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Integrating the Life Sciences from Molecule to Organism

The Physiologist

INSIDE

Generating Support for Science in the 111th Congress

Rebecca Osthus
APS Science Policy Analyst

The 2008 election cycle brings a new administration to Washington, DC this January and also ushers in the 111th Congress. With many new Members of Congress in both the House of Representatives and the Senate, now is the time for APS members to reach out and communicate the importance of supporting biomedical research through strong federal funding and sound policy making. While scientists carry out research in labs across the country, many decisions are being made in Washington, DC that will affect how they do their jobs.

The current fiscal crisis means that it is more important than ever before to make a strong case for federal investment in research. Since the completion of the doubling of the NIH budget, yearly increases have failed to keep pace with inflation, causing success rates for extramural grants to fall into the teens. Even the fight to protect the NIH budget from being cut has become an uphill battle. The outlook for the NSF is somewhat more promising. There is a plan to double the agency's budget over the next several years as part of the America COMPETES Act, but so far yearly increases have not lived up to the goals laid out by Congress.

Lawmakers are also making decisions about what regulations govern the use of animals in research, whether federally funded scientists should continue to consult for and own stock in pharmaceutical and biotechnology com-

APS Public Affairs Committee members Jennifer Uno and James Galligan met with Members of Congress in September 2008 to discuss funding for biomedical research.

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The Physiologist

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panies, and whether or not federally supported researchers should be allowed to derive new human embryonic stem cell lines.

Whether the Members of Congress that represent your district and state are newly elected or experienced public servants, it is critical to let them know that supporting research should be high on their list of priorities. Lawmakers need to hear from YOU about why these issues are important. As a scientist and a constituent, you have a unique opportunity to have input in the decision making process.

There are several ways to get in touch with your legislators—meetings, phone calls and letters are all effective means of communication depending on the topic and how much time you have to commit. To obtain contact information, visit their individual websites, which you can find by going to http://www.senate.gov or http://www.house.gov. Each website contains information about how to contact their offices both in Washington, DC and their home district. The website may also contain information about local events such as town hall meetings in their districts, which also serve as opportunities for interaction.

For more resources, access the APS Science Policy resources at http://www.the-aps.org/pa. ❖

Representative David Price (D-NC) and Jennifer Uno.

APS News

APS Makes 29 Awards to Victims of Hurricane Ike

In response to the devastation caused by Hurricane Ike to Galveston and its surroundings, the APS Council agreed to establish a Hurricane Ike Relief Fund. The Council committed $50,000 to the fund in order to help graduate students and postdoctoral fellows who were APS members in good standing or working in laboratories of APS members in good standing to recover from the Hurricane's devastation. The membership was also encouraged to contribute to the Fund in order to increase the support available to the program.

A total of 76 applications were submitted to the Hurricane Ike Relief Fund. Twenty-nine awards were made to applicants who were APS members or working in APS member laboratories. Thirty-three applications were from non-APS members and two applications were from candidates working in suspended APS member laboratories. The remaining 12 applications were incomplete, failing to provide the name of research advisors or information on the impact of Hurricane Ike on the applicant. ❖

APS Bylaw Changes

ARTICLE III. *Membership*
SECTION 1. The Society shall consist of regular, honorary, affiliate, emeritus, graduate student, undergraduate student, and sustaining associate members.

SECTION 5. *Emeritus Members.* A regular member may apply to Council for transfer to emeritus membership if that person (1) has reached the age of 65 and is retired from regular employment or (2) has been forced to retire from regular employment because of illness or disability and (3) has been a Regular member in good standing for a minimum of 10 years. An emeritus member may be restored to regular membership status on request to Council.

SECTION 6.a. Graduate *Student Members.* Any doctoral or masters program student who is actively engaged in physiological work as attested to by two regular members of the Society shall be eligible for proposal for graduate student membership. No individual may remain in this category for more than five years, without reapplying.

SECTION 6. b. Undergraduate Student Members. Any matriculated undergraduate student, as demonstrated by submission of verification of student status, who has an interest in physiology is eligible for undergraduate student. No individual may remain in this category for more than five years.

ARTICLE IV. *Officers*
The Chairpersons of the Publications Committee, the Finance Committee, the Joint Program Committee, the Education Committee, the Public Affairs, the APS Representative to the FASEB Board, and the Executive Director are ex officio members of the Council without vote; the Chairperson of the Section Advisory Committee is an ex officio member of the Council with vote. The Council may fill any interim vacancies in its membership. Council shall appoint members to all committees except the Chapter Advisory Committee, Section Advisory Committee, Joint Program Committee, Liaison with Industry Committee, Committee on Committees, and the Trainee Advisory Committee.

SECTION 4. a. *Nomination of Officers.* Nominations for PresidentElect and for members of Council will be made by ballot, on forms provided by the Executive Director, before ~~January 1~~September 30 of each Year. Each member may nominate no more than one candidate for each office. If a member wishes to nominate the same person for President-Elect and for Councillor he/she must nominate that individual for each position.

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

SECTION 2. *Finance Committee.* A Finance Committee, composed of five regular members of the Society appointed by Council, shall receive the total coordinated budget proposals annually from the Executive Director and shall determine the annual budgets, reserve funds and investments of the Society, subject to approval by the Council. The term of each member of the Finance Committee shall be three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairperson of the Committee who shall be an ex officio member of the Council, without vote. On advice of the Finance Committee and consent of Council, the Executive Director shall be empowered to appoint and compensate a ~~Business Manager~~ Director of Finance who shall assist in carrying out the functions of the Finance Committee under the supervision of the Executive Director. The Past President shall serve as a votng member of the Finance Committee. The President-Elect, President, Executive Director, the Chairperson of the Publications Committee, and the ~~Business Manager~~ Director of Finance shall be ex officio members of the Finance Committee, without vote.

SECTION 4. *Education Committee.* An Education Committee, composed of five or more regular members of the Society and representatives of such other societies as may be designated by the Council, appointed by the Council, shall conduct such educational, teaching and recruitment programs as may be required or deemed advisable. The term of each member of the Education Committee shall be three years. The Chairperson of the Committee shall be designated by the Council. On the advice of the Education Committee and consent of Council, the Executive Director shall be empowered to appoint and compensate the Director of Education Programs who shall assist in carrying out the functions of the Education Committee under the supervision of the Executive Director. ~~The Executive Director may act as executive officer of the educational programs with approval of the Council.~~ The Committee shall present an annual report to the Council and an annual budget through the Executive Director to the Finance Committee for its approvaland recommendation to Council.

SECTION 5. *Joint Program Committee.* A Joint Program Committee composed of ~~six regular members of the Society appointed by Council and~~ elected representatives of the sections and groups shall be responsible for the Society's annual spring meeting scientific programs~~of the Society~~. The term of each member shall be for three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairperson of the Committee, who shall be an ex officio member of the Council, without vote. The President-Elect and Executive Director shall be ex officio members, without vote.

ARTICLE VI. *Dues*
SECTION 2. *Nonpayment of Dues.* ~~A regular member, affiliate member or student member~~ Members whose dues are two years in arrears shall cease to be a member of the Society, unless, after payment of dues in arrears and application to the Council, he/she shall be reinstated at the next meeting by vote of the Council. It shall be the duty of the President-Elect to notify the delinquent of his/her right to request reinstatement.

ARTICLE VII. *Financial*
SECTION 1. *Operating Fund Purpose.* The Operating Fund is used to provide sufficient cash to meet daily and ongoing financial obligations of APS. The Operating Fund will contain sufficient cash to cover current expenditures.

SECTION 2. *Short-Term Fund Purpose.* The Short-Term Fund is used to meet unanticipated expenditures that exceed the Operating Fund's reserves. The Short-Term Fund is to contain approximately 50% of the value of the Operating Fund.

SECTION 3. *Long-Term Fund Purpose.* The purpose of the Long-Term Fund is to maintain a long-term reserve for significant and unanticipated expenditures and to support, with some portion of the reserve's earnings, the general operating budget of the APS. The Long-Term Fund will also provide a structure in support of endowed and Council-designated funds used to:

Support programs for the development of physiology and physiologists. Encourage communication with other disciplines of science and the community at large. Foster scientific and cultural relations with other parts of the world.

~~SECTION 1. *Society Operating Fund.* The Society Operating Fund shall consist of all funds, other than Publication Operating Funds and Publication Contingency and Reserve Funds, restricted or unrestricted, uninvested or invested, short or long term. The Executive Director shall be the responsible agent to the Council with signatory powers. Signatory powers may be delegated to the Business Manager by the Executive Director.~~

~~SECTION 2. *Publications Operating Fund.* The Publications Operating Fund shall consist of all funds that involve receipts, expenses, short term investments relating to the annual receipts, disbursements and continuing operation of the Society's publications. The Executive Director shall be the responsible agent to the Council with signatory powers. Signatory powers may be delegated to the Business Manager by the Executive Director.~~

~~SECTION 3. *Publications Contingency and Reserve Fund.* The Publications Contingency and Reserve Fund shall consist of the long term capital investments of publication earnings. The Executive Director, with advice from the Finance Committee, shall have discretionary and signatory powers, except for withdrawals. Authority for any withdrawal from this fund shall require the following five signatures: 1) the Chairperson of the Publications Committee (alternate, the senior member of the Committee); 2) the President of the Society (alternate, the President-Elect); 3) the Executive Director (alternate, the Publications Manager); 4) and 5) any two members of Council. The Finance Committee shall not recommend to Council the expenditure of any of this capital fund for non-publication purposes without the consent of the Publications Committee. The Finance Committee shall be responsible for the separate investment of the reserve fund for publications; any capital gains from such investment shall accrue to the fund (capital losses will, however, reduce its value). Any dividends, interest or income, other than capital gains, from this invested fund may be used for emergency support of any of the activities of the Society, including publications, as determined annually by the Council, but the primary goal shall be to increase the investment capital.~~ ❖

Duling Receives 6th Schmidt-Nielsen Distinguished Mentor and Scientist Award

The APS Women in Physiology Committee is pleased to announce that Brian R. Duling, Robert M. Berne Professor of Cardiovascular Research and Director of the Cardiovascular Research Center, Departments of Molecular Physiology & Biological Physics and Biomedical Engineering, University of Virginia Health Sciences Center, has been selected as the sixth recipient of the Bodil M. Schmidt-Nielsen Distinguished Mentor and Scientist Award. The Committee was extremely impressed with both his mentoring excellence and his outstanding contributions to physiological research.

Duling received his PhD at the University of Iowa. He did his postdoctoral training at the University of Virginia School of Medicine before being hired as an Instructor and then Assistant Professor in the Department of Physiology. He moved up through the ranks, including terms as Vice-Chair and Acting Chair of the Department, until being named the Robert M. Berne Chair in Cardiovascular Research in 1992 and then Director of the Cardiovascular Research Center in 1993. He continues to hold those positions today, in addition to acting as Interim Associate Dean for Graduate Studies in the School of Medicine.

Duling's research focuses on the integrative biology of the vascular system, with two broad areas of excellence. First, he is interested in the cellular and molecular basis of the regulation of arteriolar tone and blood flow, especially in striated muscle. Second, he seeks to understand the factors that control tissue oxygenation, and particularly the ways in which red cells are distributed among the microvessels. The excellence of his research has been recognized by the APS (including the Wiggers Award and the Robert M. Berne Distinguished Lectureship, both awarded by the Cardiovascular Section), but also the Microcirculatory Society (Zweifach Award), the European Microcirculatory Society (Malpighi Award), and The University of Virginia (Distinguished Scientist Award), among others.

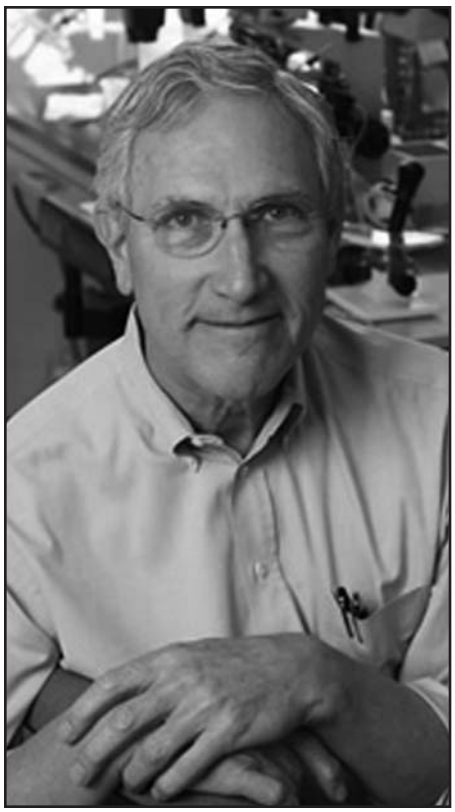


photo credit: Tom Cogill / virginia.edu

Brian Duling

Duling has successfully mentored 35 postdoctoral fellows, three clinical fellows, and seven pre-doctoral students. His mentees have gone on to successful and prominent positions (including two chairs, Senior Vice President, Chief Medical Officer, NIH Program Officer, among others) in a variety of careers: academia, industry, clinical centers, and government with national funding and numerous awards among themselves.

Duling's success as a mentor was four-fold, according to the people writing his supporting recommendation letters. *1*) He provided excellent guidance to trainees holding a range of career aspirations. He gave equal attention to trainees who desired to follow in his career footsteps and to those who aspired to an alternate career path. By spending the time to understand his trainees' career goals, Dr. Duling took steps to best facilitate each trainee's future success. *2*) He constantly demanded the best of his trainees. He stimulated individuals to work harder and think deeper than they thought possible. *3*) Through his enthusiasm in hosting visits from national/international scientists, Dr. Duling illustrated to his trainees that science transcends geographical boundaries and that colleagues can become lifelong friends in the journey of scientific discovery. This led to a great diversity in individual strengths of the researchers in his lab and generated a strong international 'spirit' within the lab. *4*) He engendered an air of "family" with members of his lab. He maintains continued contact with previous lab members by holding an annual Duling lab dinner at the yearly EB conference.

There will be a reception in Dr. Duling's honor at which he will give a talk on mentoring during the 2009 Experimental Biology meeting in New Orleans, LA. It will be held on Monday, April 20 at 12:00 PM at the Hilton Hotel. All trainees and mentors are invited to attend.

APS congratulates Dr. Duling on this well-deserved honor. ❖

Moving?

If you have moved or changed your phone, fax or Email address, please notify the APS Membership Office at 301-634-7171 or Fax to 301-634-7241. Your membership information can also be changed by visiting the Members Only portion of the APS Website at http://www.the-aps.org. ❖

11th Annual Meeting of the Nebraska Physiological Society

The 11th annual meeting of the Nebraska Physiological Society (NPS) was held on Saturday, September 6, at the Univ. of Nebraska at Omaha Thompson Alumni House, Omaha, NE. Attendance at the meeting totaled 80 registered individuals, including undergraduate and graduate students, postdoctoral fellows, and faculty members. Thirty nine research posters from five research institutions were presented. Sponsors included the American Physiological Society; the Department of Cellular and Integrative Physiology, UNMC; the Dean's Office of the College of Medicine, UNMC and The Nebraska Medical Center. Corporate sponsors were Data Sciences International, AD Instruments, North Central Instruments, and the Bruker Biospin Corporation – EPR Division.

The meeting began at 9:00 AM with welcome and introductory remarks from Thomas E. Pisarri, NPS President and Professor, Department of Biomedical Sciences at Creighton Univ.. Pisarri thanked this year's sponsors for their support. He also thanked the staff of the Department of Cellular and Integrative Physiology—Pearl Sorensen, Linda Tegeder, Janine Wilson, Cindy Norton, and Richard Robinson—for their help and support during his presidency.

Joey Granger, University of Mississippi Medical Center, presented the research keynote address, "Pathophysiology of Hypertension in Response to Placental ischemia During Pregnancy." Granger's address was followed by Young Investigator Presentations by Carol Fassbinder-Orth, Assistant Professor, Creighton University, and Jennifer Wood, Assistant Professor, Univ. of Nebraska at Lincoln. The speakers were selected to present their research projects based on the quality of their submitted abstracts. Following the Young Investigator Presentations, Dee Silverthorn, Univ. of Texas-Austin, presented the education keynote address entitled, "Teaching in the Interactive Classroom."

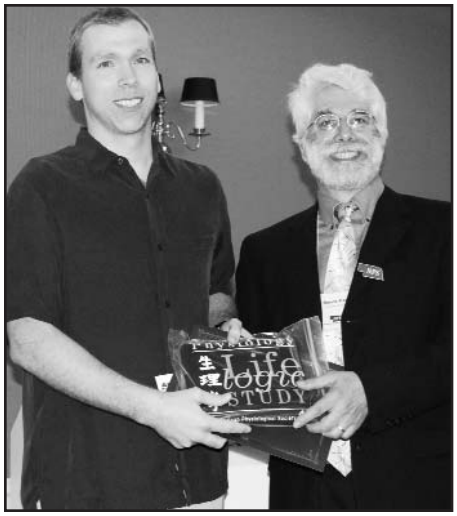
At the NPS business meeting and luncheon, Irving H. Zucker, President of American Physiological Society and Chair of the Department of Cellular and Integrative Physiology (UNMC) presented an update on the state of the APS. Zucker highlighted current programs and strategic goals of the parent society. David Holtzclaw highlighted the activities that took place during APS sponsored Phun Week and the 7th Grade College and career fair held on April 18, 2008 at Metropolitan Community College. Past president Harold D. Schultz, presented an update as NPS representative to the APS Chapter Advisory Committee.

Pisarri presented a plaque NPS Past-President Schultz, in recognition of his innovative efforts in planning the 2007 Combined Iowa-Nebraska Physiological Society Meeting. Pisarri also presented a plaque to Cindy R. Norton, Executive Director, in recognition of her ongoing dedication to the NPS and her organization of the annual meeting. PiDr. Kaushik P. Patel, Department of Cellular and Integrative Physiology, UNMC was introduced as the incoming NPS President.

The afternoon portion of the meeting was dedicated to poster viewing and judging. Posters were judged in the undergraduate, graduate, and postdoctoral categories from institutions that included the University of Nebraska at Lincoln, University of Nebraska Medical Center, Creighton University, University of South Dakota, and Wayne State College. After compiling scores from the poster judges, Pisarri presented awards to individuals in each of the categories. In the undergraduate category, award recipients were: 1st place, Sumit Kar, UNMC; 2nd place, Tiffany L. Bohlender, UNL; 3rd place, Rachael Farrar UNMC. Award recipients in the graduate category were: 1st place Lee Zucker Graduate Student Research Award, P. Richard Grimm, UNMC; 2nd place (tie), Sarah Clayton, UNMC, and Laura Liete, UNMC. In the postdoctoral category, award recipients were: 1st place, Amit Mitra, UNMC; 2nd place, Muhammad Bari, UNMC; 3rd place, Yangfeng Ding, UNMC. Recipients received certificates and monetary awards of $250 (1st place), $100 (2nd place), or $50 (3rd place). ❖

Cindy R. Norton
Executive Director,
Nebraska Physiological Society

NPS President Thomas E. Pisarri, presents an undergraduate poster award to Sumit Kar.



NPS President Thomas E. Pisarri presents the Lee Zucker Graduate Student Research Award to P. Richard Grimm.

NPS President Thomas E. Pisarri presents the postdoctoral award to Amit Mitra.

APS Membership Statistics

Total Membership **10,497**

Distribution by Employment
(7,508 respondents)

Institution	Total	Percent
Physiology Departments	1,594	21.2
Administration	26	0.3
Clinical	885	11.8
College or University	2,486	33.1
Commercial Companies	255	3.4
Community College or 2-Year Institution	10	0.1
Dental Schools	34	0.5
Government (Inc. V.A)	270	3.6
High School	5	0.1
Hospitals and Clinics	308	4.1
Institutes and Foundations	205	2.7
Medical Schools	748	10
Not-for-Profit Association	15	0.2
Other Preclinical Depts.	353	4.7
Other, please specify:	52	0.7
Private Practice	31	0.4
Public Health and Graduate Schools	90	1.2
Retired	26	0.4
Veterinary Schools	125	1.5

Distribution by Racial Background and Heritage (optional personal data)
5, 709 total respondents

Alaskan Native	2
American Indian	10
Asian or Pacific Islander	798
African American	75
Hispanic	205
Multiracial	26
Other	43
Anglo American (non Hispanic)	4,550

Distribution by Earned Degree
(8,310 respondents—includes 1,081 individuals with multiple doctorate degrees)

PhD	5,879
MD	2,153
DVM or VMD	169
DSc or ScD	88
DrMed or DMSc	23
EdD	14

Distribution by Gender
(optional personal data)

Male	7,554
Female	2,464

Distribution by Age
(optional personal data)

70+	592
60-69	1,849
50-59	2,901
40-49	2,742
30-39	2,274
20-29	1,147

Principle Type of Work
(6,798 respondents)

	%
Administration	3.59
Clinical	5.55
Research	79.83
Teaching	11.03

Distribution by Primary Section Affiliation
(9,992 respondents)

	%
Cardiovascular	23.2
Cell & Molecular Physiology	12.7
Central Nervous System	9.4
Comparative Physiology	3.9
Endocrinology & Metabolism	8.7
Environ. & Exercise Physiology	9.2
Gastro. & Liver Physiology	5.5
Neural Control & Autonomic Reg.	4.9
Renal	7.6
Respiration	9.0
Teaching of Physiology	3.3
Water & Electrolyte Homeostasis	2.6

Distribution by Group Affiliation

Epithelial Transport	1,079
History of Physiology	575
Hypoxia	810
Members in Industry	346
Muscle Biology	1,135
Physiological Genomics	409
Translational Research	354

Distribution by Primary Specialty

Anatomy	30
Biochemistry	73
Biomedical engineering	35
Biophysics	30
Cardiovascular	1,535
Cellular and tissue	238
Comparative physiology	165
Electrolytes and water balance	187
Endocrines	313
Environment	148
Exercise	185
Gastrointestinal	178
General physiology	5
Immunology	32
Lipids and steroids	41
Liver and bile	31
Minerals bones and teeth	32
Muscle	511
Neural control and autonomic reg.	63
Neurosciences	359
Renal	146
Reproduction	76
Respiration	411
Teaching	31
Transport	33
Other	31

APS Membership in The Americas

United States of America	8,110
Canada	500
Brazil	89
Mexico	37
Chile	20
Argentina	28
British West Indies	3
Peru	6
Venezuela	4
Jamaica	2
Netherland Antilles	2
Uruguay	2
Cayman Islands	1
Colombia	1
Trinidad	1

US States with More than 100 Members
(50 states plus District of Columbia Puerto Rico, Guam and US Virgin Islands)

California	819
Texas	541
New York	540
Pennsylvania	421
Massachusetts	364
Ohio	356
Illinois	348
Maryland	347
North Carolina	269
Florida	245
Michigan	229
Georgia	223
Missouri	207
Wisconsin	201

Minnesota	181
Indiana	174
Alabama	168
Colorado	164
Virginia	164
New Jersey	160
Tennessee	159
Connecticut	137
Louisiana	135
Arizona	126
Iowa	120
Washington	116
Kentucky	110
Oregon	108

APS Membership Outside The Americas
(countries with five or more members)

Japan	310
United Kingdom	195
Australia	150
Germany	123
France	97
Denmark	79
Switzerland	67
Italy	62
South Korea	52
Sweden	52
Taiwan	52
The Netherlands	48
Spain	44
Belgium	43
India	36
Israel	33
Norway	28
Turkey	28
New Zealand	27
China	25
Greece	23
Hong Kong	16
Thailand	14
Ireland	12
Nigeria	12
Portugal	12
Czech Republic	11
Hungary	11
South Africa	11
Malaysia	10
Poland	10
Singapore	9
Austria	8
Finland	7
Slovenia	7
Croatia	6
Egypt	6
Lebanon	5
Saudi Arabia	5

Other countries represented: Iran, Pakistan, Russian Federation, United Arab Emirates, Bulgaria, Estonia, Iceland, Philippines, Kuwait, Slovakia, Sudan, Belarus, Indonesia, South Korea, Luxembourg, Macedonia, Mozambique, Oman, Qatar, Romania, Serbia, Montenegro, and Ukraine.

