1}; p<0.001). When we accounted for the different contraction frequencies necessitated by our experimental manipulation, by evaluating rates of fatigue as a function of the cumulative duration of muscle activity (trial duration • duty cycle), the between condition differences disappeared. We conclude that during brief all-out exercise, rates of performance loss are determined by the cumulative duration of muscle activity.

25.3
THE EFFECT OF METABOLIC ALKALOSIS ON LOCALISED NEUROMUSCULAR FATIGUE DURING INTERMITTENT, HIGH-INTENSITY CYCLING AT A FIXED CADENCE

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Nine recreationally active participants completed four intermittent, high-intensity (30s work: 30s recovery at 120% peak power output) cycling conditions (Placebo 60 rpm (*P60*), Alkalosis 60 rpm (*A60*), Placebo 90 rpm (*P90*) and Alkalosis 90 rpm (*A90*)) implemented in a randomized manner separated by 1 week. Alkalosis was induced through ingestion of 0.3g·kg^{-1} sodium bicarbonate over a 90 min period. Peak force (maximal voluntary contraction (MVC)) was measured following each 30s work period, while neuromuscular activity was assessed via surface electromyography (sEMG). Neither the influence of cadence (60 or 90 rpm) nor alkalosis had an independent effect on the MVC fatigue profile, however a main effect for condition was evident with *P90* exhibiting a greater decline in force production when compared to all other conditions (p<0.02). Neural recruitment of the gluteus maximus (GM), vastus lateralis (VL) and medialis (VM) initially increased in all conditions but by task failure had also declined similarly across all conditions, and with the exception of GM, remained impaired 10 min post. Conduction velocity (CV) and rate of force development (RFD) declined in all conditions, however only CV remained inhibited 10 min post (p<0.05). The fatigue associated with repeated, high-intensity intermittent cycling is independent of pre-exercise acid-base manipulation or cadence.

25.4
INFLUENCE OF ALTERED DUTY CYCLE ON CRITICAL POWER DURING HANDGRIP EXERCISE

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The purpose of this study was to examine the effect of duty cycle on fatigue during handgrip exercise using the power-duration relationship. Handgrip testing was conducted at 20 contractions/min using duty cycles of either 20% or 50% time-under-tension (TUT), while concentric contraction duration was held constant. To date, 2 subjects have completed maximal incremental tests for the determination of peak power (Ppeak) and at least 3 constant power tests for the determination of critical power (CP) and W` for both 20% TUT and 50% TUT. Each subject also completed six one-handed MVCs (three per arm) which were summed together and averaged to provide a two-handed MVC. The average two-handed MVC was 809 N. Ppeak from the incremental tests were 6.25 W for 20% TUT and 5.00 W for 50% TUT. For 20% TUT, CP was 3.5 W which equated to 56% Ppeak and 32.5% MVC. For 50% TUT, CP was 3.0 W which equated to 60% Ppeak and 27.9% MVC. W` was 620 J and 412 J for 20% TUT and 50% TUT, respectively. In conclusion, a shorter duty cycle (20% TUT) leads to increased handgrip exercise performance and tolerance as seen by higher Ppeak, CP, and W` values compared to a longer duty cycle (50% TUT). Funding was provided by NASA grant NNX10AK60G awarded to TJB.

26.0: PHYSICAL ACTIVITY IS NECESSARY FOR OPTIMAL BRAIN FUNCTION

26.2
BRAIN BLOOD FLOW AND EPIDEMIOLOGY OF COGNITIVE DECLINE

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Epidemiological data indicates that habitual physical activity is protective against age related cognitive decline. Interventional studies in animals support this view and the limited longitudinal data in humans is also supportive. In this context, traditional vascular risk factors (hypertension, altered blood lipids, and diabetes) are also risk factors for age related cognitive decline. Together these findings raise the possibility that at least some of the protective effects of physical activity in maintaining cognitive function might be due in part to positive effects on the cerebral microcirculation. In this talk we will review what is known about aging and cerebral vasodilator function and how it is altered by physical activity. We will also compare and contrast what is known about physical activity and the cerebral circulation with data from other more thoroughly studied vascular beds. The main questions flowing from our analysis and the ideas outlined above are: 1) To what extent is age related cognitive decline linked to microvascular dysfunction in the cerebral circulation? 2) Could this be the triggering event? or 3) Is cognitive decline an epiphenomenon that follows other pathological changes in the brain? In either case we argue that the role of microvascular dysfunction in the cerebral circulation is under appreciated as either a primary cause or amplifier of age related cognitive decline.

26.4
POTENTIAL NEUROBIOLOGICAL MECHANISMS BETWEEN PHYSICAL ACTIVITY AND COGNITIVE FUNCTION

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Physical activity is an essential product of evolution. Our ancestors must face both physical and mental challenges for survival. The modern age may have tilted the balance of natural selection more towards mental capability. The long-term consequences of these changes are not known. However, for the time being, the price of physical inactivity may have to be paid. Recent studies suggest that physical activity influences brain structure and function across the lifespan of human beings. Physical activity appears to modulate the fundamental biological processes of the brain from gene expression to neural circuit plasticity. Not surprisingly, physical inactivity has been identified as an important risk factor for brain diseases such as the Alzheimer's type of dementia. However, significant knowledge gaps exist in our understanding a potential causal relationship between physical activity and brain structure and function. For example, at present we do not know the specific biological signal(s) or the signaling pathways which brain may use to sense changes in physical activity, they are either neural and/or humoral, regional inside the brain or from the systemic circulation. Practically, questions such as types of physical activity, influences of individual genotype, as well as a potential "does-response" relationship need to be addressed to capitalize the salutary effects of physical activity on cognitive function. The revolution of contemporary molecular biology and neuroimaging technology provide us with an unprecedented opportunity to understand the fundamental relationship between physical activity and cognitive function. (NIH R01AG033106).

26.5
HOW DOES AEROBIC EXERCISE PROTECT AGAINST DEMENTIA

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August D. Alzheimer's first patient, realizing she could not answer his questions said, "I lost myself." This poignant remark indicating lost cognitive abilities has become too frequent. 5.4 million Americans have Alzheimer disease (AD), which is the 6th leading cause of death, but it is the only one in the top 10 that can't be prevented. A recent 1 year prospective, controlled study by Erickson and colleagues reported aerobic exercise (compared to toning and stretching) in persons age range 55-80 (mean 67), resulted in increased anterior hippocampus volume correlating with improved fitness, better visual memory and increased plasma Brain Derived Neurotrophic Factor (BDNF). This study has strong epidemiological and mouse experimental support. However, it does not address a crucial question, that is, will aerobic exercise protect the brain in the setting of asymptomatic pre-Alzheimer disease, recently defined by Sperling and colleagues. From postmortem and brain amyloid (Aβ imaging studies we know that more than 80% of persons age ≥85 have significant A□ deposits. These deposits occur 10-15 years prior to AD diagnosis and provide a window of opportunity at prevention. Would exercise protect at mean age 75, when more than 40% of cognitively normal persons have Aβ deposits? This paper addresses the animal and human evidence supporting that exercise may be a broad spectrum intervention against the three commonest causes of dementia, AD, vascular disease and synuclein related dementia. Graff-Radford NR. Can exercise protect against dementia? Alzheimers Res. Ther. 2011 Feb 28;3(1):6.

27.0: THE IMPACT OF HEAT SHOCK PROTEIN EXPRESSION ON MUSCLE METABOLISM, EXERCISE CAPACITY AND DISEASE PREVENTION

27.5
TARGETING HEAT SHOCK PROTEINS IN THE PREVENTION OF INSULIN RESISTANCE

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Aging, insulin resistance, and type 2 diabetes are associated with a diminished heat stress response. The highly conserved family of proteins known as heat shock proteins (HSPs) serves as one of the body's major endogenous defense systems against oxidative stress. Although limited clinical data exist on HSPs and insulin resistance, patients with type 2 diabetes demonstrate reduced gene expression of heat shock protein 72 (HSP72), which correlates with reduced insulin sensitivity. Previous studies have demonstrated that an increase in HSP72 via heat treatment, transgenic overexpression, or pharmacologic means results in protection against diet- or obesity-induced glucose intolerance and insulin resistance. Increased understanding of HSPs indicates they are involved in a number of adaptive responses in skeletal muscle including mitochondrial biogenesis, regulation of apoptotic pathways, cytoprotection, and improvements in insulin sensitivity. Enhancing the body's endogenous defense system of HSPs, through a variety of treatment approaches including exercise and heat, could have a profound impact on future approaches to disease prevention and treatment.

29.0: INTEGRATED EXERCISE RESPONSE

29.1
JUMPING ABILITY OF LONG-DISTANCE RUNNERS

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This study was designed to investigate the jumping ability of long-distance (LD) runners in comparison with athletes of other sports. A total of 46 LD runners, 34 other event athletes, 7 ball players, and 13 healthy untrained males volunteered to participate in this study. LD runners were divided into two groups (good and poor) based on their running performance. They performed 3 vertical jumps (VJ), 3 drop jumps (DJ), and 1 exercise of 10-consecutive jumps (RJ), which were filmed at 300 Hz. Jumping height, DJ and RJ indexes were lower in LD runners than in other subjects. In particular, VJ height was less than that of healthy untrained males. Good LD runners achieved better height in VJ, DJ, and RJ and showed better indexes for these exercises than poor LD runners. The jumping movement of LD runners was characterized by smaller extension at the ankle and larger extension at the hip on take-off. In the first half of the ground contact phase, angular displacement of the lower limb joints was smaller in LD runners than in other event athletes and healthy untrained males during VJ, whereas it was larger during DJ and RJ. Similar differences were observed between good and poor LD runners. The results suggest that the jumping ability of the LD runners was less than that of the other sport athletes because of lower leg power and insufficient stretch–shortening cycle behavior. The characteristics observed in LD runners are likely influenced by duration and type of training method.

29.2
PEAK HEART RATE AND PERFORMANCE IN SEVERE HYPOXIA: DIFFERENCES BETWEEN TIBETANS AND HAN CHINESE

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The mechanism for the reduction of aerobic performance in conditions of severe hypoxia is still poorly understood. One unexplained finding is the reduction in peak heart rate observed in newcomers at altitude. Even though limitation of exercise performance is matter of muscle fibre recruitment and therefore located in the central nervous system (CNS), the signals leading the CNS to reduce or stop motor-unit recruitment remain to be better understood. A recent hypothesis is that hypoxic pulmonary vasoconstriction (HPV) leads to pulmonary hypertension, right ventricular over-load, thus limiting cardiac output and curtailing performance. Tibetans show less HPV and less performance decrement in hypoxia compared to others. We therefore compared Tibetans and Han Chinese, both living at 2300m, during running at 5000m in a hypobaric chamber, under placebo vs. inhaled furosemide (to decrease pulmonary afferent traffic) and iloprost (to decrease HPV). Tibetans had less decrement in performance going from 2300m to 5000m and reached similar maximum heart rates, independent of the intervention (heart rates always > 200 bpm); Han Chinese had lower heart rates at 5000m compared to 2300m, while furosemide partially restored maximum heart rate and iloprost improved performance. These findings are in agreement with the stated hypothesis. Since aerobic performance remains reduced at 5000m for both Tibetans and Han Chinese after intervention, additional mechanisms must be involved in the reduction of maximum aerobic exercise capacity in conditions of severe hypoxia.

29.3
SHORT-TERM EFFECTS OF INTENTIONAL BIODYNAMIC CRANIOSACRAL THERAPY ON VO2MAX AND HEART RATE RECOVERY: A PILOT STUDY

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PURPOSE: To investigate the short-term effects of biodynamic craniosacral therapy on haemodynamic and cardiopulmonary parameters during the Rockport Fitness Walking Test (RFWT), a field aerobic test. **METHODS:** Nine subjects (4 women and 5 men) underwent 3 sessions of craniosacral therapy and the RFWT thereafter in order to assess the potential changes after the treatment; six subjects (3 men and 3 women) received placebo treatment as controls. Measurements of the VO_{2max} and haemodynamics parameters were recorded at rest, before the treatments, during and after the RFWT. The results were compared by using XLSTAT 2008 software; $P \leq 0.05$ indicated a significant change. In order to increase the analytical strength, the zero statistical significance was fixed at $P \geq 0.1$. **RESULTS:** The VO_{2max} showed a significant difference ($P = 0.04$) but the Heart Rate Recovery was almost unchanged after the treatment. **CONCLUSIONS:** Biodynamic craniosacral therapy seems to have a direct influence only on the VO_{2max}.

KEYWORDS: Haemodynamic, Craniosacral Biodynamic, Rockport Fitness Walking Test, Beta-Blockers, Intention.

29.4

THE EFFECTS OF DIFFERENT MODES OF EXERCISE ON THE ASSOCIATIONS BETWEEN APPETITE AND APPETITE-RELATED GUT HORMONES

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The purpose of this study was to determine the effects of different modes of exercise (i.e. weight bearing exercise versus non-weight bearing exercise) on the associations between appetite and appetite-related gut hormones. Fifteen healthy young men (age, 24.4 yrs; maximal oxygen uptake, 47.0 ml/kg/min) participated in this study. After 12-h fasting, all subjects undertook two trials, rope skipping exercise (64.8 } 1.8% of VO2max (52.0 76.8% of VO2max), 3 sets x 10 min with 5 min interval) and bicycle ergometer exercise (63.9 } 1.9% of VO2max (52.2-74.7% of VO2max), 3 sets x 10 min with 5 min interval). Plasma concentrations of acylated ghrelin and peptide YY, and hunger evaluated by visual-analog scale were measured. Both rope skipping and bicycle ergometer exercises significantly suppressed appetite and acylated ghrelin concentrations, and increased peptide YY concentrations. In the bicycle ergometer exercise trial, exercise intensity (%VO2max) was significantly associated with delta changes in appetite and acylated ghrelin and peptide YY concentrations, but these relationships were not observed in the rope skipping exercise trial. In addition, there was a significant association between delta changes in appetite and acylated ghrelin concentrations in the bicycle ergometer exercise trial, but not in the rope skipping exercise trial. In conclusion, exercise intensity-associated changes in appetite and appetite-related gut hormones may disappear in weight bearing exercise.

29.5

VOLUNTARY WHEEL RUNNING THAT ENHANCES NEUROGENESIS DOES NOT ACTIVATE MICROGLIA IN THE MICE HIPPOCAMPUS.

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Research has shown that exercise improves neuronal plasticity, including neurogenesis, in the hippocampus of rodents. However, little is known about how exercise affects non-neuronal cells in the brain. Microglia, the brain-resident macrophages, plays a pivotal role in mediating neuroinflammatory responses in the CNS through producing pro-inflammatory cytokines. When microglia is activated by multiple types of stimuli, morphological transition from a ramified-resting state to an activated (hyper-ramified; reactive; or phagocytic) state occurs. Microglia is also known to proliferate with activation. In this study, we investigated whether voluntary wheel running which can enhance neurogenesis changes activation status of microglia in the mice hippocampus. Male C57BL/6 mice were housed with or without running wheel for 4 weeks. The brains were processed for im-munolabeling of Iba-1 (ionized calcium-binding adaptor protein-1, a marker of microglia) and DCX (doublecortin, a marker of immature neuron). Voluntary running significantly increased DCX-positive neurons in the dentate gyrus, demonstrating that the running successfully enhanced hippocampal neurogenesis. We found no changes in the density of Iba-1 positive immunoreactive materials (i.e. alterations in morphology) and the number of Iba-1 positive cells (i.e. proliferation). These results indicate that the voluntary wheel running enhances neurogenesis but did not alter activation status of microglia in the mice hippocampus.

29.6

BLOOD PRESSURE RESPONSE TO EXERCISE IS NOT RELATED TO VASCULAR ENDOTHELIAL FUNCTION IN OVERWEIGHT/OBESE ADULTS

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Overweight and obesity are associated with endothelial vasodilator and fibrinolytic dysfunction. Recently, data from the Framingham Heart Study has suggested that vascular dysfunction may contribute to exaggerated blood pressure (BP) responses during exercise. Accordingly, we determined if BP response to exercise is related to endothelial vasodilator and fibrolytic function in overweight/obese (OW/OB) adults. 92, sedentary OW/OB adults, were studied. All subjects were free of cardiometabolic disease and completed a Balke exercise treadmill test to volitional exhaustion. Blood pressure was measured at rest, stage 1, stage 2, peak exercise and 3 minutes after exercise. In 50 subjects (32M/18F; age: 55±1 yr; BMI: 29.3±0.3 kg/m^2), forearm blood flow (FBF; plethysmography) was determined in response to intra-arterial acetylcholine (4.0-16.0 µg/100mL tissue/min). In 42 subjects (27M/15F; age: 55±1 yr; BMI: 30.4±0.6 kg/m^2), total release of tissue-type plasminogen activator (t-PA) was determined *in vivo* in response to bradykinin (12.5-50.0 ng/100mL tissue/min). There were no significant relations between the peak FBF response to acetylcholine or total t-PA release and BP at rest (r=0.05; 0.07, respectively), stage 1 (r=0.01; 0.10), stage 2 (r=0.09; 0.05), peak exercise (r=0.07; 0.14), or recovery (r=0.05; 0.15). These results, in marked contrast to the Framingham Heart Study, indicate that BP response to exercise is not associated with vascular endothelial function in OW/OB adults.

29.7

REFLEX SYMPATHETIC NERVE ACTIVITY DURING STATIC HANDGRIP EXERCISE IN HUMAN METABOLIC SYNDROME

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OBJECTIVE: We tested the hypothesis that young adults with metabolic syndrome (MS) exhibit an exaggerated exercise pressor reflex, resulting in increased muscle sympathetic nerve activation (MSNA) when compared with healthy control subjects. **METHODS**: We studied 12 adults with MS (34±3 years) and 12 healthy control subjects (34±3 years). Heart rate (HR; ECG), blood pressure (BP; finger photoplethysmography), and MSNA (microneurography of the peroneal nerve) were measured during 3 interventions: (1) 2 minutes of static handgrip exercise at 15% of maximal voluntary contraction (MVC) [central command, mechanoreceptors], (2) 2 minutes of static exercise at 30% MVC [central command, mechanoreceptors and metaboreceptors], (3) 30% MVC static exercise to fatigue, followed by 2 minutes of post-exercise ischemia (PEI) [metaboreceptors]. Increases in HR, BP, and MSNA were assessed. **RESULTS**: MS subjects exhibited higher BP when compared with controls. During static exercise at both 15 and 30% MVC, increases in MSNA, BP, and HR were similar between groups. BP and MSNA remained significantly elevated from baseline during PEI and responses were similar between groups. **CONCLUSION**: These data indicate exercise pressor reflex control of MSNA is preserved in younger adults with MS. **FUNDING:** AHA 10PRE3870000, NIH HL105820, NIH RR000167.

29.8

INFLUENCE OF DUTY CYCLE ON MUSCLE DEOXY-(HB+MB) DURING RAMP HAND GRIP EXERCISE

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AIM: We tested the hypothesis that the duty cycle of handgrip exercise alters the response of muscle fractional O_2 extraction (as deoxyhemoglobin ([deoxy(Hb+Mb)]) determined via near-infrared spectroscopy (NIRS). **METHODS:** To date, 4 subjects completed incremental handgrip tests to exhaustion at duty cycles of 20% and 50% time-under-tension (TUT), with concentric contraction duration held constant. The signal was normalized to the total amplitude of the response and averaged in bins representing 0-20%, 21-40%, 41-60%, 61-80%, and 81-100% peak power output (PPO). **RESULTS:** During the 20% TUT absolute deoxy(Hb+Mb) significantly increased above baseline within 0-20% PPO. However, during 50% TUT deoxy(Hb+Mb) was only increased above baseline at work rates >60% PPO. The deoxy(Hb+Mb)] signal during 20% TUT, when normalized, tended to be greater than 50% TUT at 0-20% and 21-40% PPO (15.9±10.41% vs -5.52±10.4% and 41.1±9.7% vs 24.2±20.2%, respectively). However at work rates >40% PPO the response was similar. **CONCLUSION:** These findings suggest that during handgrip exercise with a 20% duty cycle, the deoxy-(Hb-Mb) signal (and presumably fractional O2 extraction) rapidly increases at the start of exercise, suggesting a mismatch between blood flow and metabolic rate, but with a 50% duty cycle the response slowly increases over time, indicating a better matching of muscle blood flow and oxygen uptake with increasing work rate. Funding was provided by NASA grant NNX10AK60G awarded to TJB.

29.9

CHANGES IN GLUCAGON RECEPTORS WITH FASTING AND EXERCISE: SIMILAR RESULTS BUT DIFFERENT MECHANISMS

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The purpose of this study was to compare the effects of swimming exercise and fasting periods on liver glucagon receptors (GR). Rats were randomly assigned to a rest/fed control, 90 or 180 min exercise or 6, 12 or 24hr fasting periods. Animals were sacrificed at the end of the exercise or fasting periods, blood was sampled and liver was removed rapidly. Liver plasma membranes were purified and saturation kinetics were obtained by incubation with 125I-labeled glucagon. Total liver lysates were prepared by homogenization and were analysed by electrophoresis and western blot for GR protein. No change was observed in blood glucose levels during exercise and fasting, even if hepatic glycogen concentrations were progressively depleted with both longer exercise and fasting periods. Saturating curve analysis indicated a progressively higher GR density reaching maximal significant values at 180 min of exercise and 24hr fasting periods at a level of 7.74 ± 1.74 and 7.16 ± 1.34 pmol/pg proteins in comparison to control level of 3.09 ± 0.53 pmol/pg proteins. When total GR were compared, no change was noted with exercise but increased with fasting, achieving significance at 24-hr fasting period. In conclusion, these results suggest that both prolonged exercise and fasting increased GR densities. Increased GR densities could be explained by externalization mechanisms in exercise and increased synthesis with fasting. Funded by Natural Sciences and Engineering Research Council of Canada.

29.10

THE METABOLIC RESPONSES TO EXERCISE MODE IN OVERWEIGHT/OBESE ASTHMATICS

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Asthma and overweightness/obesity (OWOB) progress concurrently and are poorly understood. This study characterized the interactions of asthma & OWOB using VO_2max testing. **METHODS:** Stable asthmatics (AS, n=10) and normal-lung individuals (NL, n=15) volunteered. Groups were similar ($p<0.05$, ANOVA) on age (AS=22±4 y; NL=22±2), height (AS=170±9 cm; NL=173±9), and FEV1/FVC (AS=83±5%, NL=80±4), but differed on BMI (AS=27.8±4.5 kg/m^2; NL=24.8±3.5), body fat (%fat, AS=20±3%; NL=14±2), FVC (AS=4.0±0.7 L, NL= 4.6±0.9); and FEV1 (AS=3.3±0.4 L, NL=3.7±0.7). There were three VO_2max trials: 1. treadmill (TM), 2. sit cycle-ergometer (Sit-CE), and 3. stand-up when RER>1.0 (Stand-CE). **RESULTS**: ANCOVA (%fat, covariate) showed differences ($p<0.05$) by group & trial, but no interactions, on VO_2max (AS: TM=32±6 ml/kg/min, Sit-CE=29±7, Stand-CE=28±8; NL: TM=41±4, Sit-CE=36±6, Stand-CE=36±4) and HR_{max} (AS: TM=189±13 bpm, Sit-CE=188±15, Stand-CE=178±17, NL: TM= 180±14, Sit-CE=174±14, Stand-CE=168±11). Group differences occurred on VO_2/HR (AS: TM=13±3 ml/bpm, Sit-CE=12±2, Stand-CE=12±3; NL: TM=18±5, Sit-CE=16±5, Stand-CE=17±4), VCO_2 (AS: TM=3.2±0.7 L/min, Sit-CE=2.8±0.8, Stand-CE=2.7±0.8; NL: TM=3.8±1.0, Sit-CE=3.2±0.7, Stand-CE=3.3±0.9), and VE (AS: TM=89±20 L/min, Sit-CE=87±25, Stand-CE=78±24; NL: TM=105±27, Sit-CE=100±31, Stand-CE=94±27). Not different was RER (AS: TM=1.26±0.09, Sit-CE=1.25±0.09, Stand-CE=1.26±0.16; NL: TM=1.25±0.09, Sit-CE=1.22±0.11, Stand-CE=1.21±0.07). Regression, %fat on VO_2max, showed R^2=23%. **CONCLUSIONS**: These findings demonstrated that, per exercise mode, metabolic responses between groups were generally parallel. The lower AS VO_2max and VO_2max-related values were due to poor physical fitness, not OWOB or cardiopulmonary limits. The study was funded by Southern Arkansas University.

29.11

EFFECT OF INTERVAL TRAINING ON CHANGES IN VO_{2MAX}: A META-ANALYSIS

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The HERITAGE study showed ≈0.4 L/min changes and marked variability in the VO_{2max} responses to continuous training (CT, ≈75% of VO_{2max} for 20 wks Bouchard et al. 2011). Smaller studies using interval training (IT) or combined IT/CT have shown much larger increases in VO_{2max} (≈1.0 L/min, Hickson et al. 1977). This raises questions about the role of exercise intensity for both mean and individual VO_{2max} responses to training. We analyzed IT and IT/CT studies published in English from 1965-2012. Inclusion criteria were: 1) ≥3 healthy sedentary/recreationally active humans <45 yrs old, 2) training duration 6-13 weeks, 3) ≥3 days/week, 4) ≥10 minutes of high intensity work, 5) ≥1:1 work/rest ratio, and 6) results reported as mean ±SD or SE. 28 studies with 308 subjects were identified. Statistical analysis used a fixed effects model with difference in means calculated with a 95% confidence interval (mean 0.436 L/min). Due to mild heterogeneity (I_2 18.1340), a random effects model was also used (mean 0.452 L/min). An estimated distribution for number of subjects vs. change in VO_{2max} was compared to Bouchard et al. We estimate all IT subjects improved VO_{2max} >0.1 L/min, and 26% of the subjects improved ≥0.7 L/min; whereas Bouchard et al. showed 7% of subjects had VO_{2max} gains of ≤0.1 L/min and 8% of subjects improved by ≥0.7 L/min. These results suggest that ideas about the trainability of VO_{2max} should be further evaluated with standarized IT or IT/CT training programs.

29.12

AN ALTERNATIVE APPROACH TO MATCHING RELATIVE WORK AND INTENSITY DOMAINS DURING INTERVAL AND CONTINUOUS EXERCISE

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Superior health benefits have been reported following interval (IE) compared to continuous exercise (CE). However, due to the methods used to match IE and CE for work and intensity, it is unclear whether work rate (WR) oscillations or the intensity domain of IE drives these benefits. PURPOSE: To determine a between-subject protocol in which both the intensity domain and work (kJ) for CE and IE are matched, highlighting the in-appropriateness of previous methods. METHODS: 7 women (age 38±6yr; BMI ≥30kg/m^2) completed a maximal ramp-incremental cycle ergometer exercise test (VO_{2max} and lactate threshold: LT) and either an IE (n=4) or CE (n=3) session. IE WR alternated between 40% Δ at 70% *i.e.* WRVO_{2peak}-WRLT) and 80s of unloaded pedalling (20W) for 30min. CE was set at 20%Δ for the duration required to achieve the same total work that each individual would have accomplished in an IE session. VO_2 was measured throughout and blood lactate (LA) every 5min. RESULTS/DISCUSSION: LA was significantly elevated above baseline (end session LA: CE 3.37±0.46; IE 4.3±2.1mmol), attaining a steady-state after 15min, thus CE and IE were both in the intended heavy-in-tensity domain. Average VO_2 during IE was calculated as 53% of VO_{2max} or a range of 94-124% of LT. Therefore, defining exercise intensity as a % of VO_{2max} would have re-sulted in CE being performed in different intensity domains, whereas our alternative ap-proach allows the influence of intensity and the WR profile to be differentiated.

29.13

INFLUENCE OF EXERCISE MODALITY ON PHYSIOLOGICAL ADAPTATIONS TO SHORT-TERM SPRINT INTERVAL TRAINING

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Short-term sprint interval training (SIT) has been shown to elicit physiological adaptations similar to long-term endurance exercise training. Most SIT studies have focused on cycle ergometer or non-motorized treadmill exercise, but the influence of exercise modality has not been directly addressed. Hypothesis: improvement in endurance exercise performance following SIT will be similar between stationary cycle ergometer (CYC), non-motorized treadmill running (RUN), and a novel exercise modality incorporating repetitive vertical jumping on a pneumatic platform (RVJ). Experimental procedures conformed to the Declaration of Helsinki. 20 sedentary/recreationally-active adults (age: 22±1 yrs; body mass index: 25.1±1.0 kg/m^2; mean±SE) were randomly assigned to RUN (*n*=8), CYC (*n*=4) or RVJ (*n*=8). Following 3 weeks of SIT (9 sessions of 4-8 repeats of 30-second "all-out" maximal exertions separated by 4 minutes of recovery), time to exhaustion while cycling (CYC) or running (RUN & RVJ) at 80% maximal oxygen uptake (VO_{2max}) was increased (*P*=0.009) with RUN (44.5±4.5 *vs.* 57.1±9.4 min) and increased to a greater extent in CYC (48.6±7.4 *vs.* 88.1±18.2 min) but was unchanged in RVJ (32.2±5.2 *vs.* 32.7±4.9 min). VO_{2max} was unaffected by SIT (*P*=0.55), regardless of exercise modality. These preliminary data suggest the SIT-induced improvements in endurance performance are influenced by exercise modality.

29.14

A SINGLE SESSION OF SPRINT INTERVAL TRAINING INCREASES TOTAL DAILY ENERGY EXPENDITURE

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High intensity sprint interval training (SIT) is known to elicit favorable physiological adaptations, including improved insulin sensitivity and glucose tolerance. However, its utility for weight loss is questionable. The objective of this ongoing study is to determine the effects of a single bout of SIT on total daily energy expenditure. 24-hour energy expenditure was determined in 5 healthy men (age: 28±3 yr; body mass index: 23.4 ±0.8 kg/m^2; mean±SE). After three days of controlled diet and maintenance of energy balance, subjects were studied in a whole-room indirect calorimeter for two consecutive days. One of these days (random order) began with a single bout of SIT (5 x 30 second "all-out" exertions on a cycle ergometer against a resistance equivalent to 7.5% body mass, separated by 4 minutes of loadless cycling). A single bout of SIT increased 24-hour energy expenditure in all subjects during an otherwise sedentary day (2463±226 *vs.* 2221±175 kcal/day; *P*=0.0015). Our preliminary data provide support for SIT as a time-efficient alternative to endurance exercise and as a strategy for weight maintenance. Support: University of Colorado Clinical and Translational Science Award (1UL1 RR025780).