Canadian Provinces with Five or More members

Ontario	236
Alberta	79
Quebec	78
British Columbia	51
Manitoba	24
Nova Scotia	13
Newfoundland	9
Saskatchewan	5

New Student Members

Chelsea Baker
Univ. of Oklahoma HSC
Matthew Burford
Univ. of Mississippi
Marius Busauskas
St. Louis Univ., MO
Johnathan Chang
SUNY Stony Brook
Matthew Conaway
Univ. of Iowa
Pedro Contreiras Pinto
Univ. Lusofona De Humanid. Portugal
Joao Da Costa Silva
Univ. of Sao Paulo, Brazil
Christopher Cottingham
Univ. of Alabama, Birmingham
Harshavardhan Deoghare
Univ. of Florida
Jessica Donnelly
Univ. of Cincinnati, OH
Edward Dostaler
Southern Connecticut State Univ.
James Ellison
Auburn Univ., AL
Zachary Elmore
Murray State Univ., KY
Jennifer Fang
Univ. of Arizona
Rachael Farrar
Univ. of Nebraska Med. Ctr.
Gordon Fisher
Auburn Univ., AL
Andrew Galpin
Ball State Univ., IN
Tim Heistek
VU Univ., Netherlands
Flavio Ivalde
Univ. of Buenos Aires, Argentina
Megan James
West Virginia Univ.
Babajide Karonwi
College of Med. of the Univ. of Nigeria
Sun Wook Kim
Univ. of Cincinnati, OH
Ivana Kuo
John Curtin Sch. of Med., Australia
Rachel Lantry
Pennsylvania State Univ.
Chang Lee
Texas A&M Univ.
Shuani Li
Univ. of South Dakota, Sch. of Med.
Kyle McCommis
Washington Univ., Sch. of Med., MO
Daniel Moraes
Univ. of Texas, Austin
Matthew Muller
Kent State Univ., OH
Ricardo Pena
Univ. of Iowa
Do Pham
Univ. of of North Carolina
Jordan Querido
Univ. of British Columbia
Arun Rooj
Univ. of Alabama, Birmingham
Tin-Han Shih
National Taiwan Normal Univ.
Jeremy Sorkin
Pennsylvania State Univ.
Mette Staehr
Inst. of Med. Biology, Denmark
Jesse Sulzer
LSU Health Sciences Center, LA
Kelly Thuet
St. Louis Univ., MO
Karla Vincent
Georgia Inst. of Tech.
Daniel W. Wesson
Boston Univ., MA
Xiaojia Zheng
Univ. of Alabama, Birmingham

New Affiliate Member

Mary T. Maher
Univ. of Arizona

New Regular Members

***Transferred from Student Membership**

Sean Raphael Abram*
Univ. of Mississippi Med. Ctr.
Anurag Agrawal
Inst. of Genom. & Int. Bio., Delhi, India
Christopher M. Ashwell
North Carolina State Univ.
Agnieszka Zofia Balkowiec
Oregon Hlth. & Sci. Univ.
John Phillip Bannister
Univ. of Tennessee, Memphis
Maria J. Barnes*
Pennington Biomed. Res. Ctr., LA
Mario O. Belledonne
Biolab Research, Rockville, MD
Olivier Birot
York Univ., Toronto, Canada
Sydella Anne Blatch*
NIH/NICHD, Bethesda, MD
C. Savio Chan
Northwestern Univ., IL
Feng Chen
Washington Univ. St. Louis, MO
Wenling Chen
Univ. of California, Los Angeles
George Thomas Cicila
Univ. of Toledo, OH
Tom William Claydon
Simon Fraser Univ., Burnaby, Canada
Kevin Edmond Crutchfield
LifeBridge Hlth. Brain/Spine Inst., MD
Julia Eve Dallman
Univ. of Miami, Coral Gables, FL
Linda L. Demer
Univ. of CA, Los Angeles, Sch. Med.
Hans C. Dreyer
Univ. of Texas Med. Branch, Galveston
Jianyang Du
Univ. of Connecticut Health Ctr.
Anthie Ellis
Australian National Univ.
Cecile Marie Gallea
NIH, Bethesda, MD
Karl R. Gegenfutner
Giessen Univ., Germany
Geoffrey Mohon Ghose
Univ. of Minnesota
Henk L. Granzier
Univ. of Arizona, Tucson
Aaron J. Gruber
Univ. of Maryland, Baltimore
Jinhu Guo
Univ. of Texas SW Med. Ctr.
ZhongMao Guo
Meharry Med. College, Nashville, TN
Taben Mary Hale*
Univ. of Arizona Coll. of Med., Phoenix
Bradley Hartman Bakken*
Univ. of Wisconsin, Madison
Denise Pestana Henriques
York Univ., Toronto, Canada
Richard Royal Hoopes
SUNY Upstate Med. Univ., Syracuse
Youko Ikeda
Univ. of Pittsburgh Sch. Med., PA
Masumi Inoue
Univ. of Occup'l Environ. Hlth., Japan
Ming Yuan Jian
Univ. of South Alabama, Mobile
Kathryn M. S. Johnson
Beloit College, WI
Ramiro Juncos
Univ. of Mississippi Med. Ctr.
David Walter Kaczka
Johns Hopkins Univ., Baltimore, MD
Makoto Kanzaki
Tohoku Univ., Japan
Keiyh E. Latham
Temple Univ. Med. Sch., PA
Philippe C. Lefebvre
INSERM-Inst. Pasteur De Lille, France
Ching-Long Lin
Univ. of Iowa
Ming De Lin*
Philips Med. Sys., Briarcliff Manor, NY
David McAlpine
Univ. College of London, UK
Ronald Lee Mellgren
Univ. of Toledo HSC, OH
Stanley Nattel
Montreal Heart Inst., Canada
Xin Ni
Second Mil. Med. Univ., Shanghai, China
John H. Olson
Arizona State Univ., Phoenix
Rotimi O. Orisatoki
Spartan HS Univ., St. Lucia, West Indies
Arnaldo F. Lopez Ruiz
Univ. of Mississippi Med. Ctr., Jackson
Abigail L. Mackey
Bispebjerg Hosp., Denmark
Andrea L. Meredith
Univ. of Maryland, Baltimore
Giuseppe Murdolo
Perugia Univ., Italy
Erik R. Nelson*
Duke Univ., Durham, NC
Eisei Noiri
Univ. Hosp., Tokyo, Japan
Thomas D. Parsons
Univ. of Pennsylvania Sch. Vet. Med.
Sergio Polakof
Univ. De Vigo, Spain
John Ramcharitar
St. Mary's Coll., MD
Ulrika Raue*
Ball State Univ., IN
Marta Elena Roque
Univ. Nacional del Sur, Argentina
Andrew T. Smith
Royal Holloway Univ., UK
Benjamin C. Thompson*
Metropolitan State Coll., CO
Miao Tian
Northwestern Univ., IL
Elizabeth I. Tietz
Univ. of Toledo Coll. Med., OH
Stylianos T. Tsakiris
Univ. of Athens, Greece
Mary C. Vagula
Gannon Univ., Erie, PA
Richard D. Wainford
Louisiana State Univ.
Sara Winges
Univ. of Minnesota
Jorgen F.P. Wojtaszewski
Copenhagen Muscle Res. Ctr., Denmark
Stephanie E. Wolfle
Australian Nat'l. Univ.
Jihong Xing
Penn State Univ., Coll. Med.

Recently Deceased Members

Beverly P. Bishop
Buffalo, NY
Edward L. Chambers
Miami, FL
Mario Gaudino
Summit NJ
Roger L. Grief
New York, NY
William Halpern
Burlington, VT
Joseph E. Hawkins
Ann Arbor, MI
Thomas F. Johnson
Silver Spring, MD
Dan R. Kenshalo
Townsend, TN
Jessica H. Lewis
Pittsburgh, PA
Samuel Meerbaum
Woodland Hills, CA
Campbell Moses
Upper Saddle River, NJ
Read R. Nielson
Oxford, OH
Austin Pritchard
Portand, OR
Oscar D. Ratnoff
Cleveland, OH
Raymond A. Russell
Fuquay Varina, NC
Alvin F. Sellers
Ithaca, NY
Arthur H. Smith
Davis, CA
Garth J. Thomas
Rochester, NY
Stanford Wessler
Andover, MA
Laurence G. Wesson
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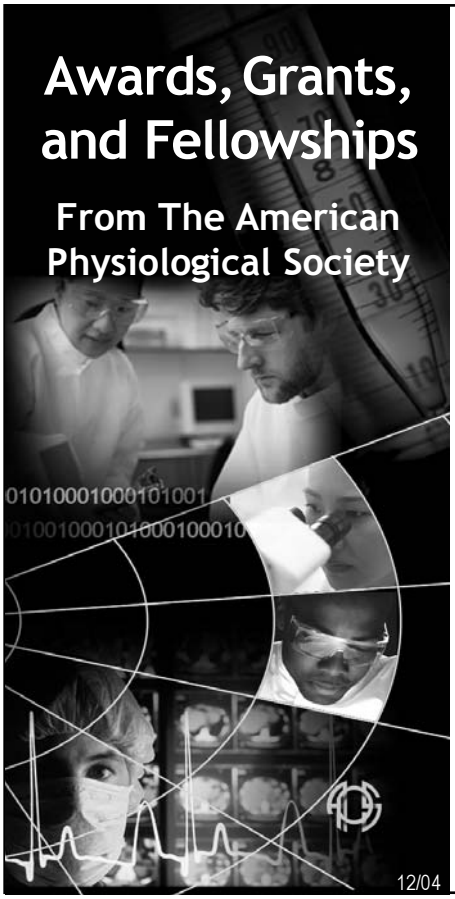
Give an award at your local school science fair!

The APS sponsors awards at local and regional science fairs on a first come, first served basis. Any APS member who participates as a judge in a local or regional science fair at an elementary, middle, or high school is eligible to apply and receive APS support. Award package includes an APS pin, t-shirt, and Certificate of Achievement for the student with the best physiology project, and a *Women Life Scientists* book for the student's teacher.

To request an award package, visit the website below. If you have questions, contact Scarletta Whitsett (*swhitsett@the-aps.org*) in the APS Education Department.

www.the-aps.org/education/sciencefair



The American Physiological Society (APS) provides leadership in the life sciences by promoting excellence and innovation in physiological research and education and by providing information to the scientific community and to the public.

The Awards, Grants, and Fellowships programs are designed to strengthen and shape the discipline through awards that support, recognize, and publicize the scholarly and research activities of APS Members.

For Full Details or Questions

...on all awards, grants and fellowships, visit the APS web site at:

www.the-aps.org/awards

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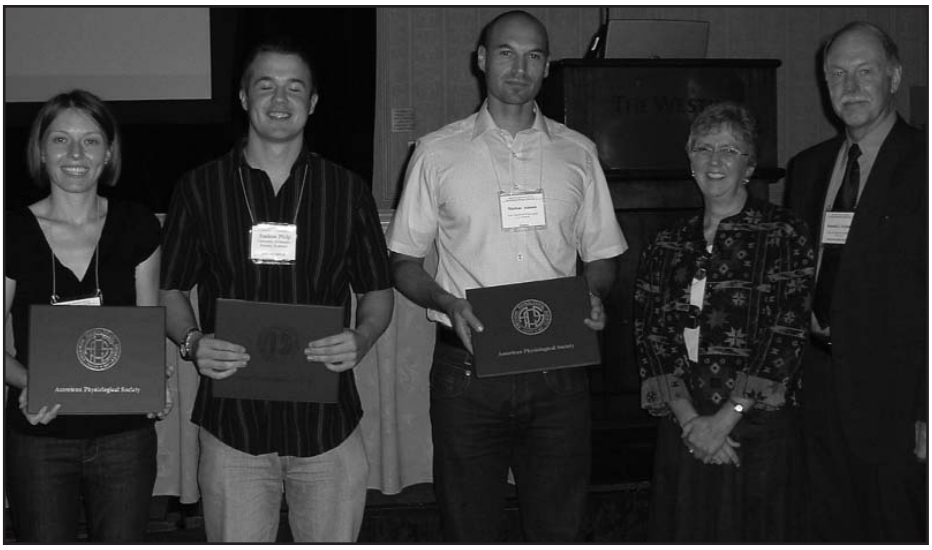
2008 APS Intersociety Meeting: The Integrative Biology of Exercise-V
September 24-27, Hilton Head, SC

The 2008 APS Intersociety Meeting: The Integrative Biology of Exercise-V was held in the sleepy southern town of Hilton Head, SC, famous for its numerous championship golf facilities and resort-like atmosphere. Intersociety Meetings are held every four years and offer concurrent symposia and exhibits. This meeting was organized by Ronald Terjung (Chair), Univ. of Missouri, Columbia, Laurie Goodyear, Harvard Medical School, Robert Grange, Virginia Tech, Gregory Allen, Univ. of California, Irvine, Michael Lindinger, Univ. of Guelph, P. Darrell Neufer, East Carolina Univ., Bente Pedersen of Rigshospitalet, Tara Haas, York Univ., Brenda Russell, Univ. of Illinois, Chicago, David Allen, Univ. of Colorado, Steven Segal, Univ. of Missouri, Columbia, Peter Reiser, Ohio State Univ., and Mark Hargreaves, Univ. of Melbourne. The program for this meeting covered recent advancements in the exercise research area as well as emerging topics.

This exciting meeting attracted 559 total registrants, including a good presence of young investigators and students. The young investigators and students accounted for 39% of the total registrants. APS members made up 29% of the attendees, closely followed by nonmembers (14%) and sponsoring societies (5%) attendees respectively. Invited speakers and chairs represented 11% and meeting exhibitors rounded out the final 2% 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 559 registrants, 8% of registrants came from Canada, 10% of registrants represented countries from Europe and the remaining 10% from Australia, New Zealand, Japan, South Korea, Brazil, Mexico, Israel and South Africa. Table 1 (below) shows the breakdown of the different registration types.

Table 1. Registration Statistics

Registrant Type	Number of Attendees (%)
APS Member	160 (29%)
Nonmember	78 (14%)
Postdoctoral	46 (8%)
Student	179 (31%)
Invited Speaker	59 (11%)
Sponsoring Societies	27 (5%)
Exhibitors	10 (2%)
Total	**559**

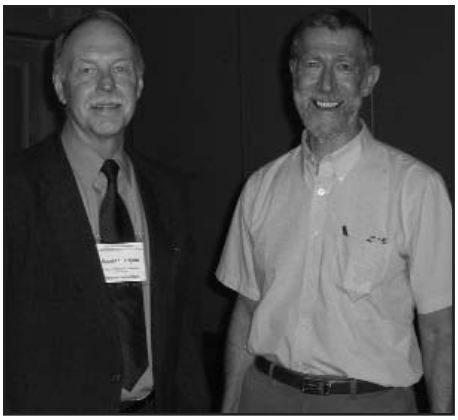


Postdoctoral travel awardees (L-R): Carol Witczak, Andrew Philp, Markus Amann, presented by Susan Bloomfield (NSBRI) and Ronald Terjung.

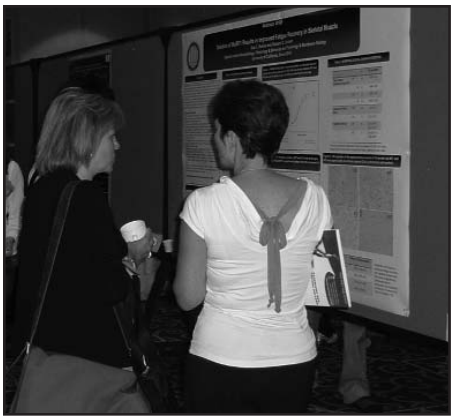
The meeting opened with an informal Opening Reception along the beach front, which gave participants the opportunity to network and catch-up with colleagues while enjoying some delicious hors d'oeuvres. The meeting program allowed for two concurrent symposia each morning and afternoon, with a total of 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.

The three day meeting also included three separate poster sessions, which included light refreshments. During these sessions, established scientists and student attendees presented their abstract work to their colleagues and peers. There were a total of 337 programmed abstracts for the meeting. Out of the abstracts that were submitted, 33% had a female first author; 13% of the submitted abstracts came from countries in Europe, closely followed by Canada with 12% and Japan with 9%.

During the meeting there was an



Meeting Organizer Ronald Terjung (left) with dinner speaker, Peter Wagner.



Meeting attendees discuss the scientific findings with other attendees.

Meeting Organizer, Ronald Terjung with some of the NIDDK awardees (L-R): Christopher Mendias, Jorge Gamboa, Farah Ramirez-Marrero and Rebecca Hasson.

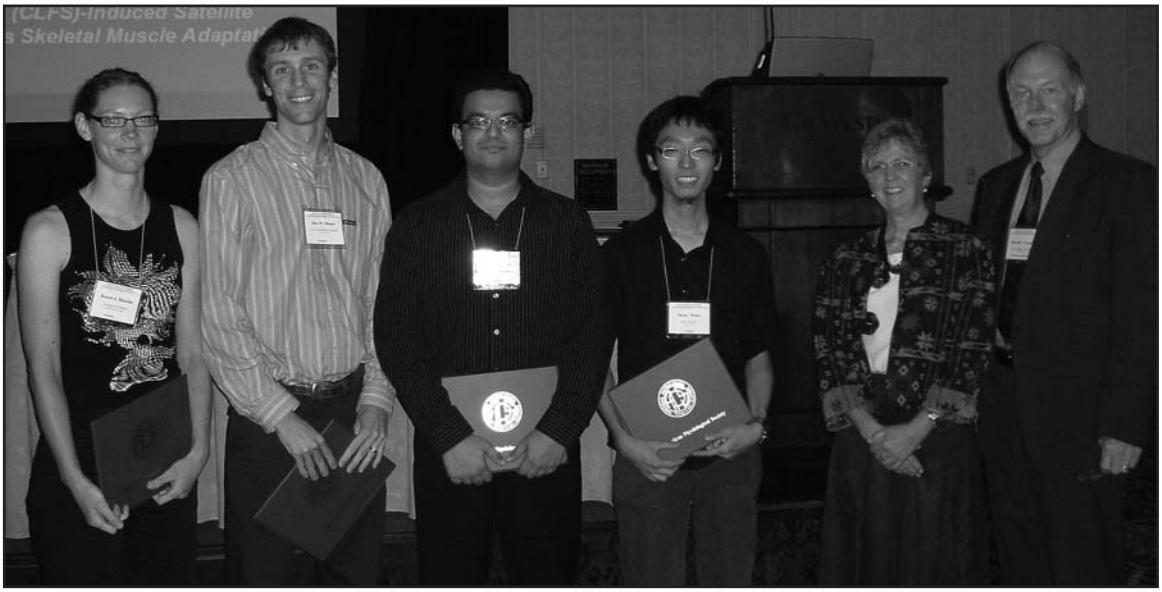
option for registrants to purchase tickets to the Port Royal Golf Club for an evening of socializing and relaxing. Located about minutes from the meeting hotel, the golf club dining room blended traditional southern elegance with traditional mouth-watering southern barbecue. Cooked over an open flame fire grill, participants enjoyed all-you-can-eat chicken, ribs, beef brisket and all the traditional barbecue side dishes, while catching up with new and old acquaintances.

The meeting closed with a Banquet and Awards Presentation, where the Meeting Organizer, Ronald Terjung presented the winners of the Research Recognition Award for Outstanding Abstract Presentation by a Graduate Student or Post-doctoral Fellow a certificate and cash prize. The postdoctoral winners of the award were: Carol Witczak, Joslin Diabetes Center, Markus Amann, Univ. of Zurich and Andrew Philp, Univ. of Dundee, UK. The student award winners were: Adeel Safdar, McMaster Univ., Alex Moore, Univ. of Missouri, Columbia, and Karen Martins, Univ. of Alberta. In addition there were two awards generously sponsored by the National Space Biomedical Research Institute. The awards went to one post-doctoral fellow and one student. The winners of the NSBRI award were: Simon Lees, Colorado State Univ. and Shogo Wada, Univ. of Tokyo.

In addition, the following were the recipients of the Porter Physiology Development Committee's Minority Travel Fellowship Award, which are provided to encourage participation of under-represented minority students: Jorge Gamboa, Univ. of Kentucky, Kirsten Granados, Univ. of Massachusetts, Rebecca Hasson, Univ. of Massachusetts, Anna Leal, Univ. of Texas Southwestern Medical Center, Christopher Mendias, Univ. of Michigan, Trudy Moore-Harrison, Univ. of North Carolina, Charlotte and Farah Ramirez-Marrero, Univ. of Puerto Rico. 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.

Peter Wagner, Univ. of California, San Diego was the Banquet Speaker, presenting unique insights into his life as a scientist and the mentors that influenced him in an entertaining presentation.

The American Physiological Society and the Organizing Committee gratefully acknowledges the financial support provided through generous educational grants from: NIAMSD, NIDDK, Merck Research Laboratories, NSBRI and Aurora Scientific, Inc. 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. ❖



Student travel awardees (L-R): Karen Martins, Alex Moore, Adeel Safdar, Shago Wado, presented by Susan Bloomfield (NSBRI) and Ronald Terjung.

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APS Represented at the National Association of Biology Teachers 2008 Professional Development Conference in Memphis

Margaret Shain (New Albany, IN), a science teacher affiliated with APS education programs since 2000, assisted APS Education Office Coordinators, Melinda Lowy and Mel Limson, in representing the APS at the National Association of Biology Teachers (NABT) 2008 Professional Development Conference in Memphis, TN. The annual national conference attracts middle and high school teachers, as well as community college and four-year college instructors or faculty from across the nation. Shain, Lowy, and Limson showcased APS education programs, fellowships, and awards at the exhibit booth throughout the three-day conference in October.

During the K-12 Outreach Symposium of education programs across the nation, Limson highlighted the development, successful growth, and expansion of the APS' Physiology Understanding Week (PhUn Week). PhUn Week is the APS' annual outreach program to K-12 classrooms.

Limson and Shain also presented a PhUn Week workshop that engaged teachers in hands-on activities developed from PhUn Week events, including a Dress-A-Scientist activity to address stereotypes and misconceptions of scientists and a group skit on the comic book *The Science of Life, Physiology Research in Action*. ❖

Science educator Margaret Shain asks the workshop audience to Dress-A-Scientist with their perceived notions of a scientist. The demonstration invariably includes a lab coat, goggles, pens, gray hair, a test tube rack, a lab animal, and a microscope. This exercise engages a discussion to debunk the stereotypical characteristics of a scientist.

Shain shares APS Education programs, resources, and the Frontiers in Physiology fellowship with life science teachers. Visitors to the APS exhibit booth appreciated the APS teacher-developed resources and give-aways, including PhUn Week backpacks, squeezy stars, the book *Women Life Scientists*, comic books, physiology timelines, career posters and brochures, and lesson plans.

Teacher participants enjoy acting out the text and drama found in the comic book, *The Science of Life, Physiology Research in Action*. The comic book explores the field of physiology, and introduces careers in physiology.

APS Receives Science Education Partnership Award

The APS Education Office received a Science Education Partnership Award (SEPA) from the National Center for Research Resources (NCRR) at the National Institutes of Health (NIH) in support for enhancing the APS' Frontiers in Physiology Professional Development Fellowship Program for precollege science teachers (http://www.frontiersinphys.org). The APS was one of 16 new awardees in 2008 through the NCRR SEPA program (http://www.nih.gov/news/health/oct2008/ncrr-30.htm).

Entitled "Six Star Science for Student-Centered Learning," the APS program provides middle and high school science teachers, their students, and the general public with tools to help them learn about the important contributions that both basic and clinical research make to public health. Through the research and professional development experiences of teachers in the program, they become knowledgeable advocates for the importance of both types of research to our understanding of the human body in both health and disease, and our development of both treatments and prevention of disease and injury. The products developed through the three-year project will be freely accessible online to teachers, students, and the general public in free, easy to access formats and will be promoted via the APS website and the National Science Digital Library.

The Frontiers fellowship program provides science teachers with a framework for creating effective student-centered learning environments within their state-mandated curricula. The project will develop and evaluate a new model summer research program for teachers that retains proven components from the established Frontiers program. The new SEPA program is built on Six Star Science, the APS framework for supporting excellence in science education for diverse students. The "Six Stars" are:

Instruction: Student-centered instruction is at the heart of exemplary science education.

Diversity: Valuing diversity among students is a defining characteristic of excellence in education.

Technology: Integrating technology to enhance learning is particularly important in science.

Authentic Assessment: To be authentic, assessment must focus on both content and process skills.

Current Content: Utilizing accurate and timely content information is central to scientific study.

Reflection: Reflecting on teaching and learning is essential to maintaining excellence in education.