29.15

A SINGLE BOUT OF SPRINT INTERVAL TRAINING IN NORMOXIA DOES NOT IMPROVE ENDURANCE EXERCISE PERFORMANCE IN HYPOXIA

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A single bout of sprint-interval training (SIT) produces very rapid favorable adaptions that include initiation of skeletal muscle mitochondrial biogenesis and increased capacity for substrate oxidation. Hypothesis: a single bout of normoxic SIT, completed 18-hours prior to hypoxic exposure, will augment hypoxic exercise performance in adult humans. Experimental procedures conformed to the Declaration of Helsinki. On two separate occasions (random order) 16 healthy men completed a time to exhaustion trial on a stationary cycle ergometer at ~65% maximal oxygen consumption (determined in normoxia) while breathing hypoxic gas (15% O_2). Subjects cycled until they were unable to maintain a cycle cadence > 40 rpm for longer than 30 consecutive seconds. 18-hours prior to one of the time to exhaustion trials subjects performed 5 repeats of 30 seconds of maximal-effort stationary cycle ergometer exercise against a fixed resistance equivalent to 7.5% of body mass in normoxia. Each 30-second effort was separated by 4 minutes of active recovery (loadless cycling). The time to exhaustion was greater in 8 out of 16 men following a single bout of SIT, but the overall effect did not attain statistical significance (33.3 ± 7.1 *vs.* 31.9 ± 7.1 min; mean ± SE; *P* = 0.63). A single bout of SIT produces very rapid and favorable physiological adaptions but does not affect subsequent endurance performance in a low oxygen environment.

29.16

HYPOXIC EXERCISE PERFORMANCE FOLLOWING INTRAVENOUS GLUCOSE ADMINISTRATION: INFLUENCE OF SYMPATHETIC INHIBITION

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Endurance exercise performance (time to exhaustion) is positively associated with basal muscle glycogen content. Sympathetic inhibition promotes insulin sensitivity and glucose clearance in hypoxia, but may impair subsequent hypoxic exercise performance, in part due to suppression of cardiac output. Hypothesis: hypoxic exercise performance following intravenous glucose feeding in a low oxygen environment will be attenuated when feeding occurs during sympathetic inhibition. Experimental procedures conformed to the Declaration of Helsinki. On two separate occasions (random order) glucose (20% glucose solution in saline; 75g) was intravenously administered over 1 hr to 10 healthy men while breathing a hypoxic gas mixture (15% O_2), with and without prior sympathetic inhibition (48-hr transdermal clonidine; 0.2 mg/d). On initiation of glucose administration the clonidine patch was removed. 3 hr after completion of glucose infusion, subjects completed a hypoxic time to exhaustion trial (stationary cycle ergometer, ~65% maximal oxygen uptake determined in normoxia). Time to exhaustion following glucose feeding with/without sympathetic inhibition was not different (22.7±5.4 *vs.* 23.5±5.1 min; mean±SE; *P*=0.73). Sympathetic inhibition protects against hypoxia-mediated insulin resistance without influencing subsequent hypoxic endurance performance.

29.17

SHORT-TERM TRAINING IMPROVES GLUCOSE TOLERANCE AND INCREASES MUSCLE GLUT4, CYTC AND COXI PROTEIN IN ELDERLY MEN

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The aim was to elucidate the molecular mechanims behind training-induced improved glucose tolerance in elderly subjects. Healthy men (n=12) aged 62 to 72 years completed 8 weeks of exercise training consisting of cycling and cross fit exercise. All subjects performed before and after the training period an incremental bicycle VO2max test and time to exhaustion during one legged knee-extensor exercise. In addition, an oral glucose tolerance test (OGTT; 1g/kg bw) with blood sampling up to 2h after and vastus lateralis muscle biopsies obtained before and 45 min after glucose intake was performed. Vo2max increased 19% and time to exhaustion increased 22% with training. While the plasma glucose response during the OGTT was unchanged, the area under the curve for plasma insulin and c-peptide was reduced following the training period. Glucose intake elicited a 2.5-3 fold increase in Akt Thr308 phosphorylation in skeletal muscle with no difference before and after training. However, basal GLUT4, cytochrome c and cytochrome oxidase I protein content in skeletal muscle was 1.2-1.3 fold higher after training than before. In conclusion, these findings suggest that short term high-intensity training may improve glucose tolerance in elderly men in part due to increased total capacity for glucose transport and substrate oxidation.

29.18

THE ADVANTAGES/DISADVANTAGES TO USING CULTURED SINGLE MUSCLE FIBERS AS AN IN VITRO MODEL TO MECHANISTICALLY RESEARCH SKELETAL MUSCLE

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Muscle cell cultures have served as an important experimental approach for many seminal discoveries in skeletal muscle. Currently, immortalized skeletal muscle rodent cells (C2C12 and L6) are the prevailing culture models. Here we demonstrate broad applications for enzymatic isolation and culturing of adult single skeletal muscle fibers (SMF). Using data from our labs, we show that cultured SMF can be used for a variety of physiological and metabolic measures. Mechanical properties can be made using systems to induce passive stretch (force transducer/length controller) or mechanical perturbation (Atomic Force Microscopy). Ionic flux (e.g. calcium transients) can be assessed using real-time imaging techniques. Further, mitochondrial function can be determined using sensitive assays designed to assess oxygen consumption. Also, it is possible to assess glucose uptake of the SMF. Using fluorescence microscopy and specific dyes one can image lipid droplets, mitochondria, and myonuclei in SMF. Lastly, cultured SMF are amenable to gain-of or loss-of function approaches through adenovirus infection or plasmid electroporation. The SMF model is not without disadvantages. Not all muscle groups are amenable to enzymatic isolation of SMF limiting which muscles can be used. In conclusion, cultured single SMF are an important model to consider for studying skeletal muscle since they represent muscle in the adult state from a function and phenotype perspective.

29.19

ACUTE EXERCISE REGULATES AMPK IN BREAST CANCER CELLS

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Cancer cells are generally characterized by a change in cellular metabolism, favouring glycolysis. AMPK regulates cellular metabolism and induces fatty acid oxidation, and has in regard to this been shown to suppress tumor cell growth. During acute exercise AMPK is activated in various tissues including muscles and adipose tissue, and we propose that acute exercise also induces AMPK activity in breast cancer cells, and that such induction is associated with decreased cancer cell growth. Methods: AMPK activation is determined in the two breast cancer cell lines, MDA-MB-231 and MCF-7, using two model systems of acute exercise. 1) In vitro, the cancer cells was incubated with human serum, obtained during an acute exercise trial in healthy young women, cycling for 2 hours at 60% Vo2max, and subsequently resting for 3 hours. 2) In vivo, tumor-bearing mice was subjected to 1 hour of swimming, after which the tumor was dissected and analysed for AMPK activation. Results: Acute exercise induces AMPK phosphorylation at the Thr 172 activation site in both cancer cells stimulated with exercise-conditioned serum and in tumors in vivo. In the in vitro system, phosphorylation at the Thr 172 site was associated the decreased viability of the MCF-7 cells. Conclusion: Acute exercise activates AMPK in breast cancer cells, and this activation might link exercise-induced alterations in breast cancer cell metabolism with the protective effect of exercise on cancer.

29.20

LACTATE AND MTORC1 ACTIVATION IN C2C12 MYOTUBES

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Low intensity exercise with blood flow restriction (BFR exercise) stimulates the mTORC1 signaling pathway in human skeletal muscle by an unknown mechanism. It has been proposed that an increase in muscle lactate indirectly activates mTORC1 signaling via an accumulation of glucose-6-phosphate (G6P). In fact, we have found a correlation between lactate accumulation during BFR exercise and an increase in protein synthesis and G6P in skeletal muscle. The aim of this study was to determine whether an increase in lactate activates mTORC1 signaling in myotubes. To address our aim, C2C12 myoblasts were grown in growth media until 90% confluency and then switched to differentiation media to allow fusion into myotubes. On the day of the experiment, myotubes were serum starved for 4 hours, nutrient starved for 30 minutes, and then a portion was treated with 0.5mM lactate for 30 minutes. The activation of mTORC1 was determined by measuring the phosphorylation status of its downstream effectors via immunoblotting. We found that when myotubes were treated with 0.5mM lactate the phosphorylation of S6K1 (Thr389), rpS6 (Ser240/244), and 4E-BP1 (Thr37/46) increased by 62, 70 and 28% respectively compared to control. In conclusion, our preliminary data suggest that an increase in muscle lactate can activate mTORC1 signaling in myotubes which may be a key mechanism underlying the ability of BFR exercise to promote muscle hypertrophy. Supported by NIH/NIAMS R01 AR049877, P30AG024832, T32HD07539.

29.21

EFFECT OF PROTEIN BLEND VS WHEY PROTEIN POST-EXERCISE INGESTION ON HUMAN SKELETAL MUSCLE AMINO ACID TRANSPORTER EXPRESSION FOLLOWING RESISTANCE EXERCISE

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We have previously demonstrated a prolonged muscle protein synthetic response with in-gestion of a protein blend following resistance exercise. The divergent aminoacidemia between ingestion of a soy-dairy protein blend (multiple amino acid release profiles) and whey protein (single rapid release) may provide a mechanism for this prolonged re-sponse. We have previously explored the separate and combined effects of exercise and crystalline amino acids on select amino acid transporter (AAT) gene expression. How in-gestion of these different intact proteins influences post-exercise AAT gene expression is unknown. Sixteen young adults were randomized into a double-blinded clinical trial and ingested ~20g of a protein blend or whey isolate (N=8 per group) 1hr after a bout of high-intensity leg resistance exercise. Muscle biopsies (vastus lateralis) were obtained at baseline and at 3 and 5h post-exercise for examination of select AAT gene expression (LAT1, PAT1, CAT1, SNAT2 & CD98). There were no group differences. Regardless of protein type the ingestion of intact protein 1 hr following resistance exercise increased mRNA expression of LAT1, PAT1, SNAT2 and CAT1 at 3hr and LAT1, CD98, CAT1 and PAT1 at 5hr post-exercise compared to baseline values. The increase in mRNA expression tended to be greatest at 5 hr. We conclude, that following resistance exercise, the

ingestion of a protein blend or whey protein equally stimulates mRNA expression of select AAT. Funding from Solae LLC.

29.22

COUNTER-INTUITIVE INCREASE IN PLASMA MYOSTATIN AFTER RESISTANCE TRAINING WITH HIGH PROTEIN DIET IN YOUNG HEALTHY SUBJECTS

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INTRODUCTION: Myostatin (MSTN) relationship with body fat amount, training status and nutrition has been widely investigated but with conflicting results. Although MSTN inhibits the Akt/mTor pathway and reduces IGF-1 some studies have shown a "paradoxical" positive correlation between MSTN and muscle mass. We investigated the influence of two months of resistance training (RT) and high protein diet on plasma myostatin, IL1, IL6, TNF-α and IGF-1.**METHODS:** Eighteen healthy volunteers, divided in an high protein diet group (HP) and normal protein diet group (NP), participated in a progressive RT. MSTN, IGF-1, IL1, IL6 and TNF-α were analyzed before and after the first and last training session. Lean body mass, muscle mass, arm muscle area and 1RM test were analyzed. **RESULTS:** MSTN showed a significant increase after the last training in the HP compared to NP. There were no significant differences in IGF-1, IL1, IL6 and TNF-α. IGF-1 showed a positive correlation with MSTN in HP after the last training (r^2=0.6456; p=0.0295). No correlations were found with other blood parameters nor with muscle analysis. **CONCLUSIONS:** We found a "paradoxical" response of plasma MSTN to HP diet after RT. The double increase of IGF-1 and MSTN could explain the overlapping of muscle mass increases in both groups and let us to argue that HP diet influence metabolic regulation of IGF-1 and MSNT upstream the same pathway. This conflicting results could reflect the complexity of MSNT release mechanism.

29.23

THE EFFECT OF MUSCLE CONTRACTION ON CACHECTIC MUSCLE MTOR SIGNALING AND PROTEIN SYNTHESIS IN APCMIN/+ MOUSE

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Cachexia is characterized by muscle mass loss regulated by disrupted protein turnover, which includes the suppression of muscle mTOR signaling and myofibrillar protein synthesis (MPS). Eccentric muscle contraction (EC) stimulates MPS and muscle mass accretion. The purpose of this study was to determine if cachectic TA muscle maintains anabolic plasticity related to EC stimulation of MPS through mTOR signaling during the progression of cachexia. Female C57BL/6 (WT) and ApcMin/+ (Min) mice performed a well-described EC protocol by stimulating the sciatic nerve (10 sets of 6 repetitions, ~ 22 minutes). The tibialis anterior (TA) muscle from one leg was stimulated, while the contralateral leg was the control. The TA muscle was harvested at 3 h, 14h, or 24h after an acute novel bout of EC. Repeated bouts of contraction were performed over 2 wks. TA muscle mass and type IIA and IIB mean fiber cross-sectional area (CSA) were reduced by cachexia. Repeated EC increased TA mass by 5% and the type IIA and IIB mean CSA by 32% and 14%, respectively. Acute EC increased 4EBP1 and p70S6K phosphorylation, but this induction was attenuated by cachexia. MPS was induced by EC but remained suppressed below WT control levels in Min mice. Acute EC also attenuated AMPK phosphorylation, which was induced by cachexia, at 3h and 14 h post EC. These data suggest repeated EC can reverse muscle wasting, but the acute induction by EC is attenuated in cachectic muscle. Funded by NIH Grant RO1CA121249-01.

29.24

EXERCISE TRAINING IMPROVES EXERCISE CAPACITY DESPITE PERSISTENT MUSCLE MITOCHONDRIAL DYSFUNCTION IN THE TAZ SHRNA MOUSE MODEL OF HUMAN BARTH SYNDROME

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Barth Syndrome is a mitochondrial disease associated with exercise intolerance and cardioskeletal myopathy resulting from mutations in the tafazzin (taz) gene. The present study characterized skeletal muscle mitochondrial function and exercise capacity of a taz shRNA mouse model of Barth Syndrome (90% taz-deficient), and examined the effect of exercise training on these parameters. Mitochondrial respiratory function was assessed in mitochondria freshly isolated from hindlimb muscles using an Oroboros O2K respirometer with pyruvate + malate as substrates. Based on results of a graded treadmill exercise test (GXT), training was conducted at 12-17 m/min, 0% grade for 60 min/d, 5d/wk. Baseline experiments revealed a 49% lower muscle mitochondrial state 3 (ADP-dependent) respiratory capacity ($P < 0.05$) and profound exercise intolerance in the taz vs. age-matched wild-type (WT) mice. Exercise training elicited a 99% increase in GXT run time in the taz mice ($P < 0.01$ vs. pre-training), but failed to increase levels to that of sedentary WT mice. Training had no effect on the yield or state 3 respiratory capacity of muscle mitochondria from taz mice, but increased indices of respiratory uncoupling vs. sedentary taz. There was no effect of training on GXT time or any mitochondrial parameters in WT mice. This study indicates that exercise training improves functional capacity of taz deficient mice without eliciting improvements in muscle mitochondrial content or respiratory function.