The project has four major goals: develop, evaluate, refine, and disseminate a model and materials to help teachers create Six Star Science learning environments within the context of their state standards-based curricula; build ongoing working relationships between basic and clinical research scientists and science teachers through research, in-service experiences, classroom visits, and online communications; promote the effective implementation of state standards for K-12 content and pedagogy—especially inquiry-based teaching, diversity strategies, and technology use; and provide a model for biomedical research societies and organizations for promoting the public understanding of basic and clinical research and facilitating improvements in science education.

Major products from the project will include the following and will be freely available online: **Six Star Science Lab Activities** are "cookbook" lessons that are part of RTs' state-mandated curricula and have been enhanced to promote student-centered learning; **"Bench to Bedside" ("BTB") Primers** are four-page handouts that highlight the RT's summer research project, related clinical research, normal physiology, and health issues.; **"Bench to Bedside" ("BTB") Podcasts** are audio/video Podcasts of the BTB Primers; **"Bench to Bedside" ("BTB") online WISE Units for Teachers and Students** provide an interactive lesson on basic and clinical research, research ethics, and public health benefits.

If any APS member is interested in hosting and mentoring a teacher for a seven to eight 8 week research experience during the summer of 2009, email Mel Limson, APS K-12 Education Programs Coordinator, at: mlimson@the-aps.org. Program information and applications (jointly submitted with a teacher) are available at: http://www.frontiersinphys.org. Applications are due no later than January 8, 2009. ❖

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Starting a Lab: How to Develop a Budget and Buy Equipment

Kimberly A. Huey, PhD
University of Illinois

In the last Mentoring Forum, you were given important advice on choosing the techniques you plan to implement in your new laboratory, as well as the personnel to perform the experiments. While these choices provided you with many new challenges, you now face the challenge of developing a budget to fund your research dreams and aspirations. Fortunately, as a new faculty member, you will likely have received a start-up package that you negotiated to cover the majority of expenditures associated with the establishment of a successful laboratory. As the name implies, a start-up package should allow you to "hit the ground running" and begin collecting meaningful data to include in subsequent grant submissions. The information you used to negotiate your start-up package will provide the basics of your initial budget. There are three major components within a lab budget: *1*) personnel (salary, benefits, meeting travel/registration); *2*) major equipment, and *3*) supplies/consumables.

Kimberly A. Huey

Personnel Costs

Personnel can constitute a large majority of your budget once you have purchased the major and/or expensive equipment necessary to conduct your research. This is especially true as you move forward in your career and your lab continues to grow in size. However, as a new investigator, your hiring decisions will determine how much of your budget is allocated for personnel. As discussed in the last Mentoring Forum, a new investigator has the opportunity to make the critical hires to begin a successful career, and these hires will likely fall into one of three categories: *1*) full or part-time laboratory technicians; *2*) postdoctoral fellows; and *3*) graduate or undergraduate students. You also likely will have the opportunity to have undergraduates working in your laboratory, but in most cases they will work for the research experience or course credit. Some—but certainly not all—universities will include the salary for a technician in your start-up package. If this is the case, having a competent technician as you begin your research career can be very important in your future successes. First, a technician can work in the lab full time without the demands of teaching or service and may be able to provide technical expertise in an area that is new to you. In addition, a technician can help train graduate and undergraduate students. A good technician will also provide your lab with some continuity, as postdoctoral fellows and graduate students may be in your lab only for a few years. However, a full-time technician can consume a large portion of your initial budget, whereas postdoctoral fellows or graduate students can often be funded from outside sources. A good postdoc can greatly improve your research productivity, as they are usually well-trained and are motivated to be productive so they can be competitive for a faculty position in several years. Similar to a technician, a postdoc can also help you train graduate and undergraduate students. Ideally, you would be able to find a postdoc who has a fellowship from institutes such as NIH or American Heart Association. Depending on the source of the fellowship, it will often cover the salary, benefits, and travel for the postdoc. In a faculty position, you will also be expected to mentor graduate students, and they may comprise the largest portion of your personnel. There are numerous ways to fund graduate students, such as pre-doctoral grants, teaching assistantships, and/or research assistantships. Pre-doctoral grants and/or teaching assistantships would not contribute to your budgetary planning, whereas research assistantships are generally funded by your start-up and/or grants. Ideally, you would like to find postdocs or graduate students that have funding for at least one year, thereby giving you time to obtain grant funding to support them further in your laboratory.

Major Equipment

Before you begin purchasing the major equipment for your laboratory, compile a list of equipment and supplies and divide it into resources that are expensive and resources that are essential to successful research. This will enable you to categorize your budget and thus utilize your funds in the most effective manner. For example, required equipment and supplies could include large/heavy equipment (refrigerators, hoods, lab shakers, centrifuges), microscopy, cell/molecular biology equipment (PCR machines, plate readers), computing and printing, general lab equipment (pipettors, microfuges, vortex), chemicals and reagents, and reference books.

With respect to major equipment, your first step is to learn about core and/or shared facilities within your institution. Most major research universities have core facilities that often include expensive equipment that is generally not within the budget of an individual investigator. For example, some universities have institutes that maintain state-of-the-art imaging equipment, such as electron and atomic force microscopes and functional MRIs. Core or shared facilities would also include equipment that you would not use on a regular basis. Consequently, it is not in your best interest to budget a significant amount of money on such equipment.

After determining the equipment that you definitely need to purchase for your independent laboratory, the first step is to receive quotes from several companies, especially when you do not need to purchase a specific model or brand. Many of the major scientific supply companies offer specialized new lab start-up

programs that provide discounts on all types of equipment and lab consumables (e.g., such as Thermo Fisher and VWR; check your other university suppliers for other similar offers). It is also important to develop a good working relationship with the local sales representatives for the companies with which you will be conducting the majority of your business. Second, you should also ask colleagues if they have any spare equipment that they are no longer using and would be willing to donate to your laboratory. Oftentimes, well-funded, senior faculty will be happy to donate older equipment when they update to the newer models. In most cases this equipment works great and can save your budget thousands of dollars. It may also be helpful to develop relationships with investigators with similar research interests/techniques who have established laboratories. In these cases, you may be able to share certain equipment or reagents. Independent of budget issues, it is always important to begin developing collaborations within your department or university.

Another non-traditional source of major equipment is companies that specialize in used laboratory equipment (e.g., eBay). You can "Google" the equipment you are interested in purchasing and often end up with an array of choices. Local appliance or big box stores are excellent sources for purchasing basic appliances, lab furniture, tools, cleaning supplies, carts, etc. While these items can be purchased from lab supply companies, the prices are significantly higher for the same item. Many universities also have arrangements with local appliance dealers to supply basic refrigerators, freezers, and microwaves.

An additional consideration if you purchase new equipment is whether to buy a service contract. A service contract can include many services beyond a general warranty, such as software updates, calibration, certification, preventative maintenance, priority service, and/or additional discounts on upgrades. Service contracts can be costly, and you can either discuss options with colleagues or make your own informed decision. Several reasons why you may chose to purchase a service contract could include reduced hassles if your equipment breaks, faster/priority repairs and a predictable expense in your budget. If a piece of equipment is critical to your work, you use it frequently, and major repairs are very expensive, a service contract may be worthwhile. In terms of budget, you will know exactly what you are going to pay in advance and will not be blindsided with a major "surprise" expense. On the other hand, you may end up paying for services that you never use and therefore paid for "peace of mind," which would extend beyond the typical one year warranty.

Supplies/Consumables

Once you have outfitted your new lab with all the appropriate major equipment, the majority of your budget will likely be spend on personnel costs. However, the daily costs of running the lab must also be considered in your laboratory budget. While the daily costs will vary depending on the number of people in your lab, the types of assays you perform, etc., a general rule is that you can plan on spending ~$1,000/month on pipette tips, tubes, glassware, cell culture supplies, gloves, etc. Additional consumable supplies, such as antibodies, enzymes, Elisa kits, and PCR kits, will add to these costs; however, items like antibodies or enzymes—if correctly stored and handled—can last for months to years. After tracking your spending over a representative period of time, you will be able to get a good estimate of how much to budget for supplies and consumables over months or years.

Staying within Budget/Tracking Spending

Following the development of an initial budget to run your laboratory, it is important to track your spending to assure that you are working within the parameters of your budget. This can be accomplished utilizing spreadsheet or database programs, such as Microsoft Excel or Access. A database program, such as Access, can be particularly helpful as you can establish a database of your money sources (start-up, grants, etc), suppliers, and a record of all your purchase orders. This can also save time with regard to purchasing supplies that you buy on a regular basis. For example, you can have a standing purchase order for pipette tips and microfuge tubes that you would just print out and give to the person in charge of ordering when you needed additional supplies. In addition, you could also modify your budget to keep it current as well as track expenditures with programs such as Quicken or Quickbooks.

Conclusions

While developing and implementing a budget for your new laboratory may be as fun as balancing your checkbook, it is indispensable to initiating a successful career. Making the most of your start-up budget, in part, can be instrumental in obtaining future grant support. Specifically, budgeting for enough personnel and the necessary equipment is the only way you will be able to generate preliminary data for your subsequent grant applications. Unfortunately, budgeting and accounting strategies are generally not part of your training as a graduate student or postdoc, and thus you must take the initiative to learn from mentors and/or colleagues the best budgeting strategies. Also remember that successful budgeting continues throughout your career, as all granting agencies expect you to present an accurate and well-documented budget for spending the money you obtain from your successful grant applications.

To comment on this article, go to http://www.the-aps.org/careers/careers1/mentor/labbudget.htm. ❖

Kimberly A. Huey, PhD, is an Assistant Professor in the Department of Kinesiology and Community Health at the University of Illinois in Champaign-Urbana, IL. She received her BS and MS in Exercise Physiology from Seattle Pacific University and the University of Arizona, respectively, and her PhD in Biomedical Sciences from the University of California, San Diego in 1999. She completed her postdoctoral fellowship in the laboratory of Dr. Kenneth Baldwin at the University of California, Irvine and in 2003 she joined the faculty at the University of Illinois as an Assistant Professor.

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Congress Revisits NIH Public Access Policy

At a hearing on September 11, 2008, the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property reviewed NIH's Public Access Policy. APS Executive Director Martin Frank testified at the hearing representing the non-profit publishing community.

The NIH instituted a voluntary Public Access Policy in early 2005, requesting that all NIH-funded researchers submit their final, peer-reviewed manuscripts to PubMed Central (PMC) no more than 12 months after publication in a journal. After two years of low submissions, Congressional appropriators included language in the FY 2008 Consolidated Appropriations Act making submission mandatory. This policy went into effect in April 2008.

The Courts, Internet, and Intellectual Property Subcommittee convened the September 11 hearing because a mandatory policy has implications for copyright law. Testifying at the hearing were Elias Zerhouni, Director, National Institutes of Health;

Ralph Oman, Pavel Professorial Lecturer in Intellectual Property Law at The George Washington University Law School and Former Register of Copyrights of the United States; Heather Dalterio Joseph, Executive Director of the Scholarly Publishing and Academic Resources Coalition (SPARC); and Martin Frank, Executive Director of the American Physiological Society.

In his opening statement, Zerhouni focused on the rapidly increasing amounts of scientific information that need to be organized and integrated functionally. He argued that a central repository will enable NIH to leverage more efficiently the recent explosion in biomedical research data. Zerhouni also said there was no evidence supporting the assertion that NIH's Policy will harm journal publishers. Joseph emphasized that the tax-paying public should be entitled to have free access to publications that result from government funded research. She also stated that libraries would be unlikely to cancel subscriptions to journals because they need to provide access to the most scientific recent literature.

Frank said that the PMC draws traffic from journal websites, which might well lead to subscription cancellations. He also highlighted the efforts of APS and other not-for-profit publishers to provide free access to journal content and the important role journals play in facilitating the peer review process. He pointed out that publishers invest heavily in the creation of articles and said that NIH's Public Access Policy diminishes copyright by limiting the publishers' ability to control distribution of the product. Oman outlined his concern that the NIH Policy dilutes the rights of copyright holders and expressed concern about the continued viability of the commercial market for scientific, technical and medical journals.

APS Executive Director Martin Frank speaks with Subcommittee Chairman Howard Berman and NIH Director Elias Zerhouni.

Martin Frank delivers opening remarks.

Questions from the committee focused on:

Is open access is a viable economic model for journals?

Who really bears the cost of peer review and publication costs?

Is this an activity best left to the private sector or should it be the responsibility of the federal government?

Would alternative models of providing access to research publications be able to achieve the goals of the NIH without compromising copyright?

House Judiciary Committee Chair John Conyers (D-MI), introduced H.R. 6845, the Fair Copyright in Research Works Act prior to the hearing. According to Subcommittee Chair Howard Berman (D-CA), H.R. 6845 would "turn back the clock to the policy framework in effect prior to the 2008 Consolidated Appropriations Act." Berman acknowledged that with the end of the 110th Congress fast approaching, there was little likelihood of action this year on the Fair Copyright in Research Works Act. However, the demonstrated interest of the committee suggests that it may be considered in the next legislative session.

To view the webcast of the hearing and read the witness statements, go to: http://judiciary.house.gov/hearings/hear_090911_1.html. ❖

APS Members Visit Capitol Hill

At the conclusion of the September meeting of the Public Affairs Committee, APS members visited several Congressional offices to highlight the importance of federal funding for biomedical research.

Committee members met with staff to Senators Sherrod Brown (D-OH), Carl Levin (D-MI), Herb Kohl (D-WI), James Inhofe (R-OK), and Patty Murray (D-WA). In the House of Representatives, meetings were with staff for Representatives Steve Chabot (R-OH), Paul Broun (R-GA), James Sensenbrenner (R-WI), Mary Fallin (R-OK), Michael Rogers (R-MI), Danny Davis (D-IL), and David Price (D-NC). In addition to those staff meetings, committee members from Georgia and North Carolina were privileged to meet personally with Representatives Broun and Price.

The meetings occurred at a critical time as Congress worked toward completion of legislation to fund government programs in the new fiscal year (FY 2009). Because funding at the NIH and NSF has failed to keep pace with inflation in recent years, APS members asked Members of Congress to consider adding funds over and above FY 2008 levels for those agencies to prevent further erosion of research capabilities and purchasing power.

The messages that committee members heard from the different offices were generally supportive of biomedical research funding, and APS members were able to make critical connections with Congressional staff that may be helpful in the future as issues related to funding and science policy arise.

Congress Extends Current Levels of Research Funding into 2009

On the last day of the 2008 fiscal year (FY), President Bush signed into law a package of legislation that extends funding for government programs at current levels until March 6, 2009.

H.R. 2638, the Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, combines five separate spending bills. Three bills are regular FY 2009 appropriations measures to fund the Department of Defense, Department of Homeland Security, and programs in Military Construction and Veterans Affairs (Mil-Con-VA). Medical and prosthetic research at the VA, which is contained in the Mil-Con-VA appropriations bill, will receive $512 million in FY 2009. This represents a $32 million increase over last year.

The package also includes relief for recent natural disasters in the Gulf Coast and Midwest, and a Continuing Resolution (CR) that extends funding for most of the remaining government agencies at FY 2008 levels, including the National Institutes of Health, the National Science Foundation and NASA.

A continuing resolution was necessary because most of the individual appropriations bills remained unfinished at the close of the fiscal year (September 30). The breakdown in the normal process was a result of partisan battles and a threat by President Bush to veto any bills that exceeded his spending goals. Rather than send the bills to the White House for a veto, Congressional appropriators chose to combine the spending measures in one bill to continue funding at current levels, with the hope that a new Congress and Administration will be able to resolve these issues next spring.

Because the NIH, NSF and NASA all received extra funds in 2008 as part of a supplemental spending measure, extension of original FY 2008 levels represents a cut for those agencies. In response, NIH issued a notice (NOT-OD-09-002) explaining that non-competing research grant awards will be funded at a rate of up to 90% of the previously committed level.

Peer Review at NIH

NIH continues to implement many of the recommendations made by the Advisory Committee to the Director, including shortening the length of grant applications, eliminating A2 applications, and creating a special designation for Early Stage Investigators (ESI). For the latest information, visit: http://enhancing-peer-review.nih.gov.

California Enacts Research Protections

On September 28 California Governor Arnold Schwarzenegger signed into law the Researcher Protection Act of 2008. The act provides added protection for California academic researchers, who over the last few years have suffered an escalation of violence and threats from animal rights extremists. The bill had been passed unanimously by both houses of the California legislature in August. Because it was approved as an "urgency statute," it became law immediately upon being signed.

Section two of the Researcher Protection Act declares that "while individuals are entitled to express their views on animal use in research and to mount protests that are protected under the First Amendment[,]… [u]nlawful acts that threaten and intimidate researchers or their families at their personal residences are not protected by the First Amendment to the United States Constitution, and are a direct threat to the academic researcher's constitutional right to academic freedom."

The law makes it a misdemeanor for someone to publish information about a researcher or his or her immediate family with the intention that the information be used "to commit a crime involving violence or a threat of violence against an academic researcher or his or her immediate family." It also permits researchers to obtain preliminary injunctions against such publication.

The legislation defines "academic research" as "any person lawfully engaged in academic research who is a student, trainee, employee, or affiliated physician of an accredited California community college, a campus of the California State University or the University of California, or a Western Association of Schools and Colleges accredited, degree granting, nonprofit institution."

Introduced in February, the bill rapidly gained support following the two August fire bombings at University of California Santa Cruz. In those incidents one researcher's car was destroyed and another researcher and his family were forced to flee their home from a second story window. Prior incidents involved broken windows, graffiti, mail containing razor blades, the flooding of a home, and a burning effigy left on a researcher's doorstep, according to a partial list provided by the University of California.

University of California President Mark G. Yudof praised the passage of the bill saying: "This law will provide law enforcement with some of the tools necessary to help protect academic

researchers so they can continue to perform ground-breaking research without the threat of violence." Yudof also thanked Assembly Member Gene Mullin (D-South San Francisco), who authored and championed the bill.

"Increasingly, the potential for innovative thought and new medical therapies is jeopardized by threats aimed at researchers and their families," Mullin said in a University of California press release. "The signing of AB 2296 sends a message that California recognizes its researchers and their families need to be protected from threats of violence." ❖

Communications

Communications Update

The Communications department successfully completed the first year of the podcast initiative and produced two new videos for our web site.

APS Posts First YouTube Video

APS posted its first YouTube video on September 8, an interview with the new *Journal of Neurophysiology,* Editor-in-Chief David Linden, professor of neuroscience at the Johns Hopkins University School of Medicine in Baltimore. You can watch the video at http://www.youtube.com/watch?v=Kqx4Bm6OAwI.

Linden's discussion about his plans for the new direction of the journal are also posted on the APS homepage. Log on to either http://www.the-aps.org/publications/jn/index.htm or http://www.the-aps.org/publications/jn/editors_message.htm to see it.

Media Coverage from the Integrative Biology of Exercise Meeting

The department produced eight releases for "The Integrative Biology of Exercise–V," which took place in September. Top-tier outlets that picked up the results included *Scientific American, Popular Science*, *Science,* Los Angles *Times, US News & World Report,* Reuters, and the Discovery Channel. The press releases are listed below, and can read in full by going to http://www.the-aps.org/press.

For Overweight Patients With Insulin Sensitivity, Even One Session Of Exercise Can Improve Metabolic Health;

Researchers Discover That Growing Up Too Fast May Mean Dying Young In Honey Bees;

Lessons From The Iditarod;

Women Do Not Recover Their Muscle Strength As Fast As Men After Wearing A Cast;

Anabolic Steroids Still Provide A Competitive Edge In Power Lifting Even Years After Doping Has Ended;

Cholesterol-Lowering Drugs and The Effect On Muscle Repair And Regeneration;

Galloping and Breathing At High Speed

New Study Links Inactivity to an Increase in Desire for More Food.

Four of the presenters discussing their work and its benefits dOnce the editing on these sessions is complete, they will be uploaded to YouTube and the APS site.

Journal Press Release Program

Four press releases based on studies from the APS journals have been distributed as follows:

Fructose sets table for weight gain without warning;

Resveratrol Prevents Fat Accumulation In Livers of 'Alcoholic' Mice;

Older People Who Diet Without Exercising Lose Valuable Muscle Mass

Substance Found In Fruits And Vegetables Reduces Likelihood Of The Flu

These also can be found on the press page, at http://www.the-aps.org/press.

Finally, the following press releases related to Society news were issued:

APS Sets Aside $50,000 to Help in Wake of Hurricane Ike;

Frank testifies in support of copyright protection for scientific publishers

Two New Episodes of the APS Podcast Series, Life Lines

Two new episodes of the APS podcast series Life Lines (13 and 14) are now available. Each episode begins with a short segment which takes a look at studies from the APS journals that have recently been in the news. Some studies have been promoted through APS press releases, while others have been promoted by the authors' institutions.

The podcast also includes a feature section and ends with a study from one of our journals. Please visit http://www.lifelines.tv to see the latest episodes. And don't forget to listen, subscribe and tell all your family, friends and students to do the same. ❖

Experimental Biology 2009

Today's Research:
Tomorrow's Health
April 18–22

CALL FOR LATE-BREAKING ABSTRACTS

Deadline for Submission: Wednesday, February 25, 2009

www.eb2009.org

Sponsors:

AAA
American Association of Anatomists

APS
The American Physiological Society

ASBMB
American Society for Biochemistry and Molecular Biology

ASIP
American Society for Investigative Pathology

ASN
American Society for Nutrition

ASPET
American Society for Pharmacology and Experimental Therapeutics

Late-breaking abstracts will be accepted beginning the week of December 7, 2008. The abstracts are for poster presentations only and will be scheduled on Wednesday, April 22, 2009.

Late-breaking abstracts must be submitted online at www.eb2009.org with the $90 abstract fee by Wednesday, February 25, 2009.

Late-breaking abstracts will be published online.

Please visit www.eb2009.org for information about the meeting, including late-breaking abstract topic categories, the preliminary program, registration and hotel information. Please contact eb@faseb.org for more information.

Register online by February 9, 2009 for the lowest registration rates. Complete hotel reservations by March 10, 2009.

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

Francois M. Abboud
Univ. of Iowa

"In Search of Autonomic Balance: The Good, the Bad and the Ugly"

SATURDAY, APRIL 18, 5:45 PM

HENRY PICKERING BOWDITCH AWARD LECTURE

Ann M. Schreihofer
Medical College of Georgia

"Cardiovascular Regulation by the Caudal Ventrolateral Medulla: The Little Nucleus that Could"

SUNDAY, APRIL 19, 5:45 PM

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

Bente Karlund Pedersen
Rigshospitalet Univ., Copenhagen

"Muscle as an Endocrine Organ: IL-6 and Other Myokines"

SUNDAY, APRIL 19, 10:30 AM

CLAUDE BERNARD DISTINGUISHED LECTURESHIP OF THE TEACHING OF PHYSIOLOGY SECTION

Stephen DiCarlo
Wayne State Univ.

"Too Much Content not Enough Thinking and too Little Fun!!"

SUNDAY, APRIL 19, 2:00 PM

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

Alicia McDonough
Univ. of Southern CA

"Life in the Fast Lane - Rapid Traffic of Sodium Transporters Maintains Volume and Blood Pressure Homeostasis

SUNDAY, APRIL 19, 3:15 PM

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

Murray Esler
Baker Heart Research Inst.

"Autonomic Dysregulation of Blood Pressure: High and Low

MONDAY, APRIL 20, 8:00 AM

ROBERT M. BERNE DISTINGUISHED LECTURESHIP OF THE CARDIOVASCULAR SECTION

D. Neil Granger
Louisiana State Univ.

"Mechanisms and Consequences of Inflammatory Cell Interactions with the Microvasculature"

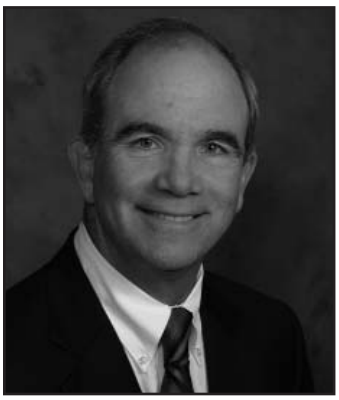
MONDAY, APRIL 20, 10:30 AM

JOSEPH ERLANGER DISTINGUISHED LECTURESHIP OF THE CENTRAL NERVOUS SYSTEM SECTION

Jeffrey Friedman
Rockefeller Univ.

"Leptin and the Homeostatic Control of Energy Balance"

MONDAY, APRIL 20, 2:00 PM

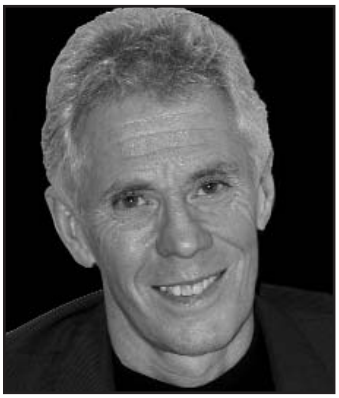


Julius H. Comroe, Jr. Distinguished Lectureship of the Respiration Section

Michael Matthay
Univ. of California, San Francisco

"The Alveolar Epithelium Under Normal and Pathological Conditions"

Monday, April 20, 2:00 pm



August Krogh Distinguished Lectureship of the Comparative & Evolutionary Physiology Section

William Milsom
Univ. of British Columbia

"Adaptive Trends in Respiratory Control: A Comparative Perspective"

Tuesday, April 21, 8:00 am

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

Susanne Henning
Univ. North Carolina, Chapel Hill

"Postnatal GI Development: the Journey from Steroids to Stem Cells"

Tuesday, April 21, 2:00 pm

Walter C. Randall Lecturer in Biomedical Ethics

Peter H. Schwartz
Indiana Univ. Center for Bioethics

"Consent and Conversation in Population-Based Genetic Research"

Tuesday, April 21, 2:00 pm

Hugh Davson Distinguished Lectureship of the Cell and Molecular Physiology Section

Jennifer L. Stow
Univ.. of Queensland

"Control Central—At the Intersection of Exocytic and Endocytic Pathways"

Monday, April 20, 3:15 pm

Carl W. Gottschalk Distinguished Lectureship of the Renal Section

Rene Bindels
Radboud Univ., Nijmegen

"A TR(i)P Through the World of Renal Calcium and Magnesium Channels"

Tuesday, April 21, 10:30 am

Solomon A. Berson Distinguished Lectureship of the Endocrinology and Metabolism Section

Paul Davis
Ordway Research Institute

"A Thyroid Hormone Receptor on Integrin αvβ3 Nongenomically Mediates Actions of the Hormone on Tumor Cell Proliferation and Angiogenesis"

Tuesday, April 21, 3:15 pm

Saturday, April 18, 2009 8:00 AM-12:00 PM

Refresher Course
Refresher Course in Renal Physiology
Education Track
Robert W. Brock and Robert L. Hester

Saturday, April 18, 2009 9:00-11:30 AM

Symposium
Microcirculatory Society President's Symposium: Live Cell Imaging of the Microcirculation: New Frontiers for Intravital Microscopy
Steve Segal

Saturday, April 18, 2009 1:00-3:00 PM

Workshop
Chronic Instrumentation in Conscious Small Animals
Education Track
J.R. Haywood and Susan Mulroney

Symposium
Communications Symposium: The Wiki Wiki Workshop: Your Fast Track to the New APS Web Site
Francis Belloni

Saturday, April 18, 2009 2:00-4:30 PM

Microcirculatory Society Workshop
Live Cell Imaging of Microcirculation: Experimental Approaches
Steve Segal

Saturday, April 18, 2009 3:15-5:15 PM

Workshop
Multi-Photon Imaging of Renal Regulatory Mechanisms in vivo
Education Track
Molecular and in vivo Imaging Track
Janos Peti-Peterdi

Symposium
Scientists and Regulatory Burden: Navigating the Rugged Landscape
Public Policy Track
J.R. Haywood and Michael Portman

Saturday, April 18, 2009 4:15-5:15 PM

Award Session
APS Water and Electrolyte Homeostasis Section Trainee Finalist Awards Symposium

Saturday, April 18, 2009 5:45-6:45 PM

Lecture
Physiology in Perspective — The Walter B. Cannon Memorial Award
Frank Abboud

Sunday, April 19, 2009 8:00-10:00 AM

Symposium
Direct Assessment of Organ Specific Sympathetic Nervous System Activity in Normal and Cardiovasuclar Disease States
Synaptic Physiology and Plasticity Track
Mark M. Knuepfer and John W. Osborn, Jr.

Symposium
Lung Injury and Treatment with Stem Cells
Stem Cells Track
Asrar B. Malik and Kishore K. Wary

Symposium
Microelectromechanical Systems in Cell Biology

Symposium
Pathogens Hijacking the Host
Immunology Track
Bruce A. Stanton and George O'Toole

Symposium
Ventilatory Control Disorders
Synaptic Physiology and Plasticity Track
Gordon S. Mitchell and Tracy L. Baker-Herman

Featured Topic
Cellular Mechanisms that Initiate and Coordinate Changes in Vascular Tone
Ion Channels and Transporters Track
Andrew P. Braun and Michael J. Davis

Featured Topic
Hypertension
Jane F. Reckelhoff and Christine Maric

Featured Topic
Ion Channels in Vascular Control: Health and Disease
Ion Channels and Transporters Track
Gregory M. Dick

Featured Topic
Muscle Fatigue
Jean-Marc Renaud

Featured Topic
Pre-conditioning and Acquired Tolerance for Protection From Exertional, Environmental, and Traumatic Injury
Thermal and Environmental Stress Track
Lisa Leon

Sunday, April 19, 2009 10:30-11:30 AM

Distinguished Lecture
Edward F. Adolph Distinguished Lectureship of the APS Environmental & Exercise Physiology Section
Metabolic Diseases Track
Bente Karlund Pedersen

Sunday, April 19, 2009 10:30 AM-12:30 PM

Tutorial
Publishing 101: Dos and Don'ts of Publishing in APS Journals
Career Development Track
Kim E. Barrett

Symposium
Approaches to Bridge the Gap between -Omics and Physiology Education
Systems Biology (-omics) Track
Albert A. de Graaf and Neema Jamshidi

Symposium
Breaking the Diffraction Barrier in Imaging of Molecules in Living Cells
Molecular and in vivo Imaging Track
Moshe Levi

Symposium
Erythrocytes and Endocrine Signaling in the Microcirculation
Metabolic Diseases Track
Randy Sprague and Mary Ellsworth

Symposium
Insights into Oxygen Signaling from Non-mammalian Animals
Hypoxia and Oxidative Stress Track
Bernard B. Rees and Nora Terwilliger

Symposium
New Functions of the Dorsomedial Hypothalamus: Thermoregulation and Beyond
Thermal and Environmental Stress Track
Andrej A. Romanovsky and Shaun F. Morrison

Symposium
Obesity, Diabetes and Cardiovascular Disease
Metabolic Diseases Track
Roger H. Unger and John W. Calvert

Featured Topic
Emerging Signaling Mechanisms in CNS Transmission and Plasticity
Synaptic Physiology and Plasticity Track
Javier E. Stern

Featured Topic
Renal Section Abstract-driven Featured Topic
TBA

Sunday, April 19, 2009 2:00-3:00 PM

Distinguished Lecture
Claude Bernard Distinguished Lectureship of the APS Teaching of Physiology Section
Education Track
Stephen DiCarlo

Sunday, April 19, 2009 3:15-4:15 PM

Distinguished Lecture
Ernest H. Starling Distinguished Lectureship of the APS Water & Electrolyte Homeostasis Section
Alicia McDonough

Sunday, April 19, 2009 3:15-5:15 PM

Physiology InFocus: Integrative and Systems Physiology: An Approach to Understanding Organ System and Disease
A Systems Approach to Disease Mechanisms
Irving H. Zucker

Lecture
Microcirculatory Society Landis Award Lecture
Aleksander S. Popel

Symposium
The Co-morbidity of Stress and Disease: Effects of Chronic Stress on Metabolism, Cardiovascular Disease and Behavior
Metabolic Diseases Track
Susan E. Mulroney and Yvette Tache

Featured Topic
The Ganglionic Synapse: Passive Relay or Locus of Autonomic Control?
Synaptic Physiology and Plasticity Track
Robin McAllen

Featured Topic
Human Thermoregulation
Thermal and Environmental Stress Track
Kathy Ryan

Featured Topic
Lipid Phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) Signaling in Nerve and Muscle
Thomas Nosek

Featured Topic
Mesenchymal Stem Cells for Injury and Repair in the Lung
Stem Cells Track
Michael A. Matthay

Featured Topic
Molecular Mechanisms and Genetics of Hypertension
Systems Biology (-omics) Track
Rhian Touyz and Mingyu Liang

Featured Topic
Teaching with Technology
Education Track
Dee U. Silverthorn

Sunday, April 19, 2009 4:15-5:15 PM

Lecture
WEH Young Investigator Award Lecture
TBA

Sunday, April 19, 2009 5:45-6:45 PM

Lecture
Henry Pickering Bowditch Award
Ann Schreihofer

Monday, April 20, 2009 8:00-9:00 AM

Distinguished Lecture
Carl Ludwig Distinguished Lectureship of the APS Neural Control & Autonomic Regulation Section
Murray Esler

Monday, April 20, 2009 8:00-10:00 AM

Symposium
Angiotensin II Type 2 Receptor: Role in Renal/Cardiovascular Function and Blood Pressure
Tahir Hussain and Helmy Siragy

Symposium
Assessment of Dynamic Renal Autoregulation: Principles and Applications
Michael J. Ryan and Branko Braam

Symposium
A. Clifford Barger Memorial Symposium: Mentoring Strategies: Beyond the Bench
Career Development Track
Karen Sweazea and My Helms

Symposium
Microcirculatory Society Young Investigator's Symposium
TBA

Symposium
Rapid Effect of Steroid Hormones
Stafford Lightman and Gordon Hager

Symposium
Writing the Test Question Isn't Enough!
Education Track
Vikki McCleary and Katherine Sukalski

Featured Topic
Lymphatic Endothelial Cells: Passive or Active Participants in Lymphatic Function?
Immunology Track
Jerome W. Breslinn and Walter L. Murfee

Featured Topic
Oxygen Signaling during Development
Hypoxia and Oxidative Stress Track
Bernd Pelster

Featured Topic
Translational Research: Innovative Approaches to Physiological Investigations
Loren E. Wold

Monday, April 20, 2009 10:30-11:30 AM

Distinguished Lecture
Robert M. Berne Distinguished Lectureship of the APS Cardiovascular Section
D. Neil Granger

Monday, April 20, 2009 10:30 AM-12:30 PM

Symposium
Fibrosis: Signaling, Physiology, and Therapies
Systems Biology (-omics) Track
Kelly R. Pitts and Craig Plato

Symposium
Leptin: From Bench to Clinical Applications
Metabolic Diseases Track
Christos Mantzoros

Featured Topic
Control of Breathing in Chronic Diseases
Synaptic Physiology and Plasticity Track
Lara Roberts DeRuisseau and Francis J. Golder

Featured Topic
Genetics of the Adaptation to Exercise
Metabolic Diseases Track
Claude Bouchard and Mark Olfert

Featured Topic
Novel Mechanisms in Alcoholic and Nonalcoholic Fatty Liver Diseases
Metabolic Diseases Track
Laura W. Schrum and Ian H. McKillop

Featured Topic
Renal Section Young Investigator Featured Topic: Novel Mechanisms of Vasopressin Regulation of Renal Function
Systems Biologhy (-omics) Track
Heddwen Brooks

Featured Topic
Regulation of Epithelial Transporters and Signaling
Ion Channels and Transporters Track
TBA

Featured Topic
Role of Sex Steroids in Cardiovascular Physiology and Pathophysiology
Michael Ryan

Featured Topic
Structure/Function of SLC4A Bicarbonate Transporters
Ion Channels and Transporters Track
Inyeong Choi and Joseph R. Casey

Featured Topic
Thermoregulation in Extreme Environments
Thermal and Environmental Stress Track
Shawn R. Noren

Monday, April 20, 2009 2:00-3:00 PM

Distinguished Lecture
Joseph Erlanger Distinguished Lectureship of the APS Central Nervous System Section
Metabolic Diseases Track
Jeffrey Friedman

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

Monday, April 20, 2009 3:15-5:15 PM

Physiology InFocus: Integrative and Systems Physiology: An Approach to Understanding Organ System and Disease
Cardiac Ion Transport and Arrhythmias
Jose Jalife

Distinguished Lecture
Hugh Davson Distinguished Lectureship of the APS Cell & Molecular Physiology Section
Jennifer Stowe

Symposium
Cardiorespiratory Afferent Processing in the Nucleus of the Solitary Tract: Not Just a Relay
Synaptic Physiology and Plasticity Track
Donald R. McCrimmon and Judith A. Neubauer

Symposium
Engineering Functional Vasculature
Song Li

Symposium
Fragile X-Associated Tremor/Ataxia Syndrome: Genotype, Animal Models, Phenotype and Intervention
Paul Hagerman

Symposium
Modulation of Endothelial Function by NADPH Oxidase
Hypoxia and Oxidative Stress Track
Masuko Ushio-Fukai and Randall S. Frey

Symposium
Novel Approaches to Elucidate Claudin Function and Paracellular Permeability
Ion Channels and Transporters Track
Alan S.L. Yu and Tong Wang

Symposium
The World Within—Impact of the Intestinal Microbiota on Whole Body Physiology and Pathophysiology
Immunology Track
Kim E. Barrett

Featured Topic
Metabolic Signaling
Metabolic Diseases Track
TBA

Featured Topic
Novel cAMP Signaling: Role of Epac
Ion Channels and Transporters Track
Fiona Murray

Monday, April 20, 2009 5:00-6:30 PM

Symposium
The Evolution of Creationism
Greg Petsko

Monday, April 20, 2009 5:45-7:15 PM

Symposium
Improving NIH peer review. Maintaining the national strategic value of peer review
Antonio Scarpa

Monday, April 19, 2009 5:45-7:45 PM

Symposium
Rising and Surviving: Elucidating Tenure and Promotion in Multiple Career Paths
Career Development Track
Caroline R. Sussman and Kamal Rahmouni

Poster Discussion
Trainee Highlights in Respiration Physiology

Tuesday, April 21, 2009 8:00-9:00 AM

Distinguished Lecture
August Krogh Distinguished Lectureship of the APS Comparative & Evolutionary Physiology Section Sponsored by Novo Nordisk Foundation
Hypoxia and Oxidative Stress Track
William Milsom

Tuesday, April 21, 2009 8:00-10:00 AM

Symposium
The Contributions of ROMK and BK Channels to Renal K Secretion
Ion Channels and Transporters Track
Jennifer L. Pluznick and Paul Welling

Symposium
Hypoxia and Stem Cells
Stem Cells Track
Hypoxia and Oxidative Stress Track
Navdeep S. Chandel and M. Celeste Simon

Symposium
Pathways to Leadership: Developing Critical Skills
Career Development Track
Holly Brevig, Andrea del Tredici and Barbara Alexander

Featured Topic
Aging, Reactive Oxygen Species, and Regulation of Arteriogenesis
Hypoxia and Oxidative Stress Track
Steven J. Miller

Featured Topic
Imaging in Renal Physiology and Pathophysiology
Molecular and in vivo Imaging Track
Alejandro R. Chade and Radu Iliescu

Featured Topic
Insulin from Regulated Expression to Regulated Secretion
Metabolic Diseases Track
John Corbett

Featured Topic
Intestinal Lumenal Antigens and Mucosal Defense Mechanisms
Immunology Track
Declan F. McCole and M. Cecilia Berin

Featured Topic
Organization, Current Progress, and Challenges in Inernational Physiome Projects
Education Track
Systems Biology Track
Daniel A. Beard

Featured Topic
Pulmonary Ion Channels
Ion Channels and Transporters Track
Michael Koval and Wolfgang Kuebler

Tuesday, April 21, 2009 10:30-11:30 AM

Distinguished Lecture
Carl W. Gottschalk Distinguished Lectureship of the APS Renal Section
Rene Bindels

Tuesday, April 21, 2009 10:30 AM -12:30 PM

Symposium
Cytoprotective Mechanisms and the Regulation of Mitochondrial Permeability Transition
Hypoxia and Oxidative Stress Track
Patrick R. Cammarata and Christopher Baines

Symposium
ENaC/ASIC Proteins as Cardiovascular Sensors
Ion Channels and Transporters Track
Heather A. Drummond

Symposium
High Throughput Discovery of Novel Ion Channel Probes: Small Molecules, Big Impact
Systems Biology (-omics) Track; Immunology Track; Ion Channels and Transporters Track
Jerod Denton and Christine Colvis

Symposium
Exercise-Induced Signaling to Phenotypic Adaptations in Skeletal Muscle
Scott Gordon

Symposium
Cardiovascular and Metabolic Actions of Leptin: Consequences in Obesity
Metabolic Diseases Track
Kamal Rahmouni and Lisa A. Cassis

Symposium
Molecular Imaging of Physiological Processes in Drug Discovery
Systems Biology; Track; Molecular and in vivo Imaging Track
Craig Plato and Michael F.A. Finley

Featured Topic
Donald Reis Memorial Symposium: Metabolic Defects in Diabetes, Obesity and Heart Failure
Metabolic Diseases Track
Steven P. Jones

Featured Topic
Breach of Epithelial Homeostasis in Gastrointestinal Cancer and Metastasis
Immunology Track
R.K. Rao

Featured Topic
ATP, Astrocytes and Central Respiratory Control
Gregory D. Funk

Symposium
Life Science Educdation in the 21st Century: Making the Science We Teach Reflect the Science We Practice
Education Track
Dee U. Silverthorn

Tuesday, April 21, 2009 2:0-300 PM

Lecture
Walter C. Randall Lecture on Biomedical Ethics
Public Policy Track
Peter H. Schwartz

Distinguished Lecture
Horace W. Davenport Distinguished Lectureship of the APS Gastrointestinal & Liver Physiology Section
Susan Henning

Tuesday, April 21, 2009 3:15-4:15 PM

Distinguished Lecture
Solomon A. Berson Distinguished Lectureship of the APS Endocrinology & Metabolism Section
Metabolic Diseases Track
Paul Davis

Tuesday, April 21, 2009 3:15-5:15 PM

Physiology InFocus: Integrative and Systems Physiology: An Approach to Understanding Organ System and Disease
An Integrative and Systems Analysis of Membrane Transport
Eric Jakobsson

Symposium
Adrenal Corticosteroid Effects in the Central Nervous System on the Long-Term Control of Blood Pressure
Synaptic Physiology and Plasticity Track
Debbie Scheuer

Symposium
Ca^{2+}-Independent Reguation of Smooth Muscle Contractility
Richard J. Paul

Symposium
Cellular Recruitment in Lung Vascular Remodeling and Pulmonary Hypertension
Stem Cells Track
Wolfgang M. Kuebler and Kurt Stenmark

Symposium
Environmental Factors in Heart Disease
Thermal and Environmental Stress Track
Aruni Bhatnagar and Robert Brook

Symposium
Genome to Epigenome: Implications of the Epigenomic Mechanisms to Physiology and Disease
Systems Biology (-omics) Track
Michael Michalkiewicz and Karen A. Lillycrop

Featured Topic
Renal Section Abstract-driven Featured Topic
TBA

Featured Topic
Wiggers Award Featured Topic
Daivd Harder

Tuesday, April 21, 2009 3:15-6:00 PM

Workshop
"Translating Your Ideas: Drug Development, Intellectual Property and the State of Academic-University Relations"
Career Development Track
Systems Biology (-omics) Track
Deborah Zucker

Tuesday, April 21, 2009 5:45-7:45 PM

APS Business Meeting

Wednesday, April 22, 2009 8:00-10:00 AM

Symposium
Adhesion Complex Related to Proteins in Myocardial Rhythm and Function
Robert S. Ross

Symposium
Development of AMPA Receptor-Containing Synapses in the CNS
Synaptic Physiology and Plasticity Track
Declan Ali and Lu-Yang Wang

Symposium
Shear Stress, Mechanosignal Transduction and Vascular Inflammatory Responses
Scott I. Simon and Anthony G. Passerini

Symposium
Proteomics Techniques in Physiology and Cell Biology
Systems Biology (-omics) Track
Moshe Levi and Mark Knepper

Symposium
Understand the Cross-Talk Between Skeletal Muscle and Adipocyte In Obesity: From In Vitro to In Vivo Analysis
Stefan Keslacy and Thomas Nosek

Featured Topic
Neuroplasticity of Autonomic Behavior in Health and Disease
Synaptic Physiology and Plasticity Track
Benedito Machado and Nanduri Prabhakar

Featured Topic
Time Domains of the Hypoxic Ventilatory Response
Hypoxia and Oxidative Stress Track
Frank L. Powell

Wednesday, April 22, 2009 10:30 AM-12:30 PM

Physiology InFocus: Integrative and Systems Physiology: An Approach to Understanding Organ System and Disease
Omics: The Changing Face of Integrative Physiology
Eugene Kolker

Symposium
The Emerging Role of MicroRNAs in Skeletal Muscle Biology
Francisco H. Andrade and John J. McCarthy

Symposium
Natriuretic Peptides in the Gastrointestinal System
Ion Channels and Transporters Track
William R. Gower, Jr. and John R. Dietz

Symposium
Systems Biology Investigations of Glucocorticoid Efficacy in Tissue Remodeling
Robert J. Freishtat and Eric P. Hoffman

Symposium
Novel Insights into Nitric Oxide Signaling
Hypoxia and Oxidative Stress Track
Jonathan S. Stamler and Charles J. Lowenstein

Symposium
Role of Electromechanical Intercellular Coupling in Cardiac Tissue: Development, Disease and Tissue Engineering Applications
Ion Channels and Transporters Track
Narine Sarvazyan and Gordana Vunjak-Novakovic

Featured Topic
Environmental Stress Responses: Cellular, Molecular, and Genetic Mechanisms
Thermal and Environmental Stress Track
Keith P. Choe

Featured Topic
The Impact of Intermittent Hypoxia on Metabolism, Vascular Dysfunction, and Atherosclerosis
Hypoxia and Oxidative Stress Track
Christopher P. O'Donnell and Vsevolod Polotsky

Featured Topic
Regulation of Epithelial Ion and Water Channels
Ion Channels and Transporters Track
TBA

Postdoctoral Positions

Postdoctoral and Research Associate Positions: St. Joseph's Hospital, Phoenix, AZ, USA. Available immediately are Postdoctoral Fellow and Research Associate positions in the following areas. *Molecular Biology of Inflammation*. The successful candidate will study lipid mediators of fever and hypothermia in systemic inflammation in rats and mice (see *PLoS Biol* 4: e284, 2006). Proficiency in molecular biology techniques is required. Additional experience in neuroanatomy or immunohistochemistry and knowledge of the pathways of prostaglandin synthesis are preferred. Extensive technical help with animal work will be provided. *Integrative Physiology of TRP Channels.* The successful candidate will study the roles of Thermo-TRP channels in body temperature regulation in health and disease by using rodent models (see *J Neurosci* 27: 7459, 2007). The same person may participate in studies of the neural pathways of thermoregulatory behaviors in rats and mice (see *PLoS ONE* 1: e1, 2006). Experience with in vivo physiology is required. Additional experience in immunohistochemistry or electrophysiology and knowledge of neuroanatomy or pharmacology of TRP channels are preferred. For all positions, mandatory requirements include an advanced degree, a track record of peer-reviewed publications, excellent computer skills, and good writing skills. To apply, send your CV, up to five reprints of full-length papers, a brief description of research interests and career goals, and names, Email addresses, and telephone numbers of at least two references to Andrej A. Romanovsky, MD, PhD, Director, Systemic Inflammation Laboratory, St. Joseph's Hospital, 350 W. Thomas Road, Phoenix, AZ 85013, USA; aromano@chw.edu.

Postdoctoral Research Associate: The Nutrition, Exercise Physiology, and Sarcopenia Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging is seeking a recent PhD graduate. The suitable candidate will have a doctoral degree in nutrition, exercise science, or physiology with related experience in skeletal muscle biology and growth-dependent intracellular signaling pathways and an interest in cellular mechanisms of aging. Laboratory experience with western blotting, immunohistochemistry and other molecular techniques is essential. Experience with animal care and handling is also greatly desirable. Candidates must be able to work independently. This is a permanent full time position. Interested candidates should send resume and cover letter to Dr. Roger Fielding, PhD at roger.fielding@tufts.edu. URL: http://www.hnrc.tufts.edu/1192109687036/HNRCA-Page-hnrca2ws_1192109688454.html

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Postdoctoral Fellowship: The Laboratory of Cell Biophysics of the School of Basic Sciences of the Swiss Federal Institute of Technology in Lausanne seeks a Postdoctoral Fellow in Cellular Biophysics . The candidates should hold a PhD degree in Biophysics, Physics or related fields. The research in the laboratory is focused on experimental and theoretical aspects of cellular calcium dynamics, cell motility and membrane proteins imaging. The laboratory is equipped with confocal and spinning disk microscopes, atomic force microscope and cell culture facilities. We are looking for a highly motivated fellow with experience in a domain related to the activity of our laboratory. We offer him (her) to develop and extend his (her) research in synergy with the physicists and biologists of the laboratory. The appointment is for up to four years starting March 2009. Please submit CV, summary of research experience and research planned as well as contact information of three references to Prof. J.-J. Meister, at the above address. For more information, please visit the Web site of the Laboratory.