29.25

EFFECTS OF THE MENSTRUAL CYCLE PHASE ON OXIDATIVE DNA DAMAGE FOLLOWING SUBMAXIMAL CYCLING EXERCISE

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PURPOSE: The purpose of this study was to determine effects of the menstrual cycle phase on oxidative DNA damage following 2 hours of prolonged cycling exercise in women. **METHODS:** Twelve recreationally active eumenorrheic women served as the subjects [Age: 20.9±0.3 year; Height: 160.1±5.6 cm; Body weight: 54.7±5.8 kg; Body fat: 21.9±3.1 %; Peak oxygen uptake (VO_2peak): 44.4±5.0 ml/kg/min (mean±SD)]. Before (Pre) and after (immediately Post and Post 24 hours) 2 hours of cycling exercise at 60%VO_2peak, spot urine was collected for later analysis of 8-hydroxy-2′-deoxyguanosine (8-OHdG; a marker of whole body DNA damage and repair) determined with high performance liquid chromatography. All subjects performed the same exercise protocol during the follicular (F: 5~8 days after the onset of the menses) and luteal (L: 22~25 days after the onset of the menses) phase. **RESULTS:** With regard to 8-OHdG level (ng/mg Creatinine), two-way (time x phase) analysis of variances (ANOVA) showed no significant main effects for time and phase or interaction (Pre: 3.2±1.2, Post: 3.3±1.1, 24h: 3.2±0.8 for F; Pre: 3.0±1.1, Post: 3.1±0.7, 24h: 3.3±0.9 for L). **CONCLUSIONS:** The findings of the present study indicate that the menstrual cycle phase appears not to influence oxidative DNA damage following 2 hours of cycling exercise at 60%VO_2peak. Supported partly by funds from the Grant-in-Aid for Scientific Research (C) in Applied Health Sciences (Grant No.23500867) of Japan Society for the Promotion of Science.

29.26

IMPAIRED EXERCISE CAPACITY IN LIFE-LONG SKELETAL MYOFIBER-SPECIFIC VEGF GENE DELETED MICE

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Exercise capacity is dependent on adequate oxygen for mitochondrial respiration in muscle. To determine whether skeletal myofiber VEGF is critical for regulating exercise capacity, adult skeletal myofiber VEGF null mice (skmVEGF-/-) and control, littermates (WT), were speed and endurance tested on a treadmill. Changes in locomotor skeletal muscle capillarity, muscle and cardiac function, and body weight were evaluated. Endurance (skmVEGF-/- 17.6 ± 4.2 min., WT 77.5 ± 24, $p<0.01$) and maximal speed (skmVEGF-/- 46 ± 10 cm/sec, WT 58.8 ± 5.6, $p<0.01$) were decreased by 80% and 10%, respectively, in skmVEGF-/- mice compared to WT. Capillary to fiber ratio was lower in VEGF-deficient plantaris (skmVEGF-/- 1.16 ± 0.2, WT 1.51 ± 0.12, $p=0.01$) but not the soleus or EDL. Time to fatigue, measured in isolated skmVEGF-/- soleus and EDL was extended by 17% and 20%, respectively ($p<0.02$). SkmVEGF-/- soleus and EDL maximal force did not differ from WT. Cardiac function (heart rate, Max Pressure, Max dP/dt, Min dP/dt, EDP and tau) was not compromised in skmVEGF-/- mice. Body weight was reduced (skmVEGF-/- 22.4 ± 2 g, WT, 19.7 ± 1, $p=0.01$), and soleus but not EDL muscle mass was lower in muscle of skmVEGF-/- compared to control ($p<0.01$). These data suggest that VEGF expressed in skeletal myofibers during development is essential for maximal exercise capacity. This limitation is not due to a deficit in cardiac or locomotor muscle contractile function but may be affected by fewer capillaries.

29.27

EFFECT OF POST-MYOCARDIAL INFARCTION EXERCISE TRAINING ON ANGIOGENESIS

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After a myocardial infarction (MI), adequate growth of new capillaries plays a crucial role in the surviving portion of myocardium. Evidence has shown that angiogenesis is inadequate in the post-MI hearts. **PURPOSE:** To investigate the effect of post-MI exercise training on myocardial angiogenesis. **METHODS:** Left ventricular (LV) MI was surgically induced on 7-wk-old rats by ligation of the left coronary artery (~35% infarction) with sham-operated animals serving as control. The survivors were assigned to three groups (n=4/group): Sham (no MI, no exercise), MIEx (MI+exercise), and MISed (MI, no exercise). Treadmill exercise training (16m/min, 5^0incline, 40min/d, 5d/wk) began at 2 wk post-MI and lasted for 8 wks. Upon completion of the exercise training, hearts were harvested. Transverse cross-sections of the myocardium were stained with CD 31 (an antibody against endothelial cells of capillaries). Capillary densities of the LV, septum, and right ventricle were measured under a light-microscope. Results: The capillary densities of LV in the Sham group (1282±125/mm^2) was higher ($p<0.05$) than both the MIEX (940±82/mm^2) and MISed (605±78/mm^2) groups. The MIEx group had higher ($p<0.05$) LV capillary density than the MISed group. The capillary densities of septum in the Sham (1523±70/mm^2) and MIEx (1247±130/mm^2) groups did not differ from each other, but both of the groups were higher ($p<0.05$) than the MISed (906±24/mm^2) group. There were no significant differences ($p>0.05$) in the capillary densities of RV among the three groups. **CONCLUSION:** These results suggest that post-MI exercise training significantly induces angiogenesis in both the viable myocardium of LV and septum. Such training effect is not observed in the RV. Supported by a grant from the NIH (RO1-HL074273).

29.28

INCREASED BASELINE BUT REDUCED ENDOTHELIAL PROGENITOR CELLS AFTER AEROBIC EXERCISE IN SUBJECTS AT CARDIOMETABOLIC RISK

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Acute exercise is able to improve the function of circulating endothelial progenitor cells (EPC) contributing for the vascular repair in healthy subjects, but it is unknown if this mechanism is presented in subjects with cardiometabolic risk (RC). This study aimed to isolate and quantify the EPC after a single bout exercise in subjects at increased CR. Five healthy subjects ??(CT group: 28±9 years) and four subjects at increased CR (CR group: 35±9 years) were enrolled. The CR group presented at least three of five criteria for the metabolic syndrome diagnosis, while the CT group presented none of them. Blood samples were collected before and 15 min after 40-min exercise or control session to isolate mononuclear cells (MNC). After seven days of MNC culture in EGM-2, the adherent cells were labeled with Dil-acLDL and FITC UEA-1 lectin by immunofluorescence. The protocol was approved by the ethics committee and performed in accordance with the Declaration of Helsinki. The CT group presented lower percentage of EPC at baseline (CT: 30±8% vs. RC: 59±5%; p=0.02). After exercise, the EPC increased in CT group (pre: 30±8% vs. post: 45±7%, p=0.04) whereas they were reduced in CR group (pre: 59±5% vs. post: 51±6%, p=0.03). There were no differences between the groups or moments in the control session (p>0.05). These results suggest that subjects at CR present an increased percentage of EPC at baseline and that a single bout of exercise decreases EPC in these subjects. Support: CAPES, CNPq, FAPERJ and Labs D´Or.

29.29

EXERCISE DECREASES THE LIPOGENIC CAPACITY OF ADIPOSE TISSUE DURING WEIGHT REGAIN

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OBJECTIVE: To assess the effect of exercise on adipose tissue metabolic gene expression during weight maintenance and the relapse to obesity. **METHODS:** Mature, obese rats were weight-reduced for 8wk with or without daily treadmill exercise. Rats were then fed a weight maintenance provision, ad libitum (relapse), or a provision that matched the energy imbalance of exercised, relapsing animals for 1d. Gene expression was measured by qPCR. 24h retention of dietary and *de novo* derived fat were assessed with nutrient tracers. **RESULTS:** Exercise attenuated the expression of genes involved in lipid uptake (CD36 & LPL), *de novo* lipogenesis (FAS, ACC1), and triacylglycerol synthesis (MGAT & DGAT) during weight regain. Most of these effects remained significant after controlling for the reduced energy balance. These observations were consistent with the metabolic data, whereby exercise reduced retention of *de novo* derived fat by 49% (p<0.01) even when controlling for the positive energy imbalance (by 34%, p<0.05). Reflective of CD36 expression, the effect of exercise on the trafficking of dietary fat to adipose tissue was explained by its attenuation of the energy imbalance. **CONCLUSION:** Exercise decreased the lipogenic capacity of adipose tissue during weight regain, both by attenuating the positive energy imbalance and by directly suppressing lipogenic gene expression. These concerted effects may explain the beneficial effects of exercise on weight regain prevention.

29.30

EFFECT OF DAILY EXERCISE ON THERMAL PREFERENCE AND HEAT-ESCAPE/COLD-SEEKING BEHAVIOR IN MICE

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The aim of the present study was to assess the effect of exercise training on behavioral thermoregulation and thermal preference in heat with dehydration, i.e. hyperosmotic condition. We use mice with/without access to a running wheel for 8 wks (WR and NWR groups, n=40 each). After the abdominal placement of a measurement device for body temperature (T_b), mice had s.c. injection of saline (1 ml/100 g of body wt; 154 or 2,500 mM, IS or HS subgroup). A mouse was placed in a box with 5 computer-controlled Peltier boards at the bottom. Three experiments were conducted for 90 min: a) board temperature of 28°C or 39°C; b) operant behavior condition; boards were set at 39°C, and the right-end board was changed at 20°C for 60 s when a mice moved on the left two board; and b) thermal mosaic; each board was set at either 15°C, 22°C, 28°C, 35°C, or 39°C with a 6-min interval. The procedures were conducted under the APS "Guiding Principals in the care and Use of Animals". In "a", the WR group showed higher T_b than the NWR group in both subgroups. In "b", the NWR group showed smaller operant counts in the HS than IS subgroup, but the WR group didn't. Thermal preference was lower in the WR than NWR group without any differences between the subgroups (e.g. 33.4±0.3°C and 34.7±0.1°C in the IS groups). Exercise training may alter behavioral thermoregulation and thermal preference, and restores thermoregulation in dehydration.

29.31

THE CARDIOVASCULAR RESPONSE TO ACUTE EXERCISE IN HYPOXIA AND HYPOBARIA

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We compared exercise cardiovascular responses during acute exposure to hypobaric and normobaric hypoxia. Thirteen healthy, physically active subjects participated in a partial repeated measures study. Each subject completed two visits in three possible conditions, consisting of exposure to low altitude (LA: 300 m), hypobaric hypoxia (HH: 4400 m) and normobaric hypoxia (NH: ambient PO_2= 91 mmHg). Subjects cycled at 50%$HR_{reserve}$ for 10 min. Expired pulmonary gas, hemodynamics measured by bioimpedance and arterial oxygen saturation (SpO_2) were collected over the final 2 min of exercise. Absolute workrate during NH and HH were not different from each other but lower than at LA. VO_2 at HH and NH were similar and lower than at LA. Exercise SpO_2 at HH (67.7±6.2%) and NH (64.4±21.9%) was lower than that at LA (97.8±1.0%), and SpO_2 was lower in NH than HH, suggesting that NH results in greater hypoxic stress. Similarly, cardiac output during NH (12.4±6.4 L/min) was higher compared to both LA (9.5±5.5 L/min) and HH (9.5±4.5 L/min), which were not different from each other. This change in cardiac output was the result of a larger stroke volume during NH (121.7±26.4 ml/beat) compared to LA (89.4±33.3 ml/beat) and HH (86.9±24.8 ml/beat), which did not differ from each other. Furthermore, mean arterial pressure was higher in NH than HH. These preliminary results suggest that there are environmental-specific responses to normobaric and hypobaric hypoxia of identical ambient PO_2. Supported by the DOD Defense Medical Research and Development Program, award number W81XWH1020199.

29.32

NITRIC OXIDE AND HUMAN SWEAT GLAND FUNCTION DURING DIRECT SUDOMOTOR NERVE ACTIVATION

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Intradermal electrical stimulation was used to activate sudomotor nerves and elicit local sweating to examine the effect of nitric oxide synthase inhibition on local sweat rate (SR) in 10 healthy adults. Two intradermal microdialysis probes were place in the skin of the dorsal aspect of the forearm and SR was monitored directly over the microdialysis probe using a small capsule (0.7 cm^2) containing a humidity sensor and thermocouple flushed with dry gas at 100 ml • min^{-1}. Two small stainless steel needles were place into the skin immediately outside of the capsule and stimulated at a current intensity of 2.5 mA for 30 sec at frequencies of 0.2, 1, 2, 4, 8, 16, 32, and 64 Hz. The stimulus-response characteristics of local SR were evaluated following 60 min of saline perfusion and following 60 min of NOS inhibition with 10 mM L-NAME. Local SR data was normalized to the peak SR response at 64 Hz during Saline perfusion. A significant increase in local SR occurred at stimulus frequencies ≥ 8 Hz in both conditions and the stimulus frequency that produced 50% of the increase in local SR was similar for both current intensities (10.1 ± 1.1 Hz). However, SR was lower during L-NAME perfusion at 16, 32, and 64 Hz (p<0.05). The peak local SR response during L-NAME averaged 81.5 ± 4.5 % of that seen during Saline perfusion (p<0.05). Atropine sulfate completely blocked the sweating response to intradermal electrical stimulation indicating that the local SR response was mediated by acetylcholine released in response to depolarization of the sympathetic cholinergic sudomotor nerves. These data support the hypothesis that nitric oxide production facilitates sweat gland function and is associated with activation of the sudomotor nerve.

29.33

THE ACTIVITY OF CYCLOOXYGENASE-1 AND -2 IN HUMAN SKELETAL MUSCLE IS ELEVATED AFTER ACUTE RESISTANCE EXERCISE INDEPENDENT OF CYCLOOXYGENASE-1 AND -2 PROTEIN CONTENT

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The purpose of this study was to evaluate cyclooxygenase (COX)-1 and -2 activity and protein levels in response to acute resistance exercise (RE) in human skeletal muscle. We hypothesized that RE would increase COX-1 but not COX-2 activity. Muscle biopsies were taken from the vastus lateralis of 9 young men (25±1 y) before, 4, and 24 hours after a bout of knee extensor RE (3 sets of 10 repetitions at 70% of maximum). Tissue was assayed for COX-1 and -2 activity (700200, Cayman Chemical). COX-1 and -2 protein was measured via Western blotting. COX-1 activity increased at 4 hours (p<0.05) compared to pre-exercise, but returned to baseline at 24 hours (PRE: 60±10, 4 hrs: 106±22, 24 hrs: 72±8 nmol PGH_2•g total $protein^{-1}$•min^{-1}). COX-2 activity was elevated at 4 and 24-hour post-RE (p<0.05, PRE: 51±7, 4 hrs: 100±19, 24 hrs: 98±14 nmol PGH_2•g total $protein^{-1}$•min^{-1}). The protein level of COX-1 was not altered with acute RE. In contrast, COX-2 protein levels were nearly 3-fold greater at 4 hours and 5-fold greater at 24 hours, when compared to pre-exercise. These data suggest that the activity of both COX-1 and -2 are elevated with acute RE but this elevation is more prolonged for COX-2. The lack of an increase in COX-1 protein, and the fact that COX-2 was continuing to increase at 24 hours, suggests that the increase in COX-1 and -2 activity with acute RE does not require an increase in COX protein. MWU Intramural Funds (CCC) and University of Arizona Sarver Heart Center Award (RJG).