Faculty Positions

Assistant Professor of Physiology at Eckerd College: Eckerd College invites applications for Assistant Professor of Physiology (tenure-track) to start in September 2009; PhD is required. Teaching responsibilities include laboratory courses in Molecular Physiology, Cell Biology and courses in the candidate's specialty area. Teaching duties consist of seven courses per academic year, including January Term and lecture/lab courses in the fall and spring semesters. Participation in the college's interdisciplinary, values-oriented general education program is required, including a regular rotation in a two-semester freshman course. Send a letter of application, vita, statement of teaching philosophy that includes areas of teaching interests, teaching evaluations if available, a description of research plans that addresses the role of undergraduates in your research, graduate and undergraduate transcripts, and three letters of recommendation by November 1 to Dr. Denise Flaherty, Natural Sciences, Eckerd College, 4200 54th Avenue S. St. Petersburg, FL, 33711. No electronic applications, please. Eckerd College, the only independent national liberal arts college in Florida, has a tradition of innovative education and teaching/mentoring excellence. [EOE]

Assistant Professor Positions: The Department of Physiology at The University of Tennessee Health Science Center (UTHSC) in Memphis invites outstanding scientists with PhD, MD, or equivalent degrees for two tenure-track faculty positions at the rank of assistant professor to begin July 1, 2009. We are searching for creative scientists who have or will establish an extramurally-funded research program and also excel at teaching medical, dental, and graduate students. UTHSC is the state's flagship academic health center with an annual budget of close to $400 million, and the Department of Physiology is currently ranked seventh based on extramural funding by the American Physiological Society. While we will consider applicants in all areas of physiology, the Department has a particular interest in recruiting candidates with experience studying the interface between immunity and vascular biology, stem cell physiology, or innovative techniques in molecular physiology. The positions are part of the expansion of the department; significant new laboratory space, a substantial start up package, and a competitive salary with an additional incentive bonus will be offered. Candidates should submit their Curriculum Vitae, a description of research interests/goals (not to exceed two pages) as a single PDF document, and arrange to have three letters of reference sent to: Gabor Tigyi, MD, PhD, Harriett Van Vleet Professor and Chair, Department of Physiology, EMail: PhysiologySearch@utmem.edu, Website:

http://physio1.utmem.edu. Applicants should have their applications complete by December 15, 2008, as review will begin upon receipt of the application. UTHSC is an equal opportunity employer. The University of Tennessee is an EEO/AA/Title VI/Title IX/Section 504/ADA/ADEA institution in the provision of its education and employment programs and services.

Assistant/Associate Professor of Physiology/Anatomy: Drake University College of Pharmacy and Health Sciences (http://www.drake.edu/cphs/) invites applications for a full-time tenure-track faculty position at the Assistant/Associate Professor level in the Department of Pharmaceutical Sciences. The position is available June 1, 2009. Requirements for the position are a doctorate in physiology/anatomy or closely related field with demonstrated experience in biomedical research. Preference is given to candidates with postdoctoral training and/or teaching experience. The successful candidate will be expected to develop innovative teaching and learning approaches for the classroom and to develop an ongoing, fundable research program. Instructional responsibilities include courses in the Pharm.D program and the undergraduate programs in the health sciences. The candidate must have a strong commitment to teaching and research mentoring at the undergraduate level. Start up funds and modern laboratory space and equipment are available. Drake University and the College of Pharmacy and Health Sciences support an interdisciplinary environment for scholarly activity; collaborative research is encouraged. Review of applicants will begin immediately and continue until the position has been filled. Salary is competitive and dependent on qualifications and experience. Interested persons should submit, electronically, a letter of interest, curriculum vita, a statement of teaching philosophy and experience, a brief summary of research interests and future research plans, and the contact information for three references to: cphssearch@drake.edu. Position description may be view at http://www.drake.edu/hr/employment/. Questions regarding the position should be directed to: Ronald Torry, PhD, Search Committee Chair, Email: Ron.Torry@drake.edu. Tel.: 515-271-2750. Drake University is an equal-opportunity employer and actively seeks applicants who reflect the diversity of the nation. No applicant shall be discriminated against on the basis of race, color, national origin, creed, religion, age, disability, sex, gender identity, sexual orientation or veteran status.

Assistant Professor in Molecular Environmental Physiology: The Department of Biological Sciences at the University of Wisconsin-Milwaukee seeks applicants for a tenure-track position in molecular environmental physiology at the rank of assistant professor. We seek candidates with research interests in the cellular and molecular mechanisms by which signaling pathways in the endocrine or nervous systems are disrupted by environmental chemicals. Candidates must have a PhD and postdoctoral experience and will be expected to establish an independent, extramurally funded research program involving MS and PhD students in an area of physiology/toxicology and eukaryotic molecular biology. Teaching responsibilities include participation in core biology courses and an advanced course in an area of specialization. To apply, please go to http://www.jobs.uwm.edu/applicants/Central?quickFind=50597. A completed application should include: cover letter, curriculum vita, statement of research goals, statement of teaching interests, and letters of professional reference. Applicants should arrange to have three letters of reference sent as pdf attachments to the departmental chair (sandgren@uwm.edu) or mailed to: Molecular Environmental Physiologist Search, Department of Biological Sciences, University of Wisconsin-Milwaukee, PO Box 413, Milwaukee, WI 53201. Screening of candidates will begin December 19, 2008 and continue until the position is filled. Appointment begins August 2009. [AA/EOE]

Tenure-track Position (Tier II Canada Research Chair): Department of Physiology, Faculty of Health Sciences, Queen's University: Queen's University is seeking an outstanding scholar in the area of regenerative medicine for a Tier II Canada Research Chair, Tenure-Track position (http://www.chairs.gc.ca/web/home_e.asp) at the Assistant Professor level. The primary appointment will be in the Department of Physiology with cross-appointment to the Faculty of Applied Science (Department of Mechanical or Chemical Engineering). The successful candidate will be an emerging leader at the interface of stem cell research in cardiovascular biology/physiology and biomedical engineering. He/she will be engaged in research applications in the general areas of cardiac repair or vascular tissue engineering and will be required to establish a leading-edge research program and pursue collaborative links with colleagues in the Cardiac, Circulatory and Respiratory Research Group, and scientists in the Faculty of Applied Science/Engineering. The candidate will supervise graduate students, teach, and make administrative contributions appropriate for the position. Queen's University is a campus with a global reputation in the heart of the vibrant Kingston community in the core of a UNESCO World Heritage site and the Thousand Islands region of south-eastern Ontario (http://www.queensu.ca/resources/pdf/about/prospectus/faculty/FacultyRecruitment2007.pdf). Applicants must hold a PhD, MD/PhD or MD degree (or the equivalent) and have a track record in stem cell research at the postdoctoral or Assistant Professor level. Applications should include a curriculum vitae and a cover letter describing relevant research, background training, and the names and contact information of three references. The Canada Research Chair Program imposes no restrictions on nominees with regard to nationality or country of residence. Applications should be sent to (hard copy preferred): Dr. John Fisher, Chair, Search Committee, Department of Physiology, Queen's University, Botterell Hall, Room 442, Kingston, ON, K7L 3N6, Canada. Review of submissions will commence January 1, 2009. The University invites applications from all qualified individuals. Queen's is committed to employment equity and diversity in the workplace and welcomes applications from women, visible minorities, aboriginal people, persons with disabilities, and persons of any sexual orientation or gender identity. The academic staff at Queen's are governed by a collective agreement between Queen's University Faculty Association and the University which is posted at http://www.qufa.ca.

Assistant Professor–Exercise Science: Michigan Technological

University is accepting applications for a tenure-track Assistant Professor position in the Department of Exercise Science, Health and Physical Education. Applicants in all fields of exercise science/kinesiology will be considered. Candidates with interests and experience in the area of motor behavior are strongly encouraged to apply. Research programs utilizing a systems approach, mathematical modeling, and/or computational analysis are particularly encouraged. The expected start date for this position is August 17, 2009. *Responsibilities / Qualifications:* Candidates must have an earned doctorate in Exercise Science or related field. Teaching responsibilities will include Motor Control, Motor Learning & Development, and other exercise science courses. Typical teaching load is two classes per semester. A successful candidate must not only demonstrate evidence of high quality teaching, but must also demonstrate a clearly defined research program. Candidates will be expected to develop a vigorous, externally-funded research program which will support graduate students and lead to peer-reviewed publications. Candidates are expected to engage in departmental, college, university, and professional service activities, including the advisement of graduate and/or undergraduate students. Salary and start-up are commensurate with experience and qualifications. 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. This rural community is known for its abundant snowfall, beautiful summers, and outstanding four-season recreational opportunities. In addition, 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 Exercise Science, Health and Physical Education is home to over 85 students in just its third year of existence. For more information about the Department, visit http://www.exsci.mtu.edu. Application instructions: Review of applications will begin December 15, 2008 and will continue until the position is filled. Candidates should send a letter of interest, curriculum vita, statements of teaching and research philosophies, and names/contact information for at least 3 references to: Dr. Jason R. Carter, Chair, Dept of Exercise Science, Health and PE, Michigan Technological University, 1400 Townsend Drive, Houghton, MI 49931. Michigan Technological University is an Equal Opportunity Educational Institution/Equal Opportunity Employer.

Assistant Professor: Animal Physiologist, Southern Illinois University Edwardsville. *Description of duties:* Animal Physiologist. Applicants should have broad training in animal physiology. The successful candidate will share responsibility for teaching an animal physiology course and will offer advanced courses in their specialty area. The successful candidate will also be expected to participate in teaching introductory courses for biology majors and non-majors, and should exhibit potential for independent and innovative research involving Master's and undergraduate students. *Qualifications Required*: A PhD in biology or related field. Relevant Postdoctoral teaching and research experience preferred. *Closing Date for Applications:* Review of applications will begin on December 12, 2008, and continue until position is filled. Submit letter of application, Statement of Teaching Philosophy, Statement of Research Interests, Curriculum Vitae, copies of official transcripts, three letters of recommendation, and no more than three reprints to: Chair, Animal Physiologist Search Committee, Department of Biological Sciences, Southern Illinois University Edwardsville, Campus Box 1651APS, Edwardsville, IL 62026-1651. SIUE is a comprehensive regional university located on a 2,660 acre campus in a semi-rural setting 25 minutes from downtown St. Louis, MO. SIUE is dedicated to excellence in undergraduate education. SIUE is a state university – benefits under state sponsored plans may not be available to holders of F1 or J1 visas. [AA/EOE]

Assistant Professor: The Pennsylvania State University, the Altoona College, invites applications for a multi-year, non-tenure track appointment in Vertebrate Anatomy and Physiology in the Division of Mathematics and Natural Sciences beginning in Fall 2009. Teaching responsibilities will include introductory level courses in biology including human biology courses for allied health majors, biology courses for non-science majors, and, depending on expertise, biology courses for science majors. Duties will consist of 12 contact hours per week in lecture and/or laboratory courses and college service, including advising. Located in the beautiful Allegheny Mountains of central Pennsylvania, Penn State Altoona is a largely residential campus of 4,000 students offering 19 baccalaureate degree programs and the first two years of 180 Penn State baccalaureate degrees. Degree offerings at Penn State Altoona will continue to expand. Only 40 miles from the University Park campus, Altoona College offers the advantages of small college teaching with the readily available resources of a major research university. The minimum requirement for this position is a PhD degree in Biology, Anatomy, Physiology, or a closely related field and teaching experience at the college level. This position is a multi-year (three-year), fixed-term appointment at the level of assistant professor and is renewable based upon performance and need. Penn State Altoona offers a competitive salary and an attractive benefits package. Applicants should send a letter of application establishing their qualifications; a current vita; a description of teaching philosophy and evidence of teaching effectiveness; transcripts (official transcripts required at the time of an interview); and three letters of reference. Applicants are strongly encouraged to submit their applications and accompanying materials electronically to mnsdiv@psu.edu in Word or PDF formats. Review of applications will begin November 15, 2008, and continue until the position is filled. Non-electronic inquiries, applications, and additional materials should be sent to: Chair Search Committee for Biology, Penn State Altoona, Box D-29064, 3000 Ivyside Park, Altoona, PA 16601-3760. For additional information about Penn State Altoona, please visit our web page at http://www.altoona.psu.edu. Penn State is committed to affirmative action, equal opportunity and the diversity of its workforce.

Assistant/ Associate Professor: Ross University School of Medicine, located on the beautiful Caribbean island of Dominica in the West Indies, invites applications for a faculty post as assistant/associate professor in Pulmonary Physiology. Our mission is to prepare highly dedicated students to become

effective, successful physicians in the United States. Basic science coursework is taught in Dominica and students then complete their clinical studies in the United States. After passing all prerequisite examinations, Ross graduates are licensed to practice medicine in all 50 states of the US. Ross University School of Medicine is a division of DeVry, Inc (NYSE:DV) Education is the primary focus of the faculty. The academic year is divided into three semesters with a new class of students admitted each semester. Lectures and other educational responsibilities continue throughout the year. Effective teachers are sought, particularly individuals who are interested in improving medical education and who work well on a team. Research opportunities exist, primarily in the area of medical education. *Essential Duties and Responsibilities: 1*) the preparation of course material (handouts etc.); *2*) the delivery of effective lectures; *3*) the preparation, administration, marking and reporting of examinations; *4*) undergo training to qualify as a facilitator in the problem-based learning program; *5*) supervise educational activities of students under actual or simulated situations; *6*) prepare instructional plans and career analyses to reflect current changes in the field; *7*) advise individuals or groups of students in academic matters and exercise professional judgment in referring students to appropriate personnel; *8*) develop new instructional materials and teaching techniques with participation in on-going reviews and revision of curriculum planning; *9*) actively participate in relevant professional activities in order to improve teaching and subject matter competence; *10*) serve on faculty committees as appointed or elected, and confer with advisory groups in order to modify course content; *11*) prepare, administer and evaluate examinations to assess the development of student accomplishments; *12*) participate in other activities as assigned by the department chair or executive dean. *Qualifications: 1*) content expertise in pulmonary physiology; *2*) ability to relate physiology to clinical scenarios; *3*) experience in computer-assisted delivery of course content; *4*) excellent communication skills in English; *5*) strong teaching skills and experience or evidence of potential; *6*) interest in medical education; *7*) desire for self improvement;.*8*) flexibility and ability to work well on a team. *Education, Experience, Knowledge and Skill: 1*) PhD, MD or MD/PhD degree in physiology; *2*) enthusiastic teacher with previous teaching experience at a North American or United Kingdom medical school. Ross University offers a competitive potentially tax-free annual salary, relocation assistance to and from the island, a deferred pension program, tuition assistance benefit, scholarship program for dependents, 100% medical benefits paid for the employee, travel benefits, a living allowance, 35 days of paid annual leave is provided along with opportunities for professional development, which includes a conference and book allowance. To apply, please visit our website http://www.rossu.edu; select Careers and complete our online application process. [EOE]

Assistant/Associate Professor: The John B. Pierce Laboratory, Yale School of Medicine, Yale University seeks a Systems Level Physiologist or Neurophysiologist conducting innovative research on hypothalamic regulatory mechanisms. The appointment will be made at the rank of Assistant Fellow or starting Associate Fellow. Co-appointment is anticipated at the equivalent rank of Assistant or Associate Professor at the Yale University School of Medicine. The successful candidate will join a multidisciplinary faculty with research interests that include the neural, behavioral, and physiological mechanisms of temperature sensitivity, fluid balance, food selection, reward, and metabolism. Now celebrating its 75th anniversary as a nonprofit laboratory dedicated to basic research in environmental physiology and health, the John B. Pierce Laboratory is an endowed institute, formally affiliated with Yale University since 1966, that makes both term and career appointments. Located immediately adjacent to the medical school campus, the Laboratory offers a unique, world-class collaborative research environment in which its faculty enjoys the added advantages of outstanding in-house technical, engineering, and design/build services, and independent business and administrative offices with exceptional grant support. The Laboratory offers competitive salary, benefits, and start-up, as well as an outstanding work environment. Applicants should submit a CV, description of research interests, set of representative publications, and names of at least three references to: scientificsearch@jbpierce.org, or to Scientific Search, John B. Pierce Laboratory, 290 Congress Avenue, New Haven, CT 06519. The search will continue until the position is filled. http://www.jbpierce.org [EOE/AA]

Assistant Professor (Glial-Neuronal Interactions/Synaptic Plasticity): The Department of Cell Biology & Neuroscience (http://cbns.ucr.edu/) at the University of California, Riverside seeks an individual whose research is focused in the area of glial-neuronal interactions/synaptic plasticity. Applicants are sought whose primary research interests are directed towards synaptic function, plasticity and glial-neuronal interactions. The department, housed in a new (2006) Biological Sciences Building encompassing 22 laboratories, provides excellent research facilities for current and future faculty members of the Department. Applicants, who must have a PhD or equivalent and postdoctoral experience, are expected to interact broadly with faculty and students in the Interdepartmental Neuroscience Graduate Program, and participate as members of the Center for Glial-Neuronal Interactions. Other possible liaisons include the Center for Nanoscale Science, Bioengineering, and the Stem Cell Center. Opportunities for teaching and mentoring are available through participation in Graduate Programs in Neuroscience (http://neuro.ucr.edu/), Cell, Molecular and Developmental Biology (http://www.cell.ucr.edu/), and Genetics, Genomics, and Bioinformatics (http://www.genetics.ucr.edu/) and participation in the undergraduate majors in neuroscience and cell biology. Send curriculum vitae, research statement, and contact information for at least three letters of reference to: Chair, Glial-Neuronal Interac-tion Search Committee, Department of Cell Biology & Neuroscience, University of California, Riverside, CA 92521 USA. Application materials may be sent by Email to: neuroscience@ucr.edu. Review of applications will begin December 15, 2008 and continue until the position is filled. Position available 1 July 2009. *The University of California is an equal opportunity/affirmative action employer.*

Assistant Professor of Anatomy, Physiology & Pathophysiology: (Graduate Program of Nurse Anesthesia): Texas Wesleyan University, founded in 1890 in Fort Worth, TX, is a United Methodist institution with a tradition of integrating the liberal arts and sciences with professional and career preparation at the undergraduate level and in selected graduate areas. Total enrollment is over 3,000 students. The University's Graduate Program of Nurse Anesthesia is currently seeking applicants for a nine-month, tenure-track position as an Assistant Professor of Anatomy, Physiology & Pathophysiology beginning August 2009. The applicant will be responsible for designing and delivering traditional instruction in graduate-level anatomy, physiology and pathophysiology to both on-campus and interactive video distance students enrolled in the Master of Science in Nurse Anesthesia and/or the Master of Health Science programs. Requirements include a PhD in physiology or closely related field with graduate coursework and research in the field of physiology. Candidates must demonstrate a strong dedication to teaching. Although not required for the position, the selected applicant may pursue research interests as desired. Applications will be reviewed until position is filled. To apply, send a current curriculum vita; a cover letter indicating position desired; official graduate-level transcripts; three letters of reference; statements of personal teaching philosophy; and, a summary of research interests to: Anatomy, Physiology & Pathophysiology Search Committee, Office of Human Resources, Texas Wesleyan University, 1201 Wesleyan, Fort Worth, TX 76105, or HR@txwes.edu. Visit http://HR.txwes.edu for full job description. [EOE]

Assistant Professor: The Department of Biology at the University of California, Riverside invites applications for a tenure-track nine-month academic position at the assistant professor rank beginning Fall 2009. A PhD in Physiology or a related field and at least one year of postdoctoral experience are required. Applicants are expected to develop a strong and externally funded research program in animal systems physiology. We seek a candidate that can bridge our existing departmental strengths in integrative and comparative physiology with campus wide strengths in biomedical and applied physiology. Opportunities include collaborations with a variety of campus research centers (http://www.cnas.ucr.edu/centers/index.html), the emerging medical school, and the University of California Natural Reserve System. All faculty members teach at the undergraduate and graduate level, and may participate in one or more interdepartmental graduate programs. Applicants should email a curriculum vita, separate statements of research and teaching interests, and up to three reprints to animalphysjob@ucr.edu. In addition, applicants should request that three letters of recommendation be sent to: Chair, Systems Physiology Search Committee, Department of Biology, University of California, Riverside, CA 92521-0334. Review of applications will begin on January 12, 2009 and will continue until the position is filled. Website: http://biology.ucr.edu. The University of California is an equal opportunity employer.

Assistant Professor: (Glial-Neuronal Interactions/Synaptic Plasticity): The Department of Cell Biology & Neuroscience (http://cbns.ucr.edu/) at the University of California, Riverside seeks an individual whose research is focused in the area of glial-neuronal interactions/synaptic plasticity. Applicants are sought whose primary research interests are directed towards synaptic function, plasticity and glial-neuronal interactions. The department, housed in a new (2006) Biological Sciences Building encompassing 22 laboratories, provides excellent research facilities for current and future faculty members of the Department. Applicants, who must have a PhD or equivalent and postdoctoral experience, are expected to interact broadly with faculty and students in the Interdepartmental Neuroscience Graduate Program, and participate as members of the Center for Glial-Neuronal Interactions. Other possible liaisons include the Center for Nanoscale Science, Bioengineering, and the Stem Cell Center. Opportunities for teaching and mentoring are available through participation in Graduate Programs in Neuroscience (http://neuro.ucr.edu/), Cell, Molecular and Developmental Biology (http://www.cell.ucr.edu/), and Genetics, Genomics, and Bioinformatics (http://www.genetics.ucr.edu/) and participation in the undergraduate majors in neuroscience and cell biology. Send curriculum vitae, research statement, and contact information for at least three letters of reference to: Chair, Glial-Neuronal Interaction Search Committee, Department of Cell Biology & Neuroscience, University of California, Riverside, CA 92521 USA. Application materials may be sent by Email to: neuroscience@ucr.edu. Review of applications will begin December 15, 2008 and continue until the position is filled. Position available 1 July 2009. [AA/EOE]

Research Positions

Animal Physiologist Position: The Department of Biological Sciences at Western Michigan University invites applications for an Animal Physiolo-gist at the Assistant or Associate Professor level beginning Fall 2009, pending budgetary approval. A PhD and relevant postdoctoral experience are required. Responsibilities will include teaching an undergraduate Human Physiology course for majors, other related courses and an upper level course in the applicant's area of expertise. Other responsibilities include establishment of a vigorous extramurally funded research program and supervision of undergraduate and graduate research in the department's BS, MS and PhD programs. Western Michigan University is a student-centered research university with a strong commitment to research excellence in the life sciences. The Carnegie Foundation for the Advancement of Teaching has placed WMU among the 76 public institutions in the nation designated as research universities with high research activity. Applicants should visit http://www.wmich.edu/hr/careers-at-wmu.htm to apply. Please submit a curriculum vitae, statement of teaching philosophy and research interests. In addition, please send three letters of recommendation to: Dr. C. Linn, Chair, Animal Physiologist Search Committee, Department of Biological Sciences, Western Michigan University, 1903 W. Michigan Avenue, Kalamazoo, MI 49008-5410, Tel.: 269-387-5615, Fax: 269-387-5609; Email: cindy.linn@wmich.edu. Review of applications will begin Oct. 15, 2008, and will continue until the position is filled. [EOE]

Tenure-Track Vertebrate Physiologist, Department of Biology, Earlham College: We seek a colleague

that is first and foremost excited about teaching physiology—in lecture, laboratory and research venues—to bright and motivated undergraduates in a nationally-ranked department, at a liberal arts college. Teaching responsibilities include physiology and anatomy course(s), an upper level specialty course, and contributions to team-taught introductory courses in cell physiology and genetics. A commitment to collaborative student-faculty research, and an ability to bridge our departmental strengths between cellular/molecular and whole organism biology are essential. Applicants who have an interest in one or more of the following are especially attractive: comparative physiology, neurophysiology, systems biology, integrative biology, use of 'omics' tools. PhD required; teaching or postdoctoral experience desirable. Review of applications begins November 15, 2008. Candidates must provide a cover letter, curriculum vitae, statement of teaching philosophy, description of research interests and arrange to have three letters of recommendation sent to Dr. Peter Blair, Dept. of Biology, Earlham College, Richmond, IN 47374. Earlham College is an Affirmative Action/Equal Opportunity Employer. We particularly encourage applications from women, racial minorities, and Quakers. (http://www.earlham.edu/~biol/).

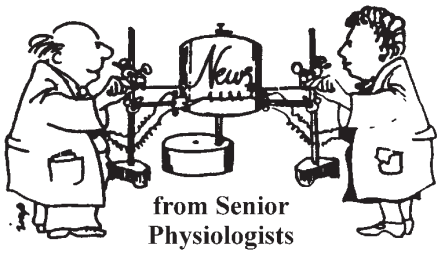
PhD Training Program in Space Life Sciences, Texas A&M University: The National Space Biomedical Research Institute (NSBRI)-sponsored PhD Training Program in Space Life Sciences at Texas A&M University (TAMU) is currently accepting applications for Fall 2009. Students participating in this program work toward a PhD in Nutrition, Kinesiology or Nuclear Engineering (Health Physics), or a MD/PhD or PhD in Medical Sciences from the Texas A&M University Health Sciences Center Graduate School of Biomedical Sciences. Students will focus their research on space environment-induced bone loss, muscle wasting, cosmic radiation damage and/or changes in metabolism. The Space Life Sciences graduate program at TAMU is designed with immersive components including: fundamental courses in space life sciences, individual research and an experiential component with work at Johnson Space Center, Brookhaven National Laboratory and/or University of Texas Medical Branch. All trainees participate in outreach by teaching elements of space life sciences in a K-12 setting. To learn more about the program, please visit http://SLSGraduateProgram.tamu.edu. The deadline for submitting an application package is February 15, 2009. For more information please contact: Lindsey Field, Texas A&M University, Program Coordinator, PhD Training Program in Space Life Sciences, 213 Kleberg Center, 2253 TAMU, College Station, TX 77843. Tel.: 979-845-0850; Fax: 979-862-1862; Email: lbfield@tamu.edu. ❖

Senior Physiologists' News

Letter to Beverly Bishop

Stone Freedberg writes: "Thanks so much for your note of congratulations. You asked me how I felt about turning 100 years old on May 30, 2008.

"So far, I feel like a stack of pancakes smothered in maple syrup. The events of May and June have been astounding. The Beth Israel Deaconess and Mr. S. B. Lewis sponsored a concert and reception in the Boston Symphony Orchestra's Higginson Hall in my honor. Helena Baillie (violin) and Julian Riem (piano) played well during a delightful evening. Harvard Medical School (HMS) made me an honorary alumnus and held a dinner with remarks. Two-hundred and fifty friends and family gathered for a separate dinner with toasts and speeches. Judith W. Freedberg, DEd, the wife of my elder son, Richard, made an especially moving speech about my wife Bea, who passed away eight years ago. I asked for donations to the A. Stone Freedberg fund for student research at HMS in lieu of gifts. It was gratifying to see the strong support that the fund received. Daniel Freedberg, the son of my younger son Leonard (HMS 1975), graduated from HMS in Jume. The ceremony was a chance to reunite with friends and family. Finally, in order to keep me



humble, the President of the United States sent a congratulatory letter, and misspelled my name.

"The years since leaving the Beth Israel in 1974 have not been filled entirely with parties and celebrations. I continued working and joined the Harvard University Health Service, serving as physician to students, staff, and faculty until 2006. I taught medicine, including physical diagnosis, to the HMS students by using their own illnesses as models. I also worked on the HMS admissions committee, including many years as chairman for the sub-committee that selected candidates from the Ivy League colleges. The work was enjoyable but the interview process needed a controlled study to examine its usefulness. I wrote a number of memorial minutes, eulogizing Herman Blumgart and Paul Zoll, among others. More recently, I wrote a paper summarizing my work from 1939-1941 on the bacteria living in human stomachs. This was done at the request of Dr. Barry Marshall, winner of the 2005 Nobel Prize for his work in peptic ulcer disease and was published as part of his book, *Helicobacter Pioneers.*

"The last 10 years have been marked by series of losses. The most difficult period was during the illness and slow death of my late wife Bea, after 65 years of marriage. Time, my family, independence (increasingly difficult), and a love of music have helped. Old patients continue to call to discuss their problems and seek advice. This helps too. "

Letter to Charles Tipton

Stephen Cain writes: "It was official as of last Saturday, the 4th. Helen and I are well and still manage to travel a fair bit. I have no scientific endeavors nor would I pretend that I could have if I wanted them. If I were any more retired, somebody would be patting me on the face with a shovel.

"As for words of wisdom for the younger folks, all I can say is more power to you. I am pretty sure that I couldn't survive in today's academe and I have the greatest respect for those that do." ❖

Lefkowitz Awarded National Medal of Science

Robert J. Lefkowitz

President Bush presented APS member Robert J. Lefkowitz, Duke University Medical Center, with the 2007 National Medal of Science on September 29th in a White House Ceremony. Lefkowitz was honored "for discovery of the seven transmembrane receptors, deemed the largest, most versatile and therapeutically accessible receptor signaling system, and for describing the general mechanism of their regulation, influencing all fields of medical practice." Lefkowitz was joined by seven others in receiving the National Medal of Science and eight receiving the National Medal of Technology and Innovations.

President John F. Kennedy awarded the first National Medal of Science in 1963. It was created by Congress in 1959 as part of Public Law 86-209. The National medal of Science has honored individuals "deserving of special recognition by reason of their outstanding contributions to knowledge in the physical, biological, mathematical, engineering, chemistry and social sciences." Four decades later, more than 400 of America's scientists, thinkers, and discovers have been honored with this medal.

APS Members Elected to the Institute of Medicine

The Institute of Medicine (IOM) announced the names of 65 new members and five foreign associates in conjunction with its 38th annual meeting. Three APS members were among the list of individuals elected to the IOM. 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.

A diversity of talent among IOM's membership is assured by the Institute's charter, which stipulates that at least one-quarter of the membership is selected from outside the health professions, for example, from such fields as the natural, social, and behavioral sciences; law; engineering; and the humanities. Current active members elect new members from among candidates nominated for their outstanding accomplishments. The newly elected members raise IOM's total active membership to 1,576 and the number of foreign associates to 89. With another 71 members holding emeritus status, IOM's total membership is now 1,736.

Newly elected APS members of the Institute of Medicine are:

Walter R. Frontera, dean, faculty of medicine, and professor, department of physical medicine and rehabilitation, department of physiology, University of Puerto Rico, San Juan;

Michael M. Merzenich, professor emeritus of otolaryngology, and founding member, Keck Center for Integrative Neuroscience, University of California, San Francisco; and

Phyllis M. Wise, provost and executive vice president; and professor of physiology, biophysics, obstetrics, and gynecology, School of Medicine and College of Arts and Sciences, University of Washington, Seattle.

Benos Receives UAB Endowed Chair

Dale J. Benos

APS Member Dale J. Benos, Chair, Department of Physiology & Biophysics, University of Alabama, was recently named as the first recipient of the University of Alabama Health Sciences Foundation Endowed Chair in Biomedical Research. Benos joined the UAB faculty in 1985, and, in 1996, was named Chair of the UAB Department of Physiology and Biophysics. Under his leadership, the Department has flourished and is consistently ranked in the upper tier of such departments in terms of research funding received, according to the ACDP. The Department's Graduate Program likewise is highly regarded.

Blaustein and Romero win Prestigious Hypertension Research Awards

APS members, Mordecai P. Blaustein, MD, professor of physiology and medicine at the University of Maryland School of Medicine, and Juan Carlos Romero, MD.

Professor of Physiology and Biophysics, Director of Hypertension Research Laboratory Mayo College of Medicine have been honored as recipients of the prestigious Novartis Award for Hypertension Research. Blaustein and Romero received the award at the annual conference of the American Heart Association's Council for High Blood Pressure Research in Atlanta, Ga., on September 19.

Blaustein's award recognizes his groundbreaking discoveries exploring the biological mechanisms by which salt raises blood pressure. During more than 40 years of work, Blaustein and his colleagues have made important basic science discoveries to explain the link between salt and hypertension. These include a hormone that originates in the body that is very similar to a plant compound called ouabain. Blaustein and his colleagues call it endogenous ouabain because it is identical to the plant compound but is endogenous to the human body. A second factor is the sodium pump, a protein that controls the amount of sodium in cells and that is regulated by ouabain. The third factor is the sodium-calcium exchanger, which Blaustein discovered. Blaustein has determined how these three factors interact and cause the contraction of blood vessels that lead to salt-dependent hypertension.

Romero's Award recognizes his seminal studies on the interaction between prostaglandins and the intrarenal renin-angiotensin system in the control of renal function, and the roles of intrarenal prostaglandins and nitric oxide in the regulation of renal hemodynamics. He also studied the role of enhanced oxidative stress in the development of increased blood pressure and reduced renal function in angiotensin II

dependent hypertension. In addition, Romero was recognized for innovative and pioneering development of imaging approaches using tri-dimensional computerized tomography allowing in vivo anatomical reconstruction of the kidney and physiological assessment of regional blood flow, filtration rate and tubular flow in the kidney thus allowing improved diagnosis of reno-vascular disease.

The Novartis Award for Hypertension Research has been presented to outstanding scientists in the field each year since 1966, when the American Heart Association first began to recognize the importance of hypertension to heart health.

Brad Jon Behnke, an Assistant Professor, is presently at the University of Florida Department of Applied Physiology and Kinesiology, Gainesville, FL. Behnke was previously at West Virginia University, Postdoctoral Research Associate Division of Exercise Physiology Morgantown, WV.

Concetta Christine DiRusso is a Professor of Department of Nutrition and Health Sciences at the University of Nebraska, Lincoln, NE. Prior to this position DiRusso was Senior Scientist in the Center of Metabolic Disease at Ordway Research Institute, Inc. Albany, NY.

Serge P. von Duvillard is presently a Professor at the University of Salzburg Department of Sport Science and Kinesiology Hallein-Rif Astralia. Prior to this position von Duvillard was Professor and Director at Texas A&M University.

Jessica Andrea Filosa is an Assistant Professor in the Department of Physiology at Medical College of Georgia, Augusta. Prior to this position Filosa was a Research Assistant Professor in the Department of Psychiatry at University of Cincinnati, Cincinnati, OH.

Robinson Luke W. Harris is a Postdoc Fellow in VXHRI Research Pavillion at the University of British Columbia, Vancouver, BC, Canada. Prior to this position Harris was a Postdoc Fellow in Fac Physical Education/Recreation at University of Alberta, AB, Canada.

John Paul Lavelle is currently an Associate Professor at Stanford University, Department of Urology, Palo Alto, CA. Previously, Lavelle was an Assistant Professor, Department of Surgery and Division of Urology University of North Carolina, Chapel Hill, NC.

Daniel E. Lemons is Dean of Science at The City College of New York, CUNY, New York, NY. Prior to this position, Lemons was an Associate Provost and Dean for Doctoral Science at Graduate Center, CUNY, Manhattan, NY.

Chunling Li is a Research Instructor at the University of Colorado, Aurora, CO. Prior to this position, Li was a Research Fellow in the Department of Medicine and Renal Division at the University of Colorado Health Science Center, Denver.

Michael P. Lisanti is a Professor in the Department of Cancer Biology at Thomas Jefferson University, Philadelphia, PA. Prior to this position Lisanti was a Professor in the Department of Molecular Pharmacology at Albert Einstein College of Medicine, Bronx, NY.

Robert A. Rose has taken a position at Dalhousie University, Assistant Professor Department of Physiology and Biophysics Halifax, Canada. Prior to this position Rose was a Postdoctoral Fellow, University Toronto, Heart and Stroke/Richard Lewar Centre, Toronto Canada.

Vicente Martinez is a Lecturer at the Autonomous University of Barcelona, Department of Cell Biology, Physiology and Immunology, Barcelona, Spain. Martinez was formerly a Principal Scientist at AstraZeneca R&D, Alderley Park, UK.

Julia Ann Moffitt is presently at Des Moines University, Department of Physiology and Pharmacology, Des Moines, IA. Moffitt was formerly at Cornell College, Mt. Vernon, IA.

Mel Silverman is a Professor in Toronto General Hospital, Toronto, Canada. Prior this position Silverman was a Professor in the Department of Medicine at University of Toronto clinical Science Division, Toronto, Canada.

Huirong Xie is a Research Fellow at the Cincinnati Children's Hospital Medical Center, Cincinnati, OH. Prior to this position Xie was a Research Fellow at Vanderbilt University, Nashville, TN. ❖

Books Received

Appetite and Food Intake: Behavioral and Physiological Considerations
Edited by Ruth B.S. Harris, Richard D. Mattes
Florida, USA: CRC Press, 2008, 360pp., illus., index, $129.95
ISBN: 9781420047837

Physiology at a Glance 2nd edition
Jeremy Ward, Roger Linden
Massachusetts, USA: Wiley Publishers, 2008, 158pp. illus, index, $35.00
ISBN: 1405177233

Obesity: Causes, Mechanisms, Prevention, and Treatment
Edited by Elliott M. Blass
Maine, Sinaure Associates, Inc., 2008, 450 pp., 80 illus., index, $54.95
ISBN: 978-0-87893-037-1

Our Marvelous Bodies: An Introduction to the Physiology of Human Health
Gerry F. Merrill
North Carolina, USA: Rutgers University Press, 2008, 240 pages, 22 illustrations, 24 tables, $39.95
ISBN: 978-0-8135-4281-2

Here are some very tasty efforts:

2007 Nobilo Sauvignon Blanc $9. This is standard New Zealand Sauvignon Blanc – fresh, clean, herbal-grassy nose with gooseberry fruit, and a palate that follows in kind. Why then this wine in the column? A) price is $4 or so less than the mainstream NZ SB range. B) Quality is still excellent C) acidity is quite moderate – I have said before that perhaps the major distinguishing feature among NZ SB's is their various levels of acidity. On average, these wines are really quite tart, and perhaps too much so for many people. Nobilo is less tart than most. The only downside is that there are richer NZ SB's out there, but that said, there is still plenty of fruit. Great everyday wine.

2005 Kirkland Meritage, Napa valley, $11. Most of you will know that "Meritage" in California = Claret in Bordeaux (ie, a blend of main Bordeaux varietals). Most of you will also know that Kirkland is the Costco brand. So Costco had this wine made for them to sell under their own label. This wine is 69% Merlot, 29% Cabernet and 2% Cabernet Franc. The nose is a bit subdued, with dark cherry and some stemmy green aspects, but the palate is really very good. The fruit is quite intense with red and dark cherry. Its main feature other than excellent fruit is the silky smooth mouthfeel that is elegant, and not at all heavy, with excellent acid, and lighter tannins, some herbal elements, light oak and spice. Very easy to drink, and the 13.5% alcohol is quite modest. There is some stemminess that stops well short of bitterness, and a hint of earth. The finish is medium long – wish it were longer – but for this price, it is a wine I would serve at a formal dinner without worry. Will it age? It could be interesting to check it yearly, but I don't think it is a real keeper. It compares with one of my perennial favorites, Estancia Meritage, which is twice the price.

Peter Wagner

Thought a review of several current release ~$6 Australian budget Shiraz listings might be interesting. There now so many since Rosemount invented this niche some years back. Here are six examples of wines that should be readily available. None are over the top in concentration or alcohol. I am reporting on all six, but feel comfortable recommending only the first 5 (actually, surprised that 5 of 6 are quite drinkable). You may well rank them differently according to your taste, so enjoy any of these top 5:

2007 Yellowtail Shiraz $6.00. The best of this bunch, this wine is not just a berry juice fruit bomb with no structure, as several such cheapo offerings tend to be. Slight mint and a touch of gamey leather on the nose with some dark plums. The palate is lush with dark fruit and hints of earth, black pepper and spice to give some complexity. It has a rich mouthfeel, soft tannins, and good acidity to provide good balance and length. It's no $30 pretender, but is much better than $6.00. This might actually last a year or two in the cellar and be interesting then.

2007 Black Swan Shiraz $6.00. Close second place, this wine took a while to open (an observation that often correlates with goodness). Slight mint and red/dark berries on the nose. The palate has ripe sweet red/dark berry fruit (but no residual sugar), vanilla, slight black pepper, light oak char, slightly higher than average acidity, soft tannins, and it really improved with time in the glass open to air.

2006 Little Penguin Shiraz $6.50. Next tier down from the two above, but still excellent value. Mint and dark fruit on the nose and palate. Quite lush and soft, but not as complex and structured as the above two. Very easy to drink.

2007 Alice White Shiraz $5.50. This wine did not have forward aromas, even with time. There was pleasant dark fruit, mint, good acidity and sweet ripe vanilla and dark berries on the palate, but it came across as very simple. I realize these words don't really convey why it ranked fourth, just not as interesting as the above.

2006 Lindemans Bin 50 Shiraz $5.00 very much like the Alice white – very easy to approach, decent dark berry fruit, but very simple. There was some spice but no mint, and while pleasant, came across as just OK. It would make a good BBQ party wine for a crowd. Can't beat the price.

2006 Jacob's Creek Shiraz $6.00. This one I did not like, simply because it had far too much tannin for the fruit and came across as harsh and hard. It was also a little tart and bitter. All symptoms of an insufficient fruit component. ❖

2009

January 15-18

The APS Professional Skills Training Course, Lake Buena Vista, FL. *Information:* Amy Feuerstein, The American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814. Tel.: 301-634-7236; Email: afeuerstein@the-aps.org; Internet: http://www.the-aps.org/education/profskills.

February 7-12

SPIE Medical Imaging Conference, Orlando, FL. *Information:* SPIE, P.O. Box 10, Ballingham, WA 98227-0010. Internet: http://www.spie.org/micall.

February 24-March1

Dissecting the Vasculature: Function, Molecular Mechanisms, and Malfunction, Vancouver, British Columbia, Canada. *Information:* Stephanie W Watts, PhD, B445 Life Sciences Building, Department of Pharmacology & Toxicology, Michigan State University, East Lansing, MI 48824-1317. Tel.: 517-353-3724; Fax: 517-353-8915; Email: wattss@msu.edu; Internet: http://www.keystonesymposia.org/9J8.

February 28-March 4

Biophysical Society's 53rd Annual Meeting, Boston, MA. *Information:* Alexandra Frager. Tel.: 301-634-7325; Fax: 301-634-7133; Email: afrager@biophysics.org; Internet: http://www.biophysics.org/2009meeting.

March 10-14

16th International Hypoxia Symposium: Hypoxia and Exercise, Alberta, Canada. *Information:* PO Box 6508, F524, c/o Altitude Research Center, Aurora, CO 80045. Fax: 720-293-7722; Email: info@hypoxia.net; Internet: http://www.hypoxia.net.

March 13-16

5th world Congress World Institute of Pain - WIP, New York, NY. *Information:* Kenes International, 1-3, Rue de Chantepoulet, PO Box 1726, CH-1211 Geneva 1, Switzerland. Tel.: +41 22 908 0488; Fax: +41 22 732 2850; Email: wip@kenes.com; Internet: http://www2.kenes.com/wip/Pages/home.aspx.

March 27

Skeletal Endocrinology, Brescia, Italy. *Information:* Internet: http://www.skeletal-endocrinology.org/presentazione.asp.

April 1-3

Human & Exercise Physiology Themed Meeting (The Physiological Society), London, UK. *Information:* Tel.: +44 (0) 207269 5715; Email: meetings@physoc.org; Internet: http://www.physoc.org/site/cms/contentEventViewEvent.asp?chapter=109&e=2448.

May 12-15

The North American Research Conference on Complementary & Integrative Medicine, Minneapolis, MN. *Information:* Internet: http://www.imconsortium-conference.org/.

May 14-16

3rd International IVI Congress, Madrid, Spain. *Information:* Internet: http://www.comtecmed.com/ivi/2009/.

May 15-17

Human Integrative Physiology: The Legacy of the Copenhagen School; in the Footsteps of Lindhard and Krogh, Copenhagen, Denmark. *Information:* Bengt Saltin, Copenhagen Muscle research Centre, Rigshopitalet, 7652, Blegdamsvej 9, DK-2100 Copenhagen. Tel. +45 35457582; Email: bengt.saltin@rh.regionh.dk.

June 4-6

The Organization for th Study of Sex Differences (OSSD) 3rd Annual Meeting, Toronto, Ontario, Canada. *Information:* Viviana Simon, 1025 Connecticut Avenue, NW, Suite 701, Washington, DC 20036. Email: viviana@ossdweb.org; Internet: http://www.ossdweb.org.

June 26-28

The First International Conference of Hydrogen Sulfide in Biology and Medicine (H2S Biology 2009), Shanghai, China. *Information:* Internet: http://www.h2sbiology2009.org.

July 11-16

XXII Congress of the International Society on Thrombosis and Haemostasis (ISTH 2009), Boston, MA. *Information:* MCI Suisse SA, Rue de Lyon 75, 1211 Geneva 13 - Switzerland. Tel.: +41 22 33 99 587; Fax: +41 22 33 99 621; Email: isth2009@mci-group.com; Internet: http://www.isth2009.com/welcome.html.

August 3-7

11th International Congress on Amino Acids, Peptides and Proteins, Vienna. *Information:* Internet: http://www.meduniwien.ac.at/ICAAP09/index.html.

October 27-30

2nd International Fascia Research Congress, Amsterdam, The Netherlands. *Information:* Faculty of Human Movement Sciences, Van der Boechorststraat 9, NL - 1081 BT Amsterdam, Tel. +31 20 59 82000, Fax. +31 20 59 88529; Internet: www.fasciacongress.org/2009.

2008 APS INTERSOCIETY MEETING

The Integrative Biology of Exercise - V

HILTON HEAD, SOUTH CAROLINA

SEPTEMBER 24-27, 2008

MEETING PROGRAM AND ABSTRACTS

2008 APS Intersociety Meeting

SPONSORED BY:

- The American Physiological Society
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- Canadian Society for Exercise Physiology

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2008 APS Intersociety Meeting

THE INTEGRATIVE BIOLOGY OF EXERCISE - V

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Steven S. Segal Univ. of Missouri, Columbia	**Mark Hargreaves** Univ. of Melbourne, Australia	**Michael Lindinger** Univ. of Guelph, Canada	**P. Darrell Neufer** East Carolina Univ., Sch. of Med.

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NIH, National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH, National Institute of Diabetes and Digestive and Kidney Diseases
Merck Research Laboratories
National Space Biomedical Research Institute
Aurora Scientific, Inc.

2008 APS Intersociety Meeting
The Integrative Biology of Exercise - V
September 24 - 27, 2008, Hilton Head, SC

Registration Opens: Wednesday, September 24, 2008, at 3:00 PM
Opening Reception: Wednesday, September 24, 2008, 6:00 – 10:00 PM

	Thursday September 25	Friday September 26	Saturday September 27
8:30-11:00 AM Concurrent Symposia	**1.0 Regulation of Peripheral Vascular Resistance** Chair: Steven S. Segal **2.0 Control of Ribosomal Biogenesis in Muscle Hypertrophy** Chair: Gregory R. Adams	**14.0 Somatic and Sympathetic Neural Control During Exercise** Chair: Gail D. Thomas **15.0 Comparative Exercise Physiology: Linking Animal Locomotion to Human Performance** Chair: Peter J. Reiser	**26.0 Signaling Mechanisms Regulating Metabolic and Transcription Processes in Skeletal Muscle** Chair: Eva R. Chin **27.0 Roles of Biomechanical Signaling in Cardiac and Skeletal Muscle** Chairs: Tara Haas and Ronald L. Terjung
Afternoon Activities	11:00 AM-12:30 PM **3.0—11.0 Poster Presentations and Exhibits** 12:30-1:30 PM Free Time 1:30-3:00 PM **Poster Presentations and Exhibits**	11:00 AM-12:30 PM **16.0—23.0 Poster Presentations and Exhibits** 12:30-1:30 PM Free Time 1:30-3:00 PM **Poster Presentations and Exhibits**	11:00 AM-12:30 PM **28.0—36.0 Poster Presentations and Exhibits** 12:30-1:30 PM Free Time 1:30-3:00 PM **Poster Presentations and Exhibits**
3:00-5:00 PM Concurrent Symposia	**12.0 Muscle as an Endocrine Organ: Intertissue Influences** Chair: Bente K. Pedersen **13.0 Stem Cells and Nuclear Domains in Skeletal and Cardiac Muscle** Chair: Brenda Russell	**24.0 Reactive Oxygen Species: Consequences on Cellular Metabolism** Chair: Michael B. Reid **25.0 Remodeling of the Extracellular Matrix of Tendon and Skeletal Muscle in Response to Exercise** Chair: Benjamin F. Miller	**37.0 Role of Inflammation in Healthy, Diseased and Aged Muscles** Chairs: James Tidball and Robert W. Grange **38.0 Sarcolemmal, T-Tubule and Intracellular Determinants of Contractile Function in Skeletal Muscle** Chairs: Michael Lindinger and Scott Trappe
Evening Events	7:00 - 10:00 PM **Special Purchase Event:** ***Evening Barbecue Buffet Dinner*** **-** *Enjoy a traditional South Carolina barbecue with your colleagues at the Port Royal Golf Club.*	5:30 – 6:30 PM **APS Education Session. Writing Your First Paper: The *Ins* and *Outs* of Authorship.** *Presented by Michael Strurek* **NSBRI Research Information Forum.** *Presented by Susan Bloomfield and Greg Adams*	7:00-10:00 PM **Banquet and Awards Presentation:** *Including a dinner lecture presented by Peter D. Wagner* Included with registration.