29.34

17-ALLYLAMINO-17-DEMETHOXYGELDANAMYCIN (17AAG) INHIBITS HSP70 RESPONSE IN RAT SKELETAL MUSCLE FOLLOWING PROLONGED ECCENTRIC EXERCISE

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The heat shock response provides cytoprotection against stress-induced cellular damage and has a cross-tolerance effect to a range of stressors including exercise. Treating mice with 17AAG has been shown to increase HSP70 synthesis in skeletal muscle and enhance recovery from exercise-induced muscle damage. However, it is not clear if this is a species specific phenomenon. We hypothesized that 17AAG would increase skeletal muscle HSP70 in rats, thereby protecting against myofibrillar damage following prolonged downhill treadmill running. Rats were randomly treated with 17AAG (40 $mg.kg^{-1}$ body wt) or DMSO 24 h prior to undertaking exercise for 90 min at 16 $m.min^{-1}$ and -16° grade. Red vastus was harvested at 24 h (EX+24h) and 48 h (EX+48h) post exercise, as well as 24 h post treatment in non-exercising groups (Non-EX). Grip strength and serum CK were measured *in vivo* prior to muscle sampling. Downhill running increased post-exercise HSP70 of both 17AAG and DMSO treated animals ($p < 0.001$) but the rise in HSP70 expression was attenuated by 17AAG in EX+24h rats ($p = 0.023$). Electron microscopy showed signs of ultrastructural abnormalities only in DMSO treated EX+24h rats. Muscle calpain and SERCA activity, grip strength and serum CK were not affected. Our data suggest that 17AAG treated rats may have experienced less eccentric contractile strain at 24 h following a moderate-intensity bout of downhill running. This study was financially supported in part by the Faculty of Health Sciences under the auspice of the University of Sydney.

30.0: SIGNALLING

30.1
GLUCOSE METABOLISM AND EFFECTS OF CONTRACTILE ACTIVITY ON SKELETAL MUSCLE GLUCOSE UPTAKE SIGNALING IN SPINAL CORD-INJURED VS. ABLE-BODIED INDIVIDUALS

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Evidence suggests that neuromuscular electrical stimulation (NMES)-induced resistance exercise (RE) in individuals with SCI can improve glucose tolerance; however the mechanisms by which these improvements occur remain unclear. Our purpose is to determine whether muscle glucose uptake signaling responds similarly to NMES resistance exercise in SCI vs. able-bodied (AB) individuals and whether glucose tolerance and whole body insulin sensitivity (WBIS) are impaired in SCI individuals.13 individuals with SCI (ASIA A, B, C; 50 ±11 y), and 13 AB individuals (42±11 y) participated. Oral glucose tolerance tests ([OGTT] at 0 [fasting], 60, 90, and 120 min-post 75 g glucose ingestion) and 80 NMES isometric contractions (~50% MVC) of the vastus lateralis muscle were completed. Muscle samples were collected before and 10 and 60 min after NMES. Western blots were performed to determine the protein levels of phosphorylated- and total Akt, AMPK2 and AS160, and total GLUT4. Muscle protein analysis is ongoing. SCI subjects had greater 60, 90 and 120 min plasma glucose and a greater increase in plasma glucose at 60, 90 and 120 min as compared to the AB individuals. The WBIS were ≈ 50% lower in the SCI group. These results suggest that glucose tolerance and insulin sensitivity are impaired in the SCI group as compared to the AB individuals. Muscle protein analysis results will be presented at the meeting.

30.2
TSC2/RHEB SIGNALING MEDIATES ERK-DEPENDENT REGULATION OF MTORC1 ACTIVITY IN SKELETAL MUSCLE CELLS

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The mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK)-dependent regulation of mammalian target of rapamycin complex 1 (mTORC1) activity and subsequent protein synthesis/cell growth has been suggested, however, the exact molecular mechanisms underlying this regulation are poorly defined in skeletal muscle. The purpose of this study was to determine the regulatory mechanism in MEK/ERK-dependent pathway leading to mTORC1 activation in skeletal muscle cells (C2C12 myoblasts). Consistent with previous studies, treatment with phorbol 12-myristate 13-acetate (PMA), an agonist of the MEK/ERK pathway, resulted in an activation of mTORC1 signaling and phosphorylation of upstream regulator tuberous sclerosis complex 2 (TSC2) at S664 site (ERK-specific residue) in C2C12 myoblasts. MEK-specific inhibitor U0126 prevented PMA-induced mTORC1 activation and TSC2-S664 phosphorylation. Overexpression of Ras homolog enriched in brain (Rheb), a downstream target of TSC2 and an mTORC1 activator, was sufficient to activate mTORC1 signaling. We also identified that, in the absence of Rheb with using siRNA knock down, PMA-induced activation of mTORC1 signaling was significantly prevented. These observations demonstrated that in C2C12 myoblasts, the MEK/ERK-dependent activation of mTORC1 is mediated through TSC2 phosphorylation and its downstream target Rheb.

30.3
METABOLIC SIGNALING IN L6 MUSCLE CELLS IN RESPONSE TO HEAT TREATMENT AND RESVERETROL

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Previous work from our laboratory demonstrates that heat treatment (HT) protects skeletal muscle from insulin resistance. The exact molecular mechanisms for the protective effects of HT on skeletal muscle are not known, but modifications of insulin signaling and mitochondrial biogenesis are two possibilities. The purpose of the present study was to identify metabolic signaling pathways modified by HT in L6 muscle cells. L6 cells were also treated with Resveretrol (RSV), a heat shock protein (HSP) inducer known to affect insulin sensitivity. L6 cells were subjected to 20 min sham (37°C) or HT (42°C), returned to 37°C and harvested 24 hours later for Western analysis. A subset of cells were treated with RSV for 3 h, sham or HT for 20 min, and returned to RSV at 37C. Cells were incubated with or without insulin for 10 minutes prior to harvest. HT increased HSP72 expression in L6 cells, and this effect was enhanced when combined with RSV. HT combined with insulin also resulted in an increase in HSP72 above levels seen with HT alone. HT resulted in an increase in phosphor-Akt, however this effect was mitigated in the presence of insulin. RSV treatment resulted in a significant increase in phosphor- AMPK and expression of PGC-1á, while HT had no effect on these proteins. Our findings indicate that HT could increase glucose uptake by increasing insulin signaling intermediates, with little to no effect on insulin-independent pathways of glucose uptake. NIH AG031575.

30.4
AEROBIC EXERCISE TRAINING INCREASES APPL1 EXPRESSION AND IMPROVES INSULIN SIGNALING IN THE LIVER OF OBESE MICE

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Investigate the effect of physical training (PT) on the expression of APPL1, TRB3 and insulin signaling in liver of diet-induced obese diabetic mice. 4-week-old male Swiss mice were distributed in 3 groups (n=18): control mice fed with standard rodent chow; sedentary mice fed with a high-fat diet (HFD); mice fed with a HFD for 16 weeks and submitted to 8-week PT (HFD exe). The swimming sessions consisted of 60-min, 5 days/week for 8 weeks, with the mice supporting an overload of 5% b.w. PT beyond have increased the basal levels and insulin-induced Akt serine phosphorylation (35%) in the liver of these obese diabetic mice, APPL1 expression and the interaction between APPL1 and Akt (46%), increased also insulin-induced GSK3ßphosphorylation levels (40%) and glycogen content (55%). Conversely, PT reduced both TRB3 expression (55%) and TRB3/Akt association (48%). The positive effects of PT on insulin action are reinforced by our findings that showed trained mice presented an increase in Foxo1 phosphorylation and a decrease in Foxo1/PGC-1a association, which was accompanied by a reduction in gluconeogenic gene expressions [PEPCK (38%) and G6Pase (44%)]. PT increases insulin action, at least in part, through the enhancement of APPL1 and the reduction of TRB3 expression in the liver of obese diabetic mice. Supported by FAPESP n° 2010/12091-2.

30.5
THE INDISPENSIBLE ROLE OF THE NEURONAL NITRIC OXIDE SYNTHASE IN THE ADAPTIVE CARDIAC EFFECTS OF EXERCISE

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Signaling via neuronal nitric oxide synthase (NOS1) greatly increases cardiac contraction. Exercise (Ex) is also known to increase myocardial contractility and results in the upregulation of NOS1 in other tissue. However, the effects of Ex on NOS1 expression in the heart and its ensuing cardiac effects have not been investigated. We *hypothesize* that NOS1 is central for the beneficial cardiac effects of Ex. Mice underwent an 8 week aerobic interval training program. Isolated ventricular myocytes from these trained mice exhibited a significant increase in NOS1 expression, nitric oxide production, contraction (shortening and Ca^{2+} transient amplitudes), SR Ca^{2+} load, SR Ca^{2+} fractional release, phospholamban Serine16 phosphorylation, and faster relaxation compared to sedentary (Sed) myocytes. Incredibly, acute NOS1 inhibition was able to reverse all of these Ex-induced changes in myocyte function back to Sed levels. Consistent with a central role of NOS1 in Ex, enhanced myocyte contraction was not observed after training NOS1 knockout (KO) mice for 8 weeks and in fact resulted in myocyte Ca^{2+} mismanagement. Ex also resulted in an increase aerobic capacity (VO_{2max}) and cardiac hypertrophy in wildtype mice; surprisingly, this was not observed in our trained NOS1KO mice. Our data demonstrate that the beneficial cardiac effects of Ex (increased VO_{2max}, physiological hypertrophy, and enhanced contraction) observed after a training period are due to NOS1 signaling. Thus, NOS1 is essential for the beneficial cardiac effects of Ex. Therefore, mimicking these beneficial effects of Ex may be obtainable by enhancing NOS1 signaling. This pathway may be a potential novel therapeutic pathway for cardiac patients that are unable/unwilling to exercise.

30.6

SMAD3 IS SUFFICIENT TO INHIBIT PROTEIN SYNTHESIS AND INDUCE MUSCLE FIBER ATROPHY IN VIVO

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Myostatin is a negative regulator of skeletal muscle mass and previous studies have shown that myostatin-induced atrophy is associated with an increase in the expression of atrogin-1. Furthermore, both myostatin, and increased levels of atrogin-1, have been shown to inhibit protein synthesis. It has also been reported that signaling through the transcription factor Smad3 is necessary for myostatin-induced atrogin-1 expression and muscle atrophy; however, it remains to be determined whether Smad3 is sufficient to induce these events, or whether Smad3 simply plays a permissive role. Thus, the aim of this study was to determine if Smad3 is sufficient to stimulate atrogin-1 promoter activity, inhibit protein synthesis and induce muscle fiber atrophy *in vivo*. To accomplish this, mouse tibialis anterior muscles were transfected via electroporation with plasmid DNA encoding LacZ (control) or Smad3 alone, or in combination with a luciferase reporter for atrogin-1 promoter activity. Muscles were collected at 3 or 7 days post electroporation and analysed for rates of protein synthesis, fiber size and luciferase activity. Our results demonstrate that overexpression of Smad3 induces an increase in atrogin-1 promoter activity and a decrease in protein synthesis and fiber size. Combined, these results provide the first evidence that Smad3 is not only necessary, but also sufficient to inhibit protein synthesis and induce atrophy *in vivo*. This work was supported by NIH grant R057347 to TAH.

30.7

ROLE OF LKB1 IN THE REGULATION OF GENE EXPRESSION AFTER SKELETAL MUSCLE CONTRACTION

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Exercise training-induced skeletal muscle adaptations result in part from altered gene expression. The necessity of liver kinase B1 (LKB1) for this increase in gene expression is unknown. Our purpose was to determine whether LKB1 is required for contraction-induced changes in gene expression. To test this, two groups of skeletal muscle-specific LKB1 knockout (KO) and control (C) mice (n=8) underwent an electrical stimulation bout of the left sciatic nerve (1 pulse/2seconds, 5 ms/pulse for 15 minutes). The right (REST) and left (STIM) gastrocnemius-plantaris-soleus complexes were then harvested immediately (for protein phosphorylation measures via western blot) or 3 hours (for RNA expression measures via RT-PCR) post STIM.AMP-activated protein kinase (AMPK) phosphorylation increased with STIM in C, but not KO muscles. Erk and p38 MAPK phosphorylation increased similarly with STIM in both genotypes. Nuclear factor kappa B (NF-kB) p65 phosphorylation tended to increase (p=0.056) with STIM in KO but not C muscles. Peroxisome-proliferator activated receptor gamma-1 alpha (PGC1α) gene expression increased 3 hours post-STIM in muscles from both genotypes, but was lower in both REST and STIM muscles of KO vs. C mice. Additionally, VEGF expression increased in C but not in KO muscles after contraction. We conclude that LKB1 is necessary for the normal regulation of gene expression in response to muscle contraction. Funded by NIAMSD Grant AR-51928 and BYU Mentoring Environment Grant.

30.8

VPS34 ACTIVITY IN HUMAN SKELETAL MUSCLE: EFFECTS OF EXERCISE AND ORAL AMINO ACIDS

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Aim: We hypothesized that oral ingestion of essential amino acids and 8% maltodextrin (EEA + carb) before and after sprint exercise increases the activity of the "amino acid sensor" Vps34 in skeletal muscle in parallel with an increased phosphorylation of p70S6k. Method: Nine healthy subjects performed three 30-s all out sprints with 20 minutes rest in between. The subjects consumed either an EAA + carb solution or flavoured water (placebo) in a randomised order. Vastus lateralis samples were obtained at rest and 140 minutes after the third sprint. Radioactive immunoprecipitation was used for determination of the hVps34 activity and p-p70S6k was assessed by immunoblotting. Results: Vps34 activity did not increase by exercise after either EEA + carb or placebo. In spite of this, p-p70S6k increased 8-fold ($p<0.05$) after EEA + carb. No increase in p-p70S6k was seen after placebo. Conclusion: This is, to the best of our knowledge, the first report of Vps34 activity in human skeletal muscle and it is suggested that activation of Vps34 is not necessary for the exercise-induced increase in p-p70S6k after EAA + carb.

30.9

THE EFFECT OF SPRINT EXERCISE ON EXPRESSION OF MYOSTATIN AND SMAD7 IN SKELETAL MUSCLE

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Aim: SMAD7, that is activated by myostatin/TGF beta- or hypoxia signaling pathways has, in vitro, been shown to decrease gene expression of myostatin. Therefore, in vivo - relationship between changes in gene expression of SMAD7 and myostatin after sprint exercise combined with activation state of transcription factors regulating gene expression of SMAD7 was studied. Method: 16 healthy subjects performed 3 bouts of sprint exercise with 20 min rest in between. Vastus lateralis samples were obtained at rest and 140 min after 3rd sprint. Gene expression of myostatin and SMAD7 was measured by RT-PCR and related to RPS18. Predicted activation of transcription factors in the myostatin/TGF beta (SMAD3) or hypoxia (HIF1-alpha) signaling pathway were evaluated by IPA (www.ingenuity.com) applied to microarray analysis data. Result: Gene expression of SMAD7 increased by 53% ($p<0.0001$) and gene expression of myostatin decreased by 52% ($p<0.0001$). Significant activation of SMAD3 ($z=2.45$, $p=0.0001$) and HIF1-alpha ($z=2.87$, $p=0.0004$) was predicted by the IPA analysis. Conclusion: The predicted activation of SMAD3 and HIF1 α supports that the increased SMAD7 expression is mediated by an increased myostatin/TGF beta- or hypoxia signaling. The results are also consistent with that SMAD7 down regulates myostatin gene expression. The decrease in myostatin gene expression after sprint exercise might be followed by activation of muscle growth and may balance the inhibitory stimulus on muscle growth by SMAD3.