Location:

The 2008 APS Intersociety Meeting: The Integrative Biology of Exercise - V will be held September 24 – 27, 2008 at the Westin Hilton Head Resort and Spa Hotel, 2 Grasslawn Avenue, Hilton Head Island, SC 29928, telephone: 1-843-681-4000 or FAX: 1-843-681-1065.

Onsite Registration Hours:

Wednesday, September 24 …….. 2:00—8:30 PM
Thursday, September 25 ……7:30 AM—5:00 PM
Friday, September 26 …….8:00 AM—5:00 PM
Saturday, September 27 …….8:30 AM—5:00 PM

On-Site Registration Fees:

APS/ACSM/CSEP Member..... $350
Retired Member $240
Nonmember..... $400
Postdoctoral..... $290
Student $240

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

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.

The press office is located in the Lady Davis room on the same floor as the conference center. The office will be open daily from 8:00 AM – 5:00 PM.

Special Purchase Event:

Tickets for the special evening event at the nearby Port Royal Golf Club will be available at the registration desk. Tickets are limited and are available on a first come, first served basis at $60 each.

The evening event is being held on Thursday, September 25 from 7:00—10:00 PM. Each ticket includes entry to the golf club, traditional South Carolina barbecue buffet dinner and beverages.

Ancillary Sessions:

APS Career Session: This special session entitled: "Writing Your First Paper: The *Ins* and *Outs* of Authorship" will be presented by Michael Sturek, member of the APS Career Opportunities in Physiology Committee. 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.

NSBRI Research Information Forum: This special session is hosted by Dr. Susan Bloomfield, NSBRI Musculoskeletal Alterations Team Associate Leader and Dr. Greg Adams, an NSBRI funded investigator, for those interested in learning more about research opportunities supported by NSBRI.

Program Objective:

The goal of the meeting is to convene an internationally recognized and interdisciplinary group of investigators focusing on the use of integrative approaches for the study of exercise involving physiology, molecular biology and genetics 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.

THURSDAY, SEPTEMBER 25, 2008

Symposium I

1.0 **REGULATION OF PERIPHERAL VASCULAR RESISTANCE**
Thurs., 8:30 - 11:00 AM, Calibogue Ballroom.

Chair: **Steven S. Segal,** *Univ. of Missouri, Columbia.*

8:30 AM **1.1** Introduction. **Steven S. Segal.** *Univ. of Missouri, Columbia.*

8:35 AM **1.2** Coordination of Arteriolar Dilation with Muscle Fiber Contraction. **Coral Murrant.** *University of Guelph.*

9:10 AM **1.3** The Role of Integrins on the Control of Skeletal Muscle Arteriolar Diameter. **Luis Martinez-Lemus.** *Univ. of Missouri, Columbia.*

9:45 AM **1.4** Microvascular Adaptations to Obesity and the Metabolic Syndrome. **Jefferson Frisbee.** *West Virginia Univ.*

10:20 AM **1.5** Exercise Versus Aging in Microvascular Control: Role of Reactive Oxygen Species. **Zoltan Ungvari.** *New York Med. Col.*

Symposium II

2.0 **CONTROL OF RIBOSOMAL BIOGENESIS IN MUSCLE HYPERTROPHY**
Thurs., 8:30 - 11:00 AM, Danner Ballroom.

Chair: **Gregory R. Adams,** *Univ. of California, Irvine.*

8:30 AM **2.1** Introduction. **Gregory R. Adams.** *Univ. of California, Irvine.*

8:35 AM **2.2** Ribosomal DNA Transcription: A Molecular Checkpoint for Cell Growth. **Lawrence I. Rothblum.** *Univ. of Oklahoma Hlth. Sci. Ctr.*

9:10 AM **2.3** Ribosomal Biogenesis and Cardiac Myocyte Hypertrophy. **Ross D. Hannan.** *Peter MacCallum Cancer Ctr., Australia.*

9:45 AM **2.4** Intracellular Signals Regulating the Adaptation of Skeletal Muscle to Mechanical Tension. **Karyn Esser.** *Univ. of Kentucky.*

10:20 AM **2.5** mTOR and the Integration Exercise and Amino Acid Nutrient Status in the Regulation of Translation. **Scot Kimball.** *Pennsylvania State Univ. Col. of Med.*

Poster Session

3.0 **CARDIOVASCULAR**
Thurs., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

1 **3.1** Sympathetic and Cardiovascular Responses during Local Saline Infusion. **J. Cui, P. McQuillan, R. Moradkhan and L. I. Sinoway.** *Penn State Heart & Vascular Inst. and Penn State Col. of Med.*

2 **3.2** Arterial Pressure and Heart Rate Alterations in Exercise Trained Rats Submitted to Orthostatic Stress. **M. Martins-Pinge and S. Borghi.** *State Univ. of Londrina, Brazil.*

3 **3.3** Moderate-intensity Resistance Training and Combined Resistance and Aerobic Training Improve Reactive Hyperemia. **H. Kawano, M. Miyachi and M. Higuchi.** *Waseda Univ., and Natl. Inst. of Hlth and Nutrition, Japan.*

4 **3.4** Optimum Aerobic Capacity Improvement. **G. Greenwell.** *Life Clinic, Valrico, Florida.*

5 **3.5** Mitochondrial KATP Channel Inhibition Blunts Arrhythmia Protection in Ischemic Exercised Hearts. **J. Quindry, L. Schrieber, P. Hosick, J. Wrieden, E. Hoyt.** *Appalachian State Univ.*

6 **3.6** Interaction Between Flexibility and Cardiorespiratory Fitness on Arterial Stiffness. **K. Yamamoto, H. Kawano, Y. Gando, Y. Ohmori, M. Iemitsu, H. Murakami, K. Sanada, M. Tanimoto, M. Higuchi, I. Tabata and M. Miyachi.** *Waseda Univ., and Natl. Inst. of Hlth. and Nutrition, Japan.*

7 **3.7** Physical Activity Estimated by Triaxial Accelerometer is an Independent Predictor of Arterial Stiffening. **Y. Gando, H. Kawano, K. Yamamoto, H. Murakami, M. Tanimoto, M. Iemitsu, Y. Ohmori, K. Sanada, I. Tabata, M. Higuchi and M. Miyachi.** *Waseda Univ., and Natl. Inst. of Hlth. and Nutrition, Japan.*

8 **3.8** CD34+/KDR+ Endothelial Progenitor Cells and Vascular Health: Exercise and Detraining. **S. Witkowski, M. Lockhard, R. Harley, N. Jenkins, E. Spangenburg and J. Hagberg.** *Univ. of Maryland, College Park, and Univ. of Maryland Sch. of Med., Baltimore.*

9 **3.9** Low Dose Estrogen Therapy does not Change Hemodynamics and Neural Responses to Static Exercise in Postmenopausal Women. **B. Oneda, C. Forjaz, J. Gusmão, D. Mion, Jr., S. Abrahão, E. Labes, A. Maggio and T. Tinucci.** *Univ. of São Paulo, Brazil.*

Board #

10 **3.10** Single and Multiple Sprint Exercise Acutely Stiffens the Central Arteries of Young Healthy Males. **M. Rakobowchuk, M. Stuckey, L. Gurr, P. J. Millar, M. J. MacDonald.** *McMaster Univ.*

11 **3.11** The Effects of Acute Isometric Handgrip on Autonomic Modulation. **P. J. Millar, M. J. MacDonald, S. R. Bray and N. McCartney.** *McMaster Univ.*

12 **3.12** Hemodynamic Responses and Cardiovascular Autonomic Regulation Following Supramaximal Exercise. **S. Goulopoulou, B. Fernhall and J. Kanaley.** *Syracuse Univ., and Univ. of Illinois at Urbana-Champaign.*

13 **3.13** The Effect of Exercise Intensity on Endothelial Function in Healthy Young Adults. **R. Hallmark, Z. Liu, G. Gaesser, E. Barrett and A. Weltman.** *Univ. of Virginia.*

14 **3.14** Multiple Sprint Exercise Acutely Decreases Stroke Volume During Recovery in Young Healthy Males. **M. MacDonald, L. Gurr, M. Rakobowchuk, M. Stuckey and P. Millar.** *McMaster Univ.*

15 **3.15** The Effects of Short-Term Endurance Exercise Training on Vascular Function in Young Males. **K. Currie and J. Goodman.** *Univ. of Toronto.*

16 **3.16** Heart Rate Responses to Transitions From Low and High Workrates Before and After Sprint Interval Training. **N. Proudfoot, M. Rakobowchuk, S. Tanguay and M. MacDonald.** *McMaster Univ.*

17 **3.17** Modeling Study of Muscle Pump, Starling Resistor and Heart Rate During Exercise. **B. Gariepy, G. Ferguson and S. Magder.** *McGill Univ.*

Poster Session

4.0 INTEGRATIVE EXERCISE RESPONSE

Thurs., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

18 **4.1** Changed Expression of Extracellular Matrix mRNA in Joint Capsule and Patella Tendon After Acute Low-intensity Treadmill Exercise. **S. Lee, T. Sakurai, H. Hatta and Y. Atomi.** *Univ. of Tokyo, Japan.*

19 **4.2** Relative Safety and Efficacy of Blood Flow Restricted Resistance Exercise. **B. Clark, T. Manini, M. Guiler, P. Williams, R. Hoffman and M. Kushnick.** *Ohio Univ., and Univ. of Florida, Gainesville.*

Board #

20 **4.3** Intermittent Hypoxia Conditioning Improves Exercise Performance, Hemodynamics, and Ventilation of Healthy Senior Men Who Avoid Exercise. **H. F. Downey, V. Shatilo, O. Korkushko, V. Ischuk and T. Serebrovskaya.** *Univ. of Texas Hlth. Sci. Ctr., Inst. Gerontol, and Bogomoletz Inst. of Physiol., Ukraine.*

21 **4.4** Exercise and Osteopathic Lymphatic Pump Treatment Increase Lymph Flow in Conscious Dogs with Normal and Ex-panded Extracellular Fluid Volume. **H. F. Downey, P. Durgam, A. Williams, Jr., A. Rajmane, H. King and S. Stoll.** *Univ. of Texas Hlth. Sci. Ctr.*

22 **4.5** Effects of Estrogens and Progesterone on AVP secretion, Thirst and Serum Sodium Concentration. **N. Stachenfeld and H. Taylor.** *Yale Univ. Sch. of Med.*

23 **4.6** Muscle Volume Decreases with Whole Body Dehydration. **L. Ploutz-Snyder, S. Cook, T. Fairchild, K. Hackney, V. Frechette and R. Ploutz-Snyder.** *Syracuse Univ., and SUNY, Upstate Med. Univ.*

24 **4.7** High Intensity Intermittent Exercise Training in Rodents: Impact on Plasma Volume and Hepatic Albumin mRNA Expression. **G. Mack, N. Bexfield, A. Parcell, K. Foote and W. B. Nelson.** *Brigham Young Univ.*

25 **4.8** Opioid-mediated Muscle Afferents Inhibit Central Motor Drive and Limit Peripheral Muscle Fatigue Tolerance in Exercising Humans. **M. Amann, L. Proctor, J. Sebranek, D. Pegelow, and J. Dempsey.** *Univ. of Zurich, Switzerland, and Univ. of Wisconsin Med. Sch.*

26 **4.9** Reverse Lactate Threshold—A Pilot Study of a High-resolution, Single-session, Anaerobic-threshold Test. **R. Dotan.** *Brock Univ., Ontario.*

27 **4.10** Effects of a 12-week Resistance Training Program on Muscle Growth and Basal Gene Expression in Young and Old Women. **U. Raue, B. Jemiolo, D. Slivka, S. Trappe.** *Ball State Univ.*

28 **4.11** The Effects of Intrinsic Aerobic Capacity and Diet on Insulin Signaling and IKK-beta Activity in Rats. **B. Bikman, T. Woodlief, R. Noland, S. Britton, L. Koch, R. Cortright, R. Lust, and G. L. Dohm.** *East Carolina Univ., Duke Univ., and Univ. of Michigan.*

Board #

29 **4.12** High Intensity Exercise Induces Immune Suppression Through Endocannabinoid Increase. **R. H. Ozdurak, P. Korkusuz and F. Korkusuz.** *Middle East Tech. Univ., Ankara, and Hacettepe Univ. Ankara, Turkey.*

30 **4.13** Acute Responses to Blood Flow Restricted Exercise. **T. Manini, B. Clark, F. Skidmore, J. Yarrow and S. Borst.** *Univ. of Florida, Gainesville, and Ohio Univ.*

31 **4.14** Locomotor Compensation in a Mouse Model of Musculoskeletal Degeneration. **T. Griffin, K. Costello, L. Setton and F. Guilak.** *Duke Univ. Med. Ctr.*

32 **4.15** The Relationship Between Aerobic Capacity, Body Composition, and Physical Activity Among Ethnic Groups. **T. Moore-Harrison, A. Hamilton, A. Knab, R. Bowen and J. T. Lightfoot.** *Univ. of North Carolina, Charlotte.*

33 **4.16** Effects of Exercise and Weight Loss on Skeletal Muscle Adipose Tissue Triglyceride Lipase. **J. Dube, P. Coen, F. Amati and B. Goodpaster.** *Univ. of Pittsburgh.*

34 **4.17** Hydrogen Ion Threshold Differs Between the Thigh and Calf Muscles During Locomotion. **S. Lee, G. Ellerby, L. Stroud and B. Soller.** *Wyle Integrated Sci. & Eng. Grp., Houston, TX, and Univ. of Massachusetts Med. Sch.*

35 **4.18** Pharmacological Blockade of the TRPv1 Receptor in Skeletal Muscle Attenuates the Exercise Pressor Reflex in Rats. **A. Leal, S. Smith, M. Williams, J. Mitchell and M. Garry.** *Univ. of Texas Southwestern Med. Ctr.*

36 **4.19** Metabolic Adaptations to Voluntary Wheel Running in Hypertensive Heart Failure Prone Rats. **R. Schultz, J. Kirwan, H. Huang, P. Waters, M. Gerdes and J. Sallow.** *Univ. of Sioux Falls, Learner Res. Inst, Cleveland Clinic and Univ. of South Dakota.*

37 **4.20** Influence of Short-Term Sprint-Interval Training on Insulin Sensitivity and Thermogenic Response to Beta-Adrenergic Stimulation In Young Adult Humans. **J. Richards, M. Lonac, T. Johnson, R. Supon, G. Ryan, W. Voyles and C. Bell.** *Colorado State Univ., Fort Collins.*

38 **4.21** Skeletal Muscle Mitochondrial Dys-function in Pulmonary Arterial Hypertension. **T. Van Horn, J. Tolle, M. Hrovat, C. Farrar, G. Lewis and D. Systrom.** *Massachusetts Gen. Hosp.*

Board #

39 **4.22** Changes in Mood and Cortisol with Exercise and Rest. **E. Queathem and A. McGillivray.** *Grinnell Col., Iowa.*

40 **4.23** Impaired Cardiac Cycle Timing Events Post-marathon as Detected Using Digital Ballistocardiography. **J. P. Neary, D. S. MacQuarrie and E. F. G. Busse.** *Univ. of Regina and Heart Force Med. Vancouver.*

41 **4.24** Gender Comparison of Muscle Gene Expression in Response to Resistance Exercise. **E. Louis, N. Luden, E. Hayes, U. Raue, B. Jemiolo and S. Trappe.** *Ball State Univ.*

42 **4.25** Gene Expression Differs in Human Vastus Lateralis and Soleus Muscles in Response to Resistance Exercise. **E. Louis, N. Luden, E. Hayes, U. Raue, B. Jemiolo and S. Trappe.** *Ball State Univ.*

43 **4.26** Adaptation of Exercise Ventilation Following Passive Heat Acclimation. **M. White, A. Beaudin and M. Walsh.** *Simon Fraser Univ.*

44 **4.27** Energetic Balance Respnse to Physical Training Did Not Change Body Weight. **F. S. A. Evangelista, T. S. Higa, F. C. Bergamo, J. A. Pinto and J. E. Krieger.** *Univ. of São Paulo, Brazil.*

45 **4.28** Running Alters the Expression of Growth Related Genes in the Vastus Lateralis and Soleus Muscles. **M. Harber, J. Crane, B. Jemiolo, T. A. Trappe and S. Trappe.** *Ball State Univ.*

46 **4.29** Protein Synthesis Response to Running in Human Vastus Lateralis and Soleus Muscles. **J. Crane, T. A. Trappe, J. Dickinson, S. Trappe and M. Harber.** *Ball State Univ.*

Poster Session

5.0 ENDOCRINE

Thurs., 11:00 AM – 3.00 PM, Archer/Barnwell Ballroom.

Board #

47 **5.1** Sex Steroid Influences on Running Distance, Duration, and Speed in C57BL/6J Mice. **R. S. Bowen, A. T. Hamilton, A. M. Knab, J. A. Rettew, T. Moore-Harrison and J. T. Lightfoot.** *Univ. of North Carolina, Charlotte.*

48 **5.2** Effect of Resistance Exercise on Muscle Steroidogenesis. **J. L. Vingren, W. J. Kraemer, D. L. Hatfield, J. M. Anderson, J. S. Volek, N. A. Ratamess, G. A. Thomas, B. L. Bailey, S. D. Flanagan, C. M. Dunn-Lewis, G. F. Solomon-Hill, J-Y. Ho, M. S. Fragala and C. M. Maresh.** *Univ. of Connecticut and Col. of New Jersey.*

Board #

49 **5.3** Exercise Stimulates Local Bioactive Androgen Metabolism in Skeletal Muscle. **K. Aizawa, M. Iemitsu, S. Maeda, K. Sato, T. Otsuki, T. Ushida, N. Mesaki and T. Akimoto.** *Univ. of Tokyo, Intnatl. Pacific Univ., Univ. of Tsukuba, St. Catharine Univ., and Teikyo Heisei Univ., Japan.*

50 **5.4** Changes in Liver Glucagon Receptor Density and Affinity with Exercise and Post-exercise in Rats. **A. Melançon, J. Lamanque, D. Foucher, M. Snilner, F. Péronnet and C. Lavoie.** *Univ. of Quebéc at Trois-Rivières and Univ. of Montréal.*

51 **5.5** Differential Gene Response to Growth Hormone Treatment. **T. Livshiz and J. Schwartz.** *Univ. of Michigan.*

52 **5.6** Effects of Exercise Training and Energy-restriction on Adiponectin Secretion by Adipose Tissue of Diet-induced Obese Rats. **M. L. Batista, Jr., A. Yamashita, F. Lira, J. C. Rosa, E. Paulino, P. Brum, C. E. Negrão, R. Santos, L. Oyama, C. M. O. Nascimento and M. Seelaender.** *Univ. of São Paulo and São Paulo Fed. Univ., Brazil.*

Poster Session

6.0 CYTOKINES

Thurs., 11:00 AM – 3:00 PM, Archer/Barnwell Ballroom.

Board #

53 **6.1** Interleukin-6 Increases cAMP, Activates AMPK and Alters Substrate Metabolism in an Adrenergic Manner. **M. Kelly, A. K. Saha and N. B. Ruderman.** *Boston Univ. Sch. of Med.*

54 **6.2** Overexpression of Suppressor of Cytokine Signaling-3 Attenuates TNF-alpha Induced Inhibition of Insulin Signaling in Cultured Myotubes. **E. Spangenburg.** *Univ. of Maryland, College Park.*

55 **6.3** Voluntary Running Improves Heat Stroke Recovery in Mice by an IL-6 Independent Mechanism. **L. Leon, M. Blaha and B. Helwig.** *USARIEM, Natick, MA.*

56 **6.4** Voluntary Exercise Attenuates Plasma Cytokine Expression in Heat Stroked Mice. **B. Helwig, N. Pucillo and L. Leon.** *USARIEM, Natick, MA.*

57 **6.5** Circulating Estradiol & Interleukin-6 Across the Pharmacologically Controlled Menstrual Cycle: Effects of Exercise. **S. Ives,** *Springfield Col., MA.*

Plan to Attend the Welcome and Opening Reception
Wednesday, September 24
6:00 – 10:00 PM
Oceanfront Pavilion

Board #

58 **6.6** Circuit Resistance Training in Women: Body Composition and Serum Cytokines Levels. **F. Ferreira, A. Medeiros, C. Nicioli, J. Nunes, R. Leite, J. Prestes, G. Shiguemoto, G. Oliveira, G. Bombarda, P. Bueno, G. Pereira, G. Dourado, R. Verzola, V. Baldissera and S. E. de Andrade-Perez.** *Fed. Univ. of São Carlos, Brazil and Univ. of Michigan.*

59 **6.7** Racial Differences in Angiogenesis Factors and Creatine Kinase Following Eccentrically-biased Exercise. **A. McKune, S. Semple, L. Smith and R. Anderson.** *Univ. of KwaZulu-Natal, South Africa, Charles Darwin Univ., Australia, Tshwane Univ. of Tech., Pretoria and Univ. of Pretoria, South Africa.*

60 **6.8** Post-exercise Anti- and Pro-inflammatory Responses to Moderate Exercise in Healthy Adults. **A. White, K. Light, L. Wendt, and A. Light.** *Univ. of Utah.*

61 **6.9** Circuit Resistance Training in Postmenopausal Women: Effects on Muscle Force and IL-6 Serum Levels. **G. Shiguemoto, J. P. Botero, J. Prestes, R. Liete, A. J. Silva, A. Frollini, C. Cavaglieri, C. T. Marin, A. Silva, V. Baldissera, S. E. de Andrade-Perez.** *Fed. Univ. of São Carlos, UNIMEP, Piraciaba, and UNICEP, São Carlo, Brazil.*

Poster Session

7.0 STEM CELLS

Thurs., 11:00 AM – 3:00 PM, Archer/Barnwell Ballroom.

Board #

62 **7.1** Hematopoiesis: 1. Erythrogenesis. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

63 **7.2** Hematopoiesis: 2. Leucogenesis. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

64 **7.3** Hematopoiesis: 3. Proliferation of Blood Platelet. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

65 **7.4** Skeletal Muscle-derived Multipotent Stem Cells are Multi-myogenic Stem Cells that can Give Rise to Skeletal, Smooth and Cardiac Muscle Cells. **T. Tamaki, Y. Uchiyama, Y. Okada, K. Tono, M. Masuda, A. Hoshi, M. Nitta and A. Akatsuka.** *Tokai Univ. Sch. of Med. Japan.*

66 **7.5** Mesenchymal Stem Cell Proliferation is Reduced by Stiff Microrods in 3D Culture. **J. Collins, T. Desai and B. Russell.** *Univ. of Illinois at Chicago and UCSF.*

Board #

67 **7.6** Activity and Prolifertion of Cardiomyocytes Derived from Mouse Embryonic Stem Cells is Regulated by Microprojections. **J. Biehl, S. Yamanaka, K. Boheler, and B. Russell.** *Univ. of Illinois at Chicago, and NIA, NIH.*

68 **7.7** Characterization of a Sca-1+CD45- Stem Cell Population Preferentially Recruited by the $\alpha 7\beta 1$ Integrin in Skeletal Muscle Following Eccentric Exercise. **J. Liu, M. C. Valero and M. Boppart.** *Univ. of Illinois, Urbana.*

69 **7.8** Stimulation of Human Satellite Cells with Erythropoietin. **H. Fischer, E. Bergh, H. Rundqvist, C. J. Sundberg, T. Gustafsson and E. Jansson.** *Karolinska Univ.*

70 **7.9** The Expression of Satellite Cell Markers in Human Skeletal Muscle. **M. Linstrom and L-E. Thornell.** *Umeå Univ.*

71 **7.10** Low Oxygen Maintains Human Satellite Cells in an Undifferentiated State and Increases Proliferation. **E. Jansson, I. Hagerman, H. Fischer and T. Gustafsson.** *Karolinska Univ.*

72 **7.11** FOXO Differentially Regulates p27Kip1 Expression In Rat Muscle Precursor Cells. **S. Lees, T. Childs and F. Booth.** *Univ. of Missouri, Columbia.*

Poster Session

8.0 MICROCIRCULATION

Thurs., 11:00 AM – 3:00 PM, Archer/Barnwell Ballroom.

Board #

73 **8.1** Oxidant Stress is Required for Endothelium-Dependent Dilation in Skeletal Muscle Arterioles. **A. Sindler, R. Reyes, and J. Delp.** *West Virginia Univ.*

74 **8.2** Effect of Acetazolamide Administration on Endothelial Function in Humans. **B. Thompson, J. Thistlethwaite, J. Gonzales and B. Scheuermann.** *Univ. of Toledo.*

75 **8.3** Microvascular Remodeling and Decreased Angiogenic Factors in the Atrophied Rat Soleus Muscle. **H. Fujino, A. Ishihara, S. Murakami, H. Kondo, I. Takeda, N. Tillakaratne, H. Zhong, R. Roy and R. Edgerton.** *Himeji Dokkyo Univ., Kyoto Univ., Suzuka Univ. of Med. Sci., Japan, and UCLA.*

76 **8.4** Effects of Hindlimb Unweighting on Conducted Vasodilation of Rat Soleus Feed Arteries. **K. Eklund, S. Friskey, P. Thorne, E. M. Hasser, and M. H. Laughlin.** *Univ. of Missouri, Columbia.*

Poster Session

9.0 PHYSICAL INACTIVITY AND CHRONIC DISEASE

Thurs., 11:00 AM – 3:00 PM, Archer/Barnwell Ballroom.

Board #

77 **9.1** MicroRNA Expression is Altered During Skeletal Muscle Atrophy. **E. Dupont-Versteegden, K. Esser, C. Peterson and J. McCarthy.** *Univ. of Kentucky.*

78 **9.2** The Relationship Between Blood Cells and Drugs. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

79 **9.3** Mysterious Chains Observed During Incubation of Blood Cells: First Report. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

80 **9.4** Relationship Between Liver Diseases and Mysterious Chain: First Report. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

81 **9.5** Relationship Between the Drugs for Diabetes and Mysterious Chain. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

82 **9.6** Relationship Between Dementia/Parkinson's Disease and Mysterious Chain. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

83 **9.7** Impairments in Factors of Muscle Aerobic Metabolism Relate to Low Inherited Exercise Capacity. **H. Kainulainen, R. Kivelä, M. Silvennoinen, M. Vuento, N. Mutanen, R. Rinnankoski, M. Lehti, H. Reunanen, T. Purhonen, L. G. Koch and S. L. Britton.** *Univ. of Jyväskylä, LIKES Res. Inst., Finland and Univ. of Michigan.*

84 **9.8** Cessation of Daily Physical Activity Leads to Tissue Specific Changes in Palmitate Oxidation in Male Rats. **M. Laye, S. Borengasser, R. S. Rector, G. Uptergrove, S. Naples, J. Ibdah, F. Booth and J. Thyfault.** *Univ. of Missouri, Columbia, and Harry S. Truman Mem. Vet. Hosp.*

85 **9.9** Reduced Daily Steps Decreases Insulin Sensitivity and Increases Intra-abdominal Fat Mass in Rats and Humans. **F. Booth, R. Olsen, R. Krough-Madsen, C. Thomsen, J. Thyfault and B. K. Pedersen.** *Univ. of Missouri, Columbia, and Univ. of Copenhagen.*

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

86 **9.10** Detrimental Effects of Inactivity on Insulin Action: Role of Energy Surplus. **B. Stephens, K. Granados, S. Malin, T. Zderic, M. Hamilton and B. Braun.** *Univ. of Massachusetts, Amherst and Univ. of Missouri, Columbia.*

87 **9.11** Physical Activity vs. Physical Fitness: Associations with Metabolic Health in Patients After Gastric Bypass Surgery, Obese and Non-obese Controls. **F. Ramirez-Marrero, M. Somaraju, B. Vaa, S. Roberts, M. Joyner and T. Curry.** *Mayo Clinic.*

88 **9.12** Influence of Exercise and Perivascular Fat on Coronary Artery Vasomotor Function in a Familial Hypercholesterolemic Porcine Model of Atherosclerosis. **A. Bunker, P. Thorne and M. H. Laughlin.** *Univ. of Missouri, Columbia.*

89 **9.13** Daily Physical Activity Prevents Aging and Obesity Induced Skeletal Muscle Insulin Resistance in the OLETF Rat. **C. R. Mikus, S. J. Borengasser, R. S. Rector, S. P. Naples, G. M. Uptergrove, M. L. Ruebel, M. J. Laye, F. W. Booth, J. A. Ibdah and J. P. Thyfault.** *Univ. of Missouri, Columbia.*

90 **9.14** Impaired Maximal Force and Reduced Fatigue Rates Characterize the Skeletal Muscle of 90% Partial Pancreatectomized Diabetic Rats. **C. Gordon, E. Cafarelli, T. Hawke and M. Riddell.** *York Univ.*

91 **9.15** High-frequency Muscle Stimulation has an Anabolic Effect on Bone and Maintains Plantarflexor Strength During Hindlimb Unloading. **J. Swift, S. Bouse, M. Nilsson, K. Baldwin, H. Hogan and S. Bloomfield.** *Texas A&M Univ. and Univ. of Calif., Irvine.*

92 **9.16** Chronic Alcohol Ingestion Induces Several Factors Associated with Skeletal Muscle Protein Degradation in HIV-1 Transgenic Rats. **J. Otis and D. Guidot.** *Emory Univ. and Atlanta VA Med. Ctr.*

93 **9.17** Effects of Inactivity and Energy Status on Appetite Regulation in Men and Women. **K. Granados, B. Stephens, S. Malin, M. Hamilton, T. Zderic and B. Braun.** *Univ. of Massachusetts, Amherst and Univ. of Missouri, Columbia.*

94 **9.18** A Community-based Program to Enhance Function and Well-being in Individuals with Chronic Pain. **M. Thurgood, A. Lagerlof, M. Rashotte, R. Dubin and C. King-VanVlack.** *Queen's Univ.*

Board #

95 **9.19** Loss of Myosin from Single Muscle Fibers in Heart Failure Patients Reduces Force Production Without Altering Myofilament Ultrastructure. **M. Miller, A. Shaw, K. Ward, D. Moulton, P. Ades, D. Maughan and M. Tolin.** *Univ. of Vermont.*

96 **9.20** Comparison of Outcome in Different Methods Using or Non-using E-wellness System. **S. Kuno, Y. Sakato, N. Zai-ma, R. Watanabe, S. Mukarami and H. Sato.** *Univ. of Tsukuba and Tsukuba Wellness Res. Corp., Japan.*

97 **9.21** Withdrawn.

98 **9.22** Ethnic/racial Differences in the Effects of Acute Exercise on Insulin Sensitivity. **R. Hasson, K. Granados, S. Chipkin and B. Braun.** *Univ. of Massachusetts.*

99 **9.23** Parvalbumin, SERCA1, and SERCA2 Expression in Skeletal Muscle is Activity-dependent Following Spinal Cord Transection and Spasticity. **R. L. Harris, D. J. Bennett, T. Gordon and C. T. Putman.** *Univ. of Alberta.*

Poster Session

10.0 OXYGEN TRANSPORT

Thurs., 11:00 AM – 3:00 PM, Archer/Barnwell Ballroom.

Board #

100 **10.1** Problems of the Blood Used for Blood Transfusion and Blood Products. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

101 **10.2** Adverse Effect by Anticoagulant and GVH. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

102 **10.3** A New Approach of Transfusion Therapy of Preserved Self-blood. **T. Matsumoto.** *Matsumoto Living Cell Res. Lab., Tokyo, Japan.*

103 **10.4** Long-term Acclimatization to Moderate Altitude: A 4-year Cross-sectional Analysis. **M. Brothers, B. Doan, A. Wile, M. Zupan, R. Wilber and W. Byrnes.** *US Air Force Acad., US Air Force Res. Lab., US Olympic Committee and Univ. of Colorado.*

Don't forget…..
Pick up your Banquet Ticket by 10:00 AM on Thursday

This banquet is free but you MUST have a ticket for entry

Board #

104 **10.5** Enlarged O_2 Deficit with CO_2-inhalation During Heavy Exercise. **L. Østergaard, K. Kjær, K. Jensen, L. B. Gladden and P. K. Pedersen.** *Univ. of Southern Denmark, and Univ. of Auburn.*

105 **10.6** Effects of Hypoxia on VO_2max and Lactate Accumulation Rate in Exercising Goats. **G. Crocker, M. Hayes, R. Weems and J. H. Jones.** *Univ. of California, Davis.*

106 **10.7** Beta-alanine Supplementation Reduces Acidosis During High-intesity Cycling, but has no Effect on Ventilation or Oxygen Uptake. **W. Derave, A. Baguet, A. Pottier, J. Bouckaert and K. Koppo.** *Ghent Univ., Belgium.*

Poster Session

11.0 BLOOD FLOW REGULATION

Thurs., 11:00 AM – 3:00 PM, Archer/Barnwell Ballroom.

Board #

107 **11.1** Skeletal Muscle Blood Flow Response to Rhythmic Exercise During Hypoperfusion in Humans. **D. Casey, B. Walker, C. Johnson, B. Wilkins, W. Schrage, M. Ceridon and M. Joyner.** *Mayo Clinic and Univ. of Wisconsin, Madison.*

108 **11.2** Myocardial Blood Flow and Adenosine A2A Receptor Density in Endurance Athletes and Untrained Men. **I. Heinonen, S. Nesteroy, K. Liukko, J. Kemppainen, K. Någren, M. Luotolahti, P. Virsu, V. Oikonen, P. Nuutila, U. R. Kujula, H. Kainulainen, R. Boushel, J. Knuuti and K. Kalliokoski.** *Univ. of Turku, Univ. of Jyväskylä, Finland and Concordia Univ., Canada.*

109 **11.3** Do Gender Differences Exist in Functional Sympatholysis? **J. K. Limberg, S. R. Schilling, A. Drezdon, M. W. Eldridge and W. G. Schrage.** *Univ. of Wisconsin, Madison.*

110 **11.4** Cerebrovascular Reactivity Following Mild Traumatic Brain Injury in Varsity Hockey Players. **T. Len, J. P. Neary, W. Duff, G. Asmundson, D. LaHue and D. Goodman.** *Univ. of Regina, and Simon Fraser Univ.*

111 **11.5** Effects of Arm Elevation on Both Hands Vasoregulation Measured by Photoplethysmography. **W. Ahn, D. Kim and J. Sim.** *Seoul Natl. Univ. Hosp., Sungkyunkwan Univ. and Univ. of Ulsan, South Korea.*

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

112 **11.6** Physical Training Expands Collateral Function Independent of Sympathetic Activation in Rats with Femoral Artery Occlusion. **H. Yang, J. Taylor, M. H. Laughlin and R. Terjung.** *Univ. of Missouri, Columbia.*

113 **11.7** Vascular Response to Acidosis During Dynamic Handgrip Exercise. **J. Thistlethwaite, J. Gonzales, B. Thompson and B. Scheuermann.** *Univ. of Toledo.*

114 **11.8** Motor Unit Distribution Affects How Rapid Onset of Vasodilation Spreads in Resistance Networks. **A. W. Moore and S. S. Segal.** *Univ. of Missouri, Columbia.*

115 **11.9** Response of Prostaglandins and Nutritive Blood Flow to 8 Weeks of Exercise Training in Aged Human Skeletal Muscle. **M. D. Choi, J. A. Carrithers, T. P. Gavin, R. M. Kraus, C. A. Evans, R. S. Ruster, D. J. Knapp, J. S. McCartney, J. P. Garry and R. C. Hickner.** *East Carolina Univ.*

116 **11.10** Limb Blood Flow and Microvascular Exchange Response to Seven Days of Exercise Training in Young and Aged Men. **R. Hickner, R. Kraus, M. D. Choi, J. Carrithers, C. Evans, R. Ruster, D. Knapp, J. McCartney, J. Garry and T. Gavin.** *East Carolina Univ.*

Symposium III

12.0 MUSCLE AS AN ENDOCRINE ORGAN: INTERTISSUE INFLUENCES

Thurs., 3:00 - 5:00 PM, Calibogue Ballroom.

Chair: **Bente K. Pedersen,** *Rigshospitalet, Denmark.*

3:00 PM **12.1** Introduction. **Bente K. Pedersen.** *Rigshospitalet, Denmark.*

3:05 PM **12.2** Muscle Cytokines: Endocrine Regulators of Metabolism. **Matthew Watt.** *Monash Univ., Australia.*

3:35 PM **12.3** Intertissue Communication Controlling Glucose Homeostasis. **Barbara Kahn.** *Boston Obesity Nutrition Res. Ctr.*

4:05 PM **12.4** IL-6 - AMPK Interactions in Skeletal Muscle. **Neil Ruderman.** *Boston Univ. Sch. of Med.*

4:35 PM **12.5** Metabolic Inflexibility: Impact of Exercise. **Bret. H. Goodpaster.** *Univ. of Pittsburgh.*

Symposium IV

13.0 STEM CELLS AND NUCLEAR DOMAINS IN SKELETAL AND CARDIAC MUSCLE

Thurs., 3:00 - 5:00 PM, Danner Ballroom.

Chair: **Brenda Russell,** *Univ. of Illinois at Chicago.*

3:00 PM **13.1** Introduction. **Brenda Russell.** *Univ. of Illinois at Chicago.*

3:05 PM **13.2** Skeletal Muscle Stem Cells: Where They Come From and What They Do. **Charlotte A. Peterson.** *Univ. of Kentucky.*

3:35 PM **13.3** Role of ECM Environment in Regulating Satellite Cell Activation. **Ron Allen.** *Univ. of Arizona.*

4:05 PM **13.4** Stem Cells and Cardiac Repair. **Loren Field.** *Indiana Univ. Perdue Univ.*

4:35 PM **13.5** Delivery of proIGF-1: Effect on Myocytes and Stem Cells Following Myocardial Infarction. **Paul H. Goldspink.** *Univ. of Illinois at Chicago.*

FRIDAY, SEPTEMBER 26, 2008

Symposium V

14.0 SOMATIC AND SYMPATHETIC NEURAL CONTROL DURING EXERCISE

Fri., 8:30 - 11:00 AM, Calibogue Ballroom.

Chair: **Gail D. Thomas,** *Univ. of Texas Southwestern Med. Ctr.*

8:30 AM **14.1** Introduction. **Gail D. Thomas.** *Univ. of Texas Southwestern Med. Ctr.*

8:35 AM **14.2** Control of Motor Unit Activity During Voluntary Contraction. **Roger Enoka.** *Univ. of Colorado, Boulder.*

9:10 AM **14.3** Central Origins and Patterns of Sympathetic Discharge in Exercising Humans. **Paul J. Fadel.** *Univ. of Missouri, Columbia.*

9:45 AM **14.4** Skeletal Muscle Reflexes and the Cardiovascular Responses to Exercise. **Scott A. Smith.** *Univ. of Texas Southwestern Med. Ctr.*

10:20 AM **14.5** Interaction of Aging and Gender in Sympathetic Control of Skeletal Muscle Blood Flow. **David N. Proctor.** *Pennsylvania State Univ.*

Symposium VI

15.0 COMPARATIVE EXERCISE PHYSIOLOGY: LINKING ANIMAL LOCOMOTION TO HUMAN PERFORMANCE

Fri., 8:30 - 11:00 AM, Danner Ballroom.

Chair: **Peter J. Reiser.** *Ohio State Univ.*

8:30 AM **15.1** Introduction. **Peter J. Reiser.** *Ohio State Univ.*

8:35 AM **15.2** Metabolic Strategies for Sustained Endurance Exercise: Lessons from the Iditarod. **Michael S. Davis.** *Oklahoma State Univ.*

9:10 AM **15.3** Specializations of Muscle Serving High Performance Motor Functions in Horses. **John W. Hermanson.** *Cornell Univ.*

9:45 AM **15.4** Comparative Exercise Physiology and Neurobiology of Mice Selectively Bred for High Voluntary Locomotor Activity. **Theodore Garland, Jr.** *Univ. of California, Riverside.*

10:20 AM **15.5** Aerial Refueling in Nectarivorous Flying Animals: Mechanisms and Convergent Evolution. **Raul K. Suarez.** *Univ. of California, Santa Barbara.*

Poster Session

16.0 EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE

Fri., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

1 **16.1** Extracellular Matrix and Biomechanical Response of Rat Tendon to Mechanical Load Exercise and Nandrolone Decanoate. **R. Marqueti, O. H. P. Ramos, E. M. Oliveira, H. F. Carvalho, S. E. A. Perez and H. S. Selistre de Araujo.** *Fed. Univ. of São Carlos, Univ. of São Paulo and UNICAMP.*

2 **16.2** Muscle Contractile and Collagen Proteins Exert Different Sensitivity to Contractions and Nutrients. **L. Holm, G. van Hall, B. F. Miller, S. Dossing and M. Kjær.** *Bispebjerg Hosp., Rigshospitalet, Denmark, and Colorado State Univ.*

3 **16.3** Matrix Metalloproteinase-Expression in Human Skeletal Muscle in Response to Exercise. **E. Rullman, J. Norrbom, A. Stromberg, D. Wågsäter, H. Rundqvist, T. Haas and T. Gustafsson.** *Karolinska Univ. and York Univ.*

4 **16.4** Impact of Gender and Chronic Resistance Training on Human Patellar Tendon Dry Mass, Collagen Content, and Collagen Cross-linking. **J. LeMoine, J. Lee and T. A. Trappe.** *Ball State Univ.*

5 **16.5** Acetaminophen but not Ibuprofen Consumption During 12-weeks of Knee Extensor Resistance Training Alters *in vivo* Patellar Tendon Properties in Older Humans. **C. Carroll, J. Dickinson, J. LeMoine, J. Haus, E. Weinheimer, C. Hollon, P. Aagaard, S. Magnusson and T. A. Trappe.** *Ball State Univ., Univ. of Southern Denmark, and Univ. of Copenhagen.*

Poster Session

17.0 **GENDER DIFFERENCES**

Fri., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

6 **17.1** Restoration of Muscle Strength Following 3-weeks of Cast Immobilization in Suppressed in Women Compared to Men. **B. Clark, T. Manini, R. Hoffman and D. Russ.** *Ohio Univ. and Univ. of Florida, Gainesville.*

7 **17.2** The Anabolic Response to Exercise Training is Greater in Older Men than Older Women. **G. Smith, D. Villareal, D. Sinacore, K. Shah and B. Mittendorfer.** *Washington Univ.*

8 **17.3** Sprint Exercise and Muscle Growth in a Gender Perspective. **M. Esbjörnsson, H. Rundqvist, T. Österlund, H. Mascher, E. Blomstrand and E. Jansson.** *Karolinska Univ.*

9 **17.4** Peak Expiratory Flow in Young Athletes. **R. Petkowicz, F. Feijo, A. Rodrigues and R. Frias.** *Grêmio Náutico União, Port Alegre, Brazil.*

10 **17.5** Sex Differences in Exercise Training Responses to Acute Hyperglycemia and Isometric Handgrip. **T. Baynard, B. Fern-hall, R. Franklin, S. Goulopoulou, R. Carhart, Jr., R. Weinstock and J. Kanaley.** *Univ. of Illinois at Urbana-Champaign, Syracuse Univ. and SUNY Upstate.*

11 **17.6** Gender Differences in Muscle Efficiency During Short-Term Exercise. **N. Cassuto, E. Snyder, S. Lalande, T. Olson and B. Johnson.** *Univ. of Arizona and Mayo Clinic.*

12 **17.7** Sex Based Differences in Resting Skeletal Muscle Suggest Men and Women are Transcriptionally *Primed* for Known Physiological Differences in Metabolism. **A. Maher, M. Fu, R. Isfort, A. Varbanov, X. Qu and M. Tarnopolsky.** *McMaster Univ. and Procter and Gamble Pharmaceuticals.*

13 **17.8** Gender Differences in Maximal Motor Unit Firing Rates. **A. Christie and G. Kamen.** *Univ. of Massachusetts.*

Poster Session

18.0 **NEURAL CONTROL**

Fri., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

14 **18.1** Motoneuron Excitability Modulation During Passive Muscle Stretching; Comparing Between Two Electromyogram Methods. **H. Hadoush, Y. Tobimatsu, H. Maejima, A. Nagatomi, H. Kimura and Y. Ito.** *Hiroshima Univ. and Natl. Rehabilitation Ctr., Japan.*

15 **18.2** Effect of Gender on the Heart Rate Variability Response to Submaximal Exercise in Dogs with Healed Myocardial Infarction. **G. Billman.** *Ohio State Univ.*

16 **18.3** Oxidative Stress in Skeletal Muscle Sensitizes Mechanoreceptors in Heart Failure. **H-J. Wang, W-Z. Wang, L. Gao, I. H. Zucker and W. Wang.** *Univ. of Nebraska Med. Ctr.*

17 **18.4** Efficacy of High-pass Filtering of Surface Electromyogram for Assessing Force Fluctuations During Steady Contraction. **Y. Yoshitake and M. Shinohara.** *Oita Univ. of Nursing & Hlth. Sci., Japan, and Georgia Inst. of Tech.*

18 **18.5** Gadolinium-sensitve Mechanogated Channels Contribute to the Stimulation of Group III but not Group IV Afferents During Dynamic Exercise. **S. Hayes, J. McCord and M. Kaufman.** *Penn. State Univ., Hershey.*

19 **18.6** Acid Sensing Ion and Epithelial Sodium Channels do Not Contribute to the Mechanoreceptor Component of the Exercise Pressor Reflex. **J. McCord, S. Hayes and M. Kaufman.** *Penn. State Univ., Hershey.*

20 **18.7** Influence of Brain Dopamine on Thermorregulation and Running Performance in Rats. **C. Coimbra, C. Balthazar and L. Leite.** *Fed. Univ. of Minas Gerais-ICB, Brazil.*

21 **18.8** Effects of a Single Bout of Aerobic Exercise in the Sympathetic Nerve Activity of Pre-dialysis Chronic Kidney Disease Patients. **D. Bosco, B. Oneda, J. Gusmão, L. Riane, C. Forjaz, D. Mion, Jr. and T. Tinucci.** *Univ. of São Paulo, Brazil.*

22 **18.9** Both Central Command and Exercise Pressor Reflex Activate Cardiac Sympathetic Nerve Activity in Decerebrate Cats. **H. Tsuchimochi, S. Hayes, J. McCord and M. Kaufman.** *Penn. State Univ., Hershey.*

23 **18.10** Exercise Normalizes Enhanced Neuronal Excitability of Hypothalamic Preautonomic Neurons of Hypertensive Rats. **J. Stern, P. Sonner, F. Silva and L. Michelini.** *Med. Coll. of Georgia, and Univ. of São Paulo, Brazil.*

Board #

24 **18.11** Heightened Sympathetic Nerve Activity Increases Fluctuations in Motor Output. **S. Vohra, A. Johnson and M. Shinohara.** *Georgia Inst. of Tech.*

25 **18.12** The Effect of Contraction Mode and Intensity on Agonist/Antagonist Co-activation. **R. Polen, B. Byrd and D. Pincivero.** *Univ. of Toledo.*

26 **18.13** Spontaneous Physical Activity Triggers Neuroplasticity Events in Rat Spinal Cord. **M. Andrade, J. Pedroso and G. Chadi.** *Univ. of São Paulo.*

Poster Session

19.0 MUSCLE FUNCTION AND