31.0: INFLAMMATION

31.1

PGC-1A IS REQUIRED TO PREVENT AN AGE-ASSOCIATED INCREASE IN TNFA AND FOR DECREASED TNFA PROTEIN IN SKELETAL MUSCLE WITH COMBINED EXERCISE TRAINING AND RESVERATROL

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The aim was to investigate whether lifelong exercise training and/or resveratrol supplementation can prevent an age-associated increase in plasma TNFα and skeletal muscle (SkM), adipose tissue (AT) and liver TNFα protein and whether PGC-1α plays a role in these effects. Plasma, SkM, AT and liver were obtained from young (3 month) and old (15 months) whole body PGC-1α knockout (KO) and wild type (WT) littermate mice. The old mice were either untrained or exercise trained together with obtaining either chow diet or resveratrol supplementation. The young mice were untrained and received chow. In SkM, TNFα protein was higher in PGC-1α KO mice than in WT, whereas no genotype differences were observed in TNFα protein in AT or liver. There was a tendency towards higher plasma TNFα in PGC-1α KO mice than WT. No age-associated change was apparent in TNFα protein in WT mice in any of the tissues, but SkM TNFα protein was higher in old than young PGC-1α KO mice. In addition, a combination of exercise training and resveratrol decreased SkM TNFα protein in WT mice, but not PGC-1α KO mice. No effect of exercise training and/or resveratrol on TNFα protein was observed in liver or AT. In conclusion, the present study indicates a role of PGC-1α in regulating TNFα protein in SkM and suggests that reduced PGC-1α levels may lead to increased TNFα protein expression with aging. Furthermore, PGC-1α is required for the ability of exercise and resveratrol to decrease TNFα protein in SkM.

31.2

EXERCISE REVERSES HIGH-FAT DIET INDUCED NEUROPATHY IN PRE-DIABETIC MICE

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Overweight humans display manifestations of diabetic neuropathy before developing overt diabetes and high-fat (HF) feeding in rodents induces painful neuropathy characterized by mechanical hypersensitivity. We hypothesized exercise would attenuate HF diet induced neuropathy. Also, mitochondrial function in the lumbar dorsal root ganglia and spinal inflammation in sedentary mice were assessed to determine their role in the pathogenesis underlying HF diet induced neuropathy. Male C57Bl/6 mice were randomized into four groups: standard diet sedentary (StdSed), HF diet sedentary (HFSed), standard diet exercise (StdEx), or HF diet exercise (HFEx). Exercise groups were housed in cages with free access to running wheels. HF fed mice displayed mechanical hypersensitivity starting at week 4. Exercise attenuated mechanical hypersensitivity beginning at week 8 and restored mechanical sensitivity to normal levels by week 12 in HF fed mice. HF feeding did not affect mitochondrial respiration, protein expression of oxidative phosphorylation complexes, or spinal microglial activation. TNF □ was increased in the spinal dorsal horn of HFSed compared to StdSed. Spinal inflammation may be an important factor involved in the pathogenesis of HF diet induced neuropathy, and future experiments will examine the effects of exercise on inflammation. Exercise reverses HF diet induced neuropathy in mice suggesting exercise intervention may improve neuropathy in humans. Supported by NIH 5T32 HD057850-02.

31.3

ACUTE EXERCISE IMPROVES INSULIN SIGNALING AND REDUCES INFLAMMATORY PROTEINS IN SKELETAL MUSCLE OF AGED RATS

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Investigate whether the improvement in insulin action, associated with acute exercise in old rats is dependent on the modulation of pIRS-1Ser307, JNK, IkBalfa, PTP-1B and iNOS proteins. Eight Wistar rats were used per group (young group - rats of 3 months of age), old sedentary rats (group OS: 27 months of age), and exercised 27-month-old rats (group OE). The animals swam for two 1.5-h long bouts, separated by a 45-min rest period. Sixteen hours of exercise protocol both portions of gastrocnemius (red and white fibers) were ablated and were evaluated expression and/or phosphorylation of proteins Akt, JNK, IkBalfa, PTP-1B, IRS-1307, iNOS in the skeletal muscle by immunoblot e immunoprecipitation. Our results show that the increase in insulin-induced Akt serine phosphorylation was less evident in OS rats, and exercise partially reversed this alteration. Aging led to an increase in Ser307 phosphorylation of IRS-1, and this was reversed by exercise in the skeletal muscle, in parallel with a reduction in pJNK and IkBalfa degradation. Moreover, aging induced an increase in the expression of PTP-1B, iNOS and attenuated insulin signaling in the muscle of rats, a phenomenon that was reversed by exercise. These results provide new insights into the mechanisms by which exercise restores insulin sensitivity during aging. Supported by FAPESP n° 2010/12091-2 and 2010/12718-5.

31.4
FRACTALKINE–INDUCED IN EXERCISED HUMAN SKELETAL MUSCLE AND STIMULATES MYOBLAST PROLIFERATION

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Human myoblasts have been demonstrated to secrete the chemokines fractalkine, MDC and MCP-1, all factors chemotactic for monocytes/ macrophages. In addition, human myoblasts express CX3CR1, the receptor for fractalkine, suggesting a possible autocrine signaling mechanism. In the current study, muscle biopsies from the m. vastus lateralis were obtained up to 24 h after 1 h of cycle exercise in 10 healthy individuals and in 6 age-matched controls at the same timepoints without cycling, The mRNA and protein levels of fractalkine, MDC and MCP-1 were measured in the biopsies. The mRNA-level of fractalkine was significantly up-regulated in the cycling subjects at 30 minutes post exercise, and then went back to resting levels. This was followed by an increase in fractalkine protein levels at 2h post exercise. Neither fractalkine mRNA or protein levels changed in the control subjects. For MDC and MCP-1, the RNA levels went up with the exercise bout but were also upregulated in the control subjects. Based on these results, the effects of fractalkine stimulation of human myoblasts was investigated. Fractalkine was demonstrated to induce increased proliferation measured using BrdU. To conclude, fractalkine is an exercise induced chemokine with a proliferative effect on myoblasts. The induced expression of MDC and MCP-1 in the control subjects stresses the importance of control biopsies in experiments with multiple biopsies.

31.5
INFLAMMATION AND THE HYPERTRIGLYCERIDEMIC WAIST PHENOTYPE

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The hypertriglyceridemic waist (HTGW) phenotype may be a simple tool to identify patients with excess visceral adiposity and, we hypothesize, with low-grade inflammation that may promote insulin resistance. The purpose of this study was to determine whether the HTGW phenotype is associated with the presence of markers of systemic inflammation. Adults (n=98) were measured for waist circumference (WC), triglycerides (TG), C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-α (TNF) before interventions were applied. HTGW phenotype was defined as TG concentration ≥133 mg/dl and WC ≥85cm in women and TG concentration ≥177 mg/dl and WC ≥90cm in men. A HTGW score (scale of 0, 1, 2) was assessed using the number of criteria met by each participant. Modest relationships were observed between logCRP and the HTGW score (polyserial correlation = 0.33, p=0.0014) and for logIL-6 and HTGW phenotype (polyserial correlation = 0.36, p=0.0002). No evidence was found for a relationship between logTNF and HTGW phenotype (polyserial correlation = 0.06, p=0.61). Correlations of similar strength for blood pressure and of greater strength for log10 of the insulin concentration (polyserial correlation = 0.48, p<0.0001) were measured. In conclusion, there is an association between HTGW phenotype and markers of systemic inflammation, but the direct association with plasma insulin is stronger. This study was funded by a grant from the American Heart Association to MPM.

31.6
INFLUENCE OF FITNESS AND ADIPOSITY ON WHOLE BLOOD RESPONSE TO A MSH TREATMENT

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The melanocortin system has anti-inflammatory effects on circulating leukocytes. The purpose of this project was to determine if fitness and/or adiposity influence whole blood response to α-melanocyte stimulating hormone (MSH) treatment. Seventy-two men and women (44±5 yrs) were grouped as lean/fit (LF=20), lean/sedentary (LS=16), overweight/fit (OF=16), and overweight/sedentary (OS=16). Whole blood was cultured (24h, 5%CO_2, 37°) with no stimulant (CON), with αMSH^{-14}M (MSH) or with lipopolysaccharide (LPS, 1ng·mL^{1}) in the presence of MSH. IL-10 and TNF-α pro-duction were assessed. Plasma interleukin-6 (IL-6) was greater in the sedentary compared to fit groups (1.52±0.3, 0.89 □0.3 pg•mL, respectively) and in the overweight compared to lean groups (1.6□0.04, 0.84□□pg $^{-1}$, respectively). C-reactive protein (CRP) was greater in the overweight compared to lean groups (3.1 □0.3, 0.83□0.3, respectively). IL-10 increased (P=0.014) with MSH treatment in obese subjects (MSH 3.7 □0.7, CON 1.9□0.3 g·mL^{-1}) but did not change in lean (MSH 2.9 □0.39, CON 3.1□0.77 pg $^{-1}$)mL. There was a main effect (P=0.002) of MSH treatment for TNF (CON 3□0.3, MSH 4.5□0.5 pg•mL) which was driven by the OS group. LPS in-creased IL-10 and TNF-a production. MSH had no effect on LPS-IL10, however, it in-creased LPS-TNF production (LPS 1126□72, LPS+MSH^{4}M 1178□ 77 pg•mL^{-1}, main effect, P=0.22). Whole blood response to MSH treatment appears to be associated with body composition more so than fitness.

31.7
THE INFLUENCE OF FITNESS AND ADIPOSITY ON MELANOCORTIN-1 AND MELANOCORTIN-3 RECEPTORS ON MONOCYTES

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While it is known that exercise improves health by reducing systemic inflammation, potential mechanisms remain to be elucidated. The purpose of this study was to examine the influence of activity level and adiposity on the anti-inflammatory melanocortin system as a potential mediator of systemic inflammation. Seventy-two men and women (44¡À5 yrs) were grouped as lean/active (LA=20), lean/sedentary (LS=16), overweight/active (OA=16), and overweight/sedentary (OS=16). Using flow cytometry, circulating monocytes were classified as high inflammatory (CD16+) or low inflammatory (CD16-). Mean fluorescence intensity (MFI) was analyzed for cell surface expression of melanocortin receptor-1 (MC1R) and melanocortin receptor-3 (MC3R). MFI of MC1R and MC3R was significantly greater (p¡Ü0.01) in CD16+ (246¡À20 & 492¡À42 MFI, respectively) cells compared to CD16- cells (127¡À6 &167¡À10 MFI, respectively). On CD16- cells, MC3R expression was lower (p=0.03) in LA (128.58¡À4.47 MFI) compared to OA (196.4¡À23.23 MFI), and MC1R expression was greater in males (140¡À9 MFI) compared to females (113¡À9 MFI). The percentage of monocytes expressing MC1R on CD16- cells was greater (p=0.046) in LS (97.18¡À4.43%) compared to LA (83.12¡À3.96%) and OS (89.43¡À3.96%). MCR expression is greatest on CD16+ monocytes, and there appears to be an influence of body composition, physical activity, and sex on MC1R and MC3R expression on CD16- monocytes.

31.8
EFFECT OF EXERCISE ON T CELLS IN CANCER SURVIVORS

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PURPOSE: Cancer therapies increase the relative proportion of terminally differentiated senescent T cells relative to naive T cells. Our objective was to evaluate the effect of exercise on percentages of various T cell subsets in cancer survivors pre and post an exercise intervention. **METHODS:** Sixteen cancer survivors were recruited from the Rocky Mountain Cancer Rehabilitation Institute and completed a 12 week whole-body exercise training program. Prior to and upon completion blood was drawn and T cell phenotypes were analyzed by six color flow cytometry. **RESULTS:** All but one of the patients had completed treatment at the time of enrollment. Preliminary analysis shows a mean decrease in the CD4:CD8 T cell ratio from 2.1 to 1.8 during the exercise intervention. CD8 senescent T cells decreased in 10 subjects while 6 had an increase. Unactivated, naïve CD8 T cells declined in 9 subjects and 7 subjects had an increase. This trend differs from CD4 naïve T cells, with 10 subjects having an increase in this cell subtype and 6 a decrease. **CONCLUSION:** We are one of the first to evaluate chronic changes in the T cell compartment of cancer survivors who participate in ongoing exercise training. These very preliminary results suggest exercise may enhance immune function in cancer survivors by altering T cell proportions which are disrupted by adjuvant cancer therapies. Funded by a UNMC SAHP Pilot Research Grant.

31.9
ESTROGEN STATUS AND THE IL-6 RESPONSE TO PROLONGED ENDURANCE EXERCISE

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The influence of estrogen (E2) status on IL-6 response to prolonged endurance exercise was examined in 16 eummenorrheic women. Treadmill runs were performed at ~65% VO2max for 60-90 min (X=71.3±3.8 min [±SE]) in the mid-follicular (Low E2) and mid-luteal (High E2) phases of the menstrual cycle. Blood samples were taken at Rest, immediately post exercise (IE), and 30 min, 24 h and 72 h into recovery (R) from exercise trials. Trials were randomized and controlled for prior exercise, environmental conditions, diet, and hydration status. Blood was analyzed for E2 (Rest only) and IL-6 using ELISA assays and examined via an ANOVA. All subjects exhibited a 2x-4x increase in E2 from the Low E2 to the High E2 ($p<0.05$). Heart rate and VO2 increased ($p<0.01$) as exercise progressed in each trial, but did not differ between the Low and High E2 trials. The IL-6 responses were significantly elevated from Rest at IE and 30 min R in both Low and High E2 trials; however, the magnitude of these increases were greater (25-85%) in the Low E2 than the High E2 trial ($p<0.05$). At 24 h and 72 h R no differences were noted for IL-6 between the trials. These findings indicated elevations in E2 in women are associated with a lower acute IL-6 response to prolonged endurance exercise.

31.10
EFFECTS OF HABITUAL PHYSICAL ACTIVITY LEVEL AND ACUTE EXERCISE ON MARKERS OF SYSTEMIC INFLAMMATION AND CARDIOMETABOLIC RISK IN OVERWEIGHT/OBESE ADULTS

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The aim of this study was to examine the influence of habitual physical activity (PA) level and acute exercise on markers of systemic inflammation and cardiometabolic risk in overweight-to-mildly obese adults. We collected a blood sample after an overnight fast, and measured ambulatory blood pressure (BP) over 7h in 9 INACTIVE (<30min PA/week) and 15 ACTIVE (>2.5h vigorous PA/week) overweight/obese adults (ACTIVE group measured after 3d without exercise). After baseline measures, all subjects exercised for 1h at 70% HRmax, and maintained an energy-balanced diet for the day. We measured ambulatory BP again and collected a fasting blood sample the next morning. VO2peak was significantly greater in ACTIVE vs. INACTIVE (30±3 vs. 23±2 ml/kg/min, p=0.04) but as designed, body mass (89±3 vs. 89±3 kg) and %body fat (34±2 vs. 37±2%) were not different between groups. HOMA-IR (3.1±0.4 vs. 4.8±0.6, P=0.07), and plasma IL-1β (3.9±0.7 vs. 6.5±1.4, P=0.09) tended to be lower in ACTIVE vs. INACTIVE, but BP, and plasma IL-6, TNF-α, and MCP-1 were not different between groups. Acute exercise improved HOMA-IR in both groups, and lowered ambulatory systolic BP in the INACTIVE group only. Acute exercise tended to lower plasma IL-1β in the INACTIVE group, and there was no longer a trend for differences in IL-1β between groups. These data suggest a habitually inactive lifestyle may elevate circulating IL-1β in overweight/obese adults, and a single session of exercise may ameliorate this effect.

31.11
ANTI-INFLAMMATORY MEDICATIONS AND OTHER POTENTIAL CONFOUNDING VARIABLES FOR STRENGTH GAIN FROM RESISTANCE TRAINING FOR OLDER ADULTS

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Our work is investigating the role of inflammation in adaptation to resistance training for older adults. Previously, subjects (N=8, 68±6 yrs), who were not taking anti-inflammatory drugs, significantly increased knee extension strength after training (30±6%, P<0.001). Strength gain was strongly correlated with muscle expression of cytokines and growth factors (R>0.8, P<0.05). The current analysis determined if using anti-inflammatory drugs or supplements will confound the results of a follow-up study. Subjects (N=14, 70±2 yrs) completed 35 training sessions targeting the thigh at 80% of capability. Drug and supplement data was collected from medical records and subject report. Products were included in the analysis that have anti-inflammatory properties and were taken by 5 or more subjects. Knee extension strength increased significantly after training (27±2%, P<0.001). Regression analysis indicated that using non-steroidal anti-inflammatory drugs, aspirin, statins, fish oil, or multi- or B or D vitamins was not correlated with strength gain (P>0.05). Strength gain was also not correlated with age, time to complete the program, and baseline strength and thigh composition. The results suggest that these variables will not confound analyses of inflammation and adaptation using vastus biopsies collected from these subjects before and after training. Funded by South Central VA Healthcare Network.

31.12
EFFECTS OF PRIOR EXERCISE ON THE INFLAMMATORY RESPONSE TO A HIGH-FAT MEAL IN YOUNG MEN

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Consumption of a high-fat meal (HFM) increases circulating levels of triglycerides (TG) and inflammatory markers. Acute exercise ameliorates the TG response to a HFM, but the effects of exercise on circulating inflammatory markers are not fully understood. The objective of this study was to investigate the effects of prior exercise on the response of circulating inflammatory cytokines to a HFM. Blood samples were obtained from 10 healthy men at 0 hrs and 4 hrs after ingestion of a HFM either with or without ~50 min of endurance exercise at 70% of VO2max on the preceding day. Plasma interleukin-6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α) and leptin concentrations were measured by ELISA. The HFM increased IL-6 by 120% when preceded by exercise (P=0.06), but only by 54% without prior exercise. Similar responses were found for IL-8 [33% increase with prior exercise ($p<0.05$), but no significant increase without prior exercise]. No significant effects of the HFM or exercise were observed for TNF-α. We observed an effect of prior exercise on leptin concentrations (-17% at both time points vs. no exercise; $P<0.05$). The HFM significantly decreased leptin concentrations (-11%, $P<0.05$ for both trials). As both exercise and consumption of a HFM can independently increase IL-6 and IL-8 concentrations, it is possible that the two stimuli interact to create an inflammatory response that is independent of the exercise-induced reduction in leptin concentrations.

31.13
INFLUENCE OF SHORT TERM SPRINT INTERVAL TRAINING ON SKELETAL MUSCLE INFLAMMATION

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Short-term sprint interval training (SIT) has many health benefits, including improved glucose regulation and insulin sensitivity, however the exact mechanism by which these benefits are bestowed is unclear. Inflammation adversely affects insulin sensitivity, thus we have investigated the hypothesis that short-term SIT decreases skeletal muscle inflammation in adult humans. Experimental procedures conformed to the Declaration of Helsinki. 14 young, healthy sedentary/recreationally-active adults completed 6 sessions of SIT (between 4 and 7 "all-out" maximal 30-second efforts on a cycle ergometer, separated by 4 minutes of light recovery) over 2 weeks. Skeletal muscle (vastus lateralis) was sampled prior to and 96-hours following training. SIT did not affect skeletal muscle inflammation, as represented by the phosphorylation of JNK relative to total JNK abundance (0.95 ± 0.35 *vs.* 0.76 ± 0.24; mean ± SE; $P = 0.42$), and the phosphorylation of IκB-β to total IκB-β abundance (0.66 ± 0.09 *vs.* 0.74 ± 0.17; $P = 0.48$). These preliminary data suggest that the mechanism by which SIT improves insulin sensitivity, at least in young and apparently healthy adults, is not via decreased skeletal muscle inflammation.

32.0: LATE-BREAKING ABSTRACTS

32.1
ABSENCE OF MALONYL-COA DECARBOXYLASE (MCD) IMPACTS ENDURANCE EXERCISE CAPACITY AND REPROGRAMS SKELETAL MUSCLE MITOCHONDRIAL METABOLISM

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Malonyl-CoA decarboxylase (MCD) degrades cytoplasmic malonyl-CoA, a potent biological inhibitor of the outer mitochondrial carnitine palmitoyltransferase 1 (CPT1). Young mice lacking MCD shift fuel use to favor glucose oxidation and resist high fat diet-induced insulin resistance. In the current studies we address how lifelong inhibition of β-oxidation affects whole-body metabolism, skeletal muscle and mitochondrial function in older aged mice. 15mo. old $MCD^{-/-}$ mice displayed equivalent running capacities with lower sub-maximal VO_2 and higher RER values versus controls. In contrast, $MCD^{-/-}$ mice showedmarkedly reduced endurance running capabilities suggesting a relative inability to produce energy from fat catabolism. *In vitro* muscle fatigue studies revealed elevated lactate and reduced force production by MCD deficient musclesversus controls. Interestingly, isolated muscle mitochondria (a system lacking cytosolicmalonyl-CoA) displayed higher rates of ^{14}C-palmitate oxidation and palmitoylcarnitine-supported OXPHOSin the $MCD^{-/-}$groupwhereas the electron transport system was largely unaffected by loss of MCD. These studies support the idea that MCD deficiencyresults in reprogramming of muscle mitochondria toward enhanced capacity for β-oxidation with no overt deficits in mitochondrial function; however, this remodeling is insufficient to overcome malonyl-CoA-mediated inhibition of CPT1 in intact working skeletal muscles. (Ellison Medical Foundation (TK) and R01HL101189 (DM)).

32.2
REDUCTIONS OF PEPCK IN ADIPOSE TISSUES FROM CD36 KO MICE

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Exercise induces phosphoenolpyruvate carboxykinase (PEPCK) mRNA expression in adipose tissue, a key enzyme involved in fatty acid (FA) re-esterification. CD36 is a transmembrane protein highly expressed in adipose tissue and plays a key role in FA uptake and lipolysis. The aim of this study was to determine 1) if PEPCK expression is reduced in adipose tissue from CD36 knockout (KO) mice 2) if this was secondary to reductions in lipolysis; and 3) if exercise induced PEPCK mRNA expression is attenuated in adipose tissue from CD36 KO mice. PEPCK mRNA and protein expression in epididymal white adipose tissue (EWAT) were reduced from CD36KO mice compared to age matched (16 weeks of age) wild type (WT) mice, and this was associated with increased FFA/glycerol *ex vivo* in EWAT from CD36 KO mice. Basal and norepinephrine (NE) (1μM) stimulated glycerol and FFA release *ex vivo* in EWAT were attenuated from CD36 KO mice compared to WT mice. CAY10499 (2μM), a hormone sensitive lipase (HSL) inhibitor, partially impaired basal and NE (1μM) induced lipolysis, and this was related to reduced basal and NE induced PEPCK mRNA expression in cultured EWAT. An acute bout of treadmill running (15meter/min, 5% incline, 90mins) induced PEPCK mRNA to a similar extent from WT and CD36 KO mice. In summary, our data demonstrates that CD36 controls the expression of PEPCK in mouse adipose tissue. Our data would suggest that reductions in PEPCK may be secondary to decreased lipolysis. This work was supported by a Bridge Funding Operating Grant from the Canadian Institutes of Health Research, Institute of Nutrition, Metabolism and Diabetes to DCW. DCW is a Tier II Canada Research Chair and Canadian Diabetes Association Scholar.

32.3

INDUCTION OF SIRT1 BY RELOADING ON ATROPHIED SOLEUS MUSCLE IN MICE

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Loading is one of hypertrophic stimuli for skeletal muscle. Sirtuin 1 (SIRT1) is considered to be implicated in lifespan extension. SIRT1 induction by mechanical stretch plays a role in preventing of oxidative stress. However, SIRT1 expression in response to unloading and reloading on skeletal muscle is still unclear. The purpose of this study was to investigate the effects of unloading and reloading on SIRT1 expression in skeletal muscle. Male mice (C57BL/6J) were subjected to continuous hindlimb suspension for 2 weeks. Immediately after the suspension, ambulation recovery was allowed. Soleus muscles of suspended group were dissected bilaterally before, immediately after, 2 and 4 weeks after the suspension. Immediately after the suspension, expression levels of SIRT1 in soleus muscle showed a trend to increase, then significantly increased during reloading. Oxidative stress induced by unloading and reloading on skeletal muscle might be different. This study was supported, in part, by KAKENHI (22240071, 24650411, 24650407) from Japan Society for the Promotion of Science and the Science Research Promotion and the Promotion and Mutual Aid Corporation for Private Schools of Japan.

32.4

A PILOT STUDY OF PHYSIOLOGIC CORRELATES TO SUBMAXIMAL AND MAXIMAL EXERCISE IN PATIENTS WITH IPF

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The relationship between maximal cardiopulmonary exercise testing (CPX) and submaximal exercise in patients with idiopathic pulmonary fibrosis (IPF) is poorly understood. CPX and the 6-minute walk test (6MWT) were compared with a focus on exercise tolerance (ET) and systemic oxidant stress (OS) in IPF patients. ***Methods.*** Nineteen IPF subjects underwent cycle ergometry CPX and 6MWT. Blood samples were obtained for 15-F_{2t}-isoprostanes (IP) before and immediately after CPX. CPX and 6MWT dependent variables were cycling duration (CD) and distance (6MWTD), respectively. Correlation and multivariate linear regression (MVLR) analyses were performed. ***Results.*** Significant correlations ($p<0.05$) among CPX measures and CD included peak oxygen consumption (O_2) and carbon dioxide (CO_2) production as well as resting and peak end-tidal oxygen ($PETO_2$) and carbon dioxide ($PETCO_2$) with the greatest correlation between $PETO_2$ and CD ($r= -0.66$). Significant correlations ($p<0.05$) among CPX measures and 6MWTD included resting $PETO_2$ and $PETCO_2$, peak respiratory rate, and peak IP with the greatest correlation between peak IP and 6MWTD ($r=0.87$). MVLR found all but resting $PETO_2$ and $PETCO_2$ significant predictors of CD (model $r^2=0.86$). MVLR found only peak IP to be a significant predictor of 6MWTD (model $r^2=0.91$). ***Conclusions.*** CPX measures explain a substantial proportion of maximal ET, but explain very little of submaximal ET in IPF patients. However, submaximal ET is substantially explained by OS.

32.5

IMPACT OF VOLUNTARY WHEEL RUNNING AND TREADMILL EXERCISE TRAINING ON HEPATIC MITOCHONDRIAL METABOLISM AND FUNCTION

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It is well known that exercise training increases skeletal muscle mitochondrial content and function; however, hepatic mitochondrial adaptations to exercise are largely unknown. Here we sought to determine the effects of various exercise modalities on measures of hepatic mitochondrial function. Sprague Dawley rats were randomly assigned (n=5-8 per group) to sedentary (SED), voluntary wheel running (VWR), treadmill endurance exercise (EndEx; 30m/min, 60 min/d, 5d/wk), or treadmill interval sprint training (IST; 50 m/min, 6x2.5 min bouts, 5 d/wk) groups for a 4 week intervention. Preliminary findings indicate thathepatic mitochondrial 1-^{14}C palmitate oxidation to CO_2tended to be increased only in the VWR group ($p=0.15$) compared to the sedentary condition. Although, all exercise interventions tended to increase hepatic mitochondrial 2-^{14}C pyruvate oxidation to CO_2 (an index of mitochondrial TCA cycle flux) by 20-40%. Moreover, 1-^{14}C pyruvate oxidation to CO_2 (an index of pyruvate dehydrogenase activity) was increased 10-25% with each exercise intervention. Furthermore, each exercise group also exhibited 25-30% greater maximal uncoupled mitochondrial respiration compared with SED animals. In conclusion, these preliminary findings suggest that 4 weeks of exercise induces increases in hepatic mitochondrial function and metabolism. These findings need to be confirmed in a larger study cohort. Supported by NIH T32 AR 048523-07 (JAF and EMM),NIH DK088940 (JPT), and VHA-CDA2 IK2BX001299-01 (RSR).

32.6

ACUTE RESISTANCE TRAINING AFFECTS APOPTOSIS AND MIGRATION OF LYMPHOCYTES

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The purpose was to examine lymphocyte subsets (CD4+ and CD8+) apoptosis and migration to an acute session with different rest interval lengths of RT in accordance with ACSM. 12 untrained young men (N=3) and women (N=9) performed an familiarization, test-retest and two acute RT sessions (3 sets of 9 exercises: chest press, leg press, front lat pull-down, seated leg extension, up right row, seated leg curl, triceps extension, calf rise and biceps curl) with two different rest intervals between sets and exercises (1 min and 3 min) separated by 5 days in a balanced, randomized order in accordance with Declaration of Helsinki. Lymphocyte subsets (CD4+ and CD8+) were assessed for apoptosis (annexin V+) and cellular migration (CX_3CR1).CD4+ and CD8+ cells count displayed no statistically changes after Hyper-1 and Hyper-3 ($p>0.05$). Increase in the percentage of CD4+ positive for annexin V+ and CX_3CR1+ cells immediately after and 24h post Hyper-1 ($p < 0.05$). Percentage of CD4+ positive for annexin V+ increased 2h and 24h post on Hyper-3, and decrease for CXCR1+ in same time-points ($p < 0.05$). Increase in CD8+ positive for annexin V+ and CX_3CR1+ immediately after, 2h and 24h post Hyper-1 and Hyper-3 ($p< 0.05$). No differences between Hyper-1 and Hyper-3 in the same time-points analysis ($p > 0.05$). In conclusion, RT sessions inaccordance to ACSM, increase the apoptosis and migration of CD4+ and CD8+ lymphocytes even 24 h after exercise, with minimal effects of rest interval length. Financial support was provided by the Consellho Nacional de DesenvolvimentoCientífico e Tecnológico (CNPq) and by the Kinesiology, Recreation, and Sport Depaterment from the Western Kentucky University, USA.

32.7

BRONCHODILATION DURING EXERCISE IN PATIENTS WITH CYSTIC FIBROSIS, COMPARISON TO ALBUTEROL ADMINISTRATION

Meghan C. McCue, Courtney M. Wheatley, Sarah E. Baker, Mary A. Morgan, Eric C. Wong, Monika Sattler, and Eric M. Snyder

Moderate intensity exercise causes bronchodilation and can also improve mucocilary clearance. Cystic fibrosis (CF) patients are treated with albuterol to promote bronchodilation and to possibly stimulate mucocilicary beat frequency. Fitness has been associated with improved survival in CF patients and attenuation of the yearly 2-3% expected decline in pulmonary function. We sought to compare the effects of albuterol and moderate intensity exercise on bronchodilation in patients with CF. Sixteen patients with CF and 16 healthy control subjects underwent pulmonary function testing at baseline, 30, and 60 minutes post-albuterol administration. On a separate day subjects performed a maximal expiratory flow-volume maneuver to determine airway function at baseline and at 50% VO_{2peak}. Percent change in forced expiratory flow at 25-75% of the forced vital capacity (FEF_{25-75}) was significantly greater with moderate intensity exercise than at 30 or 60 minutes post-albuterol administration in CF patients, while there was no difference in percent change FEF_{25-75} between albuterol and exercise in the healthy control subjects (change from baseline: 30min post albuterol=23±5 vs. 9±4%, 60min post albuterol=22±5 vs. 12±3%; 50% VO_{2peak}=17±4 vs. 22±3% for healthy and CF, respectively). Our results suggest that moderate intensity exercise promotes greater bronchodilation than albuterol administration in CF patients. HL108962.

32.8

CRITICAL LOAD ESTIMATION BY DIFFERENT MATHEMATICAL MODELS IN SWIMMING RATS

Claudio Alexandre Gobatto, Pedro Paulo Menezes Scariot, Luiz Fernando Paulino Ribeiro, Fúlvia de Barros Manchado-Gobatto
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The aim of this study was to verify the viability on critical load (CL) estimate (aerobic capacity marker) using three different mathematics models. Nine male *Wistar* rats (40 days old) were submitted to exhaustive swimming efforts against 9, 11, 13 and 15% of their body weight (bw), in four consecutive days. Times to exhaustion (T_{EX}) were considered as the moment at which all coordinated movements ceased and the animal could no longer return to the surface. CL was estimated using 3 models: Lin-1= linear 1 (load *vs* $1/T_{EX}$), Lin-2=linear 2 (impulse *vs* T_{EX}) and Hyp= hyperbolic model (load *vs* T_{EX}). Anova one-way and intraclass correlation coefficients (ICC) was employed (significance at $P<0.05$). The results showed that the coefficients of determination for Lin-1, Lin-2 and Hyp models were highly applicable (0.97 to 0,99) and no significant differences were found among CL (%bw) estimated from the Hyp (7.8±1.1), Lin-1 (7.8±1.2) and Lin-2 (7.9±1.1) models, with significant relationships (ICC ≥0.87) among them. Critical Power model have been adopted as an interesting alternative (non-invasive method) for estimates of aerobic capacity in biomedical research in laboratory animals. Despite of largely explored in sportive modalities for humans and rodents submitted to treadmill running, scarce information exists regarding CL in swimming. Thus, our results attest the viability of CL estimation for accesses aerobic capacity independently of mathematical model. Financial Support: FAPESP (Proc no. 09/14040-9) and CNPq (Proc no. 305650/2009-2).

32.9
INTERLEUKIN-6, EPINEPHRINE AND THE REGULATION OF SKELETAL MUSCLE LIPOLYSIS

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IL-6 secretion is increased from skeletal muscle during exercise and is thought to stimulate lipolysis [2]. Epinephrine also stimulates skeletal muscle triacylglycerol breakdown, however, the interaction between these two in the control of skeletal muscle lipolysis is not known. Therefore, the purpose of this investigation was to determine if IL-6 is necessary for the stimulatory effects of epinephrine on lipolysis in mouse skeletal muscle. Soleus and EDL muscles from wildtype (WT) and IL-$6^{-/-}$ mice were incubated with 1uM epinephrine for 60 minutes. Glycerol concentration in the media was measured as an index of *ex vivo* lipolysis (n=6). In a separate set of experiments, muscles were incubated with or without epinephrine for 30 minutes to determine signalling mechanisms (n=10). Glycerol concentration in the media was increased ~70% by epinephrine in solei of WT mice. In IL-$6^{-/-}$ mice, lipolysis was elevated in the basal state but not further increased with epinephrine. The response to epinephrine was not detectable in EDL, indicating a distinct fiber type difference in fuel mobilization. Differences in lipolysis between WT and IL-$6^{-/-}$ mice cannot be explained by changes in total protein content of key lipolytic enzymes p42/44 MAPK, ATGL or HSL Our data demonstrate that the deletion of IL-6 increases basal lipolysis in skeletal muscle and that this may preclude a further increase by epinephrine. [1] Febbraio MA, Pedersen BK. Muscle-derived interleukin-6: mechanisms for action and possible biological roles. FASEB J 2002; 16: 1335- 1347. [2] Kelly M, Gauthier MS, Saha A, Ruderman N. Activation of AMP-activated protein kinase by interleukin-6 in rat skeletal muscle. Diabetes 2009; 58: 1953-1960.

32.10
HSP70 REGULATES THE SKELETAL MUSCLE INFLAMMATORY RESPONSE FOLLOWING INJURY

Sarah M. Senf, Travis M. Howard, and Andrew R. Judge
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The current study determined the requirement of Hsp70 for the skeletal muscle inflammatory response following injury and subsequent regeneration. Muscle injury was induced in WT and Hsp$70^{-/-}$ mice via either cardiotoxin (CTX) injury or muscle disuse and reloading. Muscles from Hsp$70^{-/-}$ mice had an impaired inflammatory response compared to WT 1 day post CTX-injury, as indicated by reduced immunostaining for neutrophils and pro-inflammatory macrophages, and reduced mRNA levels of immune cell-specific markers and pro-inflammatory cytokines. In contrast, at later time points Hsp$70^{-/-}$ mice showed further elevations in pro-inflammatory markers above WT, and impaired regeneration. Importantly, the blunted immune response in Hsp$70^{-/-}$ mice was rescued via a single injection of rHsp70 protein into the muscle at the time of injury, indicating that extracellular Hsp70 released from damaged muscle may initiate the inflammatory response. Since immune cell infiltration following injury can also contribute to secondary muscle damage, we determined the morphology of muscles from WT and Hsp$70^{-/-}$ mice following muscle reloading injury, and indeed found preservation of muscle fibers in Hsp$70^{-/-}$ mice. However, at later time points, Hsp$70^{-/-}$ mice showed impaired regeneration. In conclusion, these data indicate that Hsp70 is necessary for the immune response following muscle injury and is further required for normal muscle regeneration. Supported by grants R03AR056418 & R01AR060209-02 to A.R.Judge.

32.11
ROLE OF THE NOVEL TISSUE-SPECIFIC PGC-1 AND ERR-INDUCED REGULATOR PERM1 IN MUSCLE

Yoshitake Cho[1], Bethany Hazen[1], Aaron Russell[2], Anastasia Kralli[1].
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Mitochondria and oxidative metabolism are critical for maintaining skeletal and cardiac muscle function. The expression of genes important for mitochondrial biogenesis and oxidative metabolism are under the control of transcriptional coactivators of the PGC-1 family and orphan nuclear receptors of the ERR (Estrogen-related receptor) subfamily. Deregulation of PGC-1/ERR signaling is associated with decreased muscle performance, muscle wasting and heart failure. The mechanism(s) by which ERRs and PGC-1 regulate muscle-specific pathways are not fully understood. In a search for factors that enable PGC-1/ERR function in muscle, we identified a so far uncharacterized muscle-specific protein that is induced by PGC-1s and ERRs, and is predicted to be nuclear. We have named this novel protein PERM1, for PGC-1 and ERR-induced Regulator in Muscle. Expression of PERM1 in C2C12 myotubes enhances the expression of selective PGC-1/ERR target genes that are important for energy production, contractile function, and glucose/lipid metabolism. Endogenous PERM1 is required for the expression of the same genes and for PGC-1-induced mitochondrial biogenesis. Our ongoing studies support a role for PERM1 in regulating muscle-specific pathways important for energy metabolism and contractile function. Elucidation of PERM1 function could provide novel therapeutic targets for treating muscle and heart diseases.

32.12
INTERLEUKIN-6 AND ADIPOSE TISSUE INSULIN RESISTANCE DURING THE RECOVERY FROM EXERCISE

Laura Castellani[1], Christopher G.R. Perry[2], Jared Root-McCaig[1], and David C. Wright[1]
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Interleukin-6 (IL-6) expression is increased in adipose tissue after exercise, however, the functional significance of this increase is unknown. The current study aimed to define the relationship between increases in IL-6 signalling and adipose tissue metabolism following a single bout of exercise. Male C57BL/6J mice ran for 2-hours on a motorized treadmill (15 metres/minute, 5% incline). Immediately following exercise IL-6 mRNA expression was elevated in epididymal white adipose tissue (eWAT). This was accompanied by a subsequent increase in IL-6 protein content and SOCS-3 mRNA 4 hours after exercise. At this time point circulating IL-6 levels were not elevated. To ascertain a functional association between elevated IL-6 signalling and adipose tissue metabolism we assessed in vivo insulin signalling. Insulin-stimulated Protein Kinase B (PKB) phosphorylation was blunted in eWAT from mice that had run 4 hours previously compared to sedentary controls and this was associated with an attenuated reduction in plasma glycerol and fatty acid levels following insulin injection. Insulin-stimulated PKB phosphorylation was intact in triceps muscle and liver. Our results demonstrate an association between adipose tissue IL-6 signalling and the development of adipose tissue insulin resistance during the recovery from exercise. This may be advantageous in the provision of fatty acids to liver and skeletal to be used as a fuel source, while sparing glucose for glycogen synthesis.

32.13
ELUCIDATING THE ROLE OF HISTONE DEACETYLASES IN SKELETAL MUSCLE ATROPHY

Michael E. Walsh[1], Arunabh Bhattachrya[1,2] and Holly Van Remmen[1,2,3]
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Motor neurons form a specialized synapse with skeletal muscle known as the neuromuscular junction, and degeneration of the NMJ has been implicated in disease and aging. Recently, a role for histone deacetylases (HDACs) in the regulation of the adult neuromuscular system has been established. HDACs are a family of enzymes that remove acetyl groups from the lysines of histone and non-histone proteins. HDACs regulate a number of transcription factors required for the maintenance of the adult neuromuscular system, including MyoD, myogenin and myocyte enhancer factor 2. HDAC4 and HDAC5 knockout mice are protected against surgical denervation, and pharmacological inhibition of histone deacetylases is protective in multiple models of neuromuscular disease. In this study, we examined the effect of sodium butyrate (NaBu), a histone deacetylase inhibitor, on muscle atrophy in a model of sciatic nerve crush and in age-related muscle atrophy.We demonstrate that NaBu increases histone acetylation *in vivo* and protects against the muscle loss induced by nerve crush. The control-fed mice lost22% of their gastrocnemius mass while the NaBu-fed mice lost only 11% one week after surgery. NaBu protects against the loss of cross sectional area and prevents the induction of atrogin-1, which has been implicated in neuromuscular disease. Our laboratory has reported extensive neuromuscular changes with age. Intriguingly, we have found an increase in HDAC4 protein levels in skeletal muscle from 31 month old C57BL/6 mice. Preliminary results indicate that sodium butyrate protects against age-related muscle atrophy in female mice.Future studies will determine the mechanism by which sodium butyrate protects against neuromuscular atrophy. This work was funded by the UTHSC at San Antonio Biology of Aging Training Grant to Steve N. Austad(MEW T32AG021890-10).

33.0: HOT TOPICS IN EXERCISE PHYSIOLOGY

33.3
MITOCHONDRIA, HYPERGLYCEMIA, REDOX AND CARDIAC DYSFUNCTION IN TYPE 2 DIABETES

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In type 2 diabetes (T2DM), hyperglycemia (HG) and increased sympathetic drivealter mitochondria energetic/redox properties, decreasing the organelle's functionality. These perturbations may prompt or sustain basal low-cardiac performance and limited exercise capacity. In T2DM (*db/db*) mouse hearts, we recently reported that altered energetic/redox balance in mitochondria is associated with the triggering ofintracellular oxidizing conditions leading to cardiac mechanical dysfunction under HG and -adrenergic stimulation (to simulate increased workload). Dysfunctional mitochondria and HG act as permanent drivers of redox imbalance impairing excitation-contraction coupling in the T2DM heart. Glutathione (GSH) or the fatty acid palmitate (Palm)

rescued cardiac redox milieuand mechanical function. Metabolomics data indicate that HG elicits an unfavorable intracellular redox/energetic status by propelling a permanent redox imbalance driven by glucose shunt to polyol pathways and apparent blockage of glycolysis. Palm oxidation in the presence of HG appears to relievesuch blockage, improving the redox environment and the ATP yield, thus resulting beneficial for the T2DM heart, at least in the short-term. The addition of Palm under energetic/redox stress appears to alleviate the adverse metabolic remodeling elicited by HG in the T2DM heart. Preliminarily, we conclude that in the presence of poor glycemic control, the diabetic patient's inability to cope with increased cardiac work demand largely stems from mitochondrial and HG-elicited redox/energetic disarrangements that mutually influence each other, leading to myocyte or whole-heart mechanical dysfunction.

34.0: UNIFIED CELLULAR AND MOLECULAR MECHANISM OF MUSCLE HYPERTROPHY

34.2
THE ROLE OF MTOR IN SKELETAL MUSCLE HYPERTROPHY

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Mechanical stimuli play a major role in the regulation of skeletal muscle mass and the maintenance of muscle mass contributes significantly to disease prevention and issues associated with the quality of life. Although the link between mechanical signals and the regulation of muscle mass has been recognized for decades, the mechanisms involved in converting mechanical information into the molecular events that control this process remain poorly defined. Nevertheless, our knowledge of these mechanisms is advancing. For example, recent studies indicate that signaling through a protein kinase called the mammalian target of rapamycin (mTOR) plays a central role in this event. Hence, this seminar will begin with a summary of the evidence which implicates mTOR in the mechanical regulation of muscle mass. We will then explore the current knowledge of how mechanical stimuli are thought activate mTOR signaling. In particular, we will focus on studies which indicate that mechanical stimuli activate mTOR signaling through an atypical mechanism that is distinct from the core pathways employed by growth factors and nutrients. Furthermore, we will discuss the evidence which suggests that phosphatidic acid may be a key component of this pathway. Finally, we will present preliminary data which might suggest that mechanical stimuli activate signaling through a unique pool of mTOR that is not associated with the classic mTOR complex 1. Funding provide by NIH grant R01AR057347.

34.3
MYOSTATIN AND THE CONTROL OF MUSCLE SIZE

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Since its discovery in 1997, MSTN (MSTN) has become recognized as a critical regulator of skeletal muscle growth. Pharmacological or genetic inactivation of MSTN results in significant muscle growth in a wide variety of organisms, including cow, mouse, and human. MSTN influences muscle growth through multiple pathways; specifically, MSTN inhibits proliferation and differentiation of myogenic precursors during muscle development and adult muscle regeneration and inhibits protein accretion of adult muscle fibers through inhibition of muscle protein synthesis and increased muscle protein degradation. The pathways through which MSTN accomplishes these processes include canonical signaling through the activin receptor IIb-SMAD transcriptional pathway as well as cross-talk through the Akt-mTOR, MAP kinase, and Wnt pathways. Expression and activity of MSTN is in turn regulated by a variety of different inputs and changes in MSTN expression/activity appear to be a crucial contributor to changes in muscle size in response to both physiological and pathological alterations in muscle growth. Expression of MSTN is regulated by both transcriptional and post-transcriptional mechanisms; our laboratory has shown that expression of MSTN is transcriptionally under the control of FoxO, SMAD, and C/EBP transcription factors and post-transcriptionally regulated by the microRNAs miR-27a and b. Activity of MSTN is also tightly regulated, by members of the follistatin family, expression of which are in turn altered during periods of muscle remodeling and growth. Thus MSTN has been demonstrated to be a critical node in the regulation of muscle growth.

NOTES

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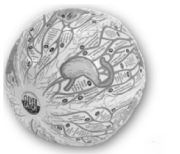

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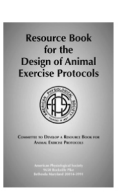

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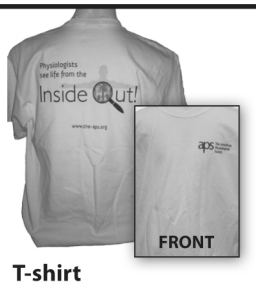

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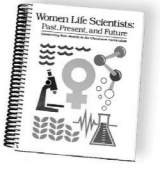

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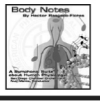

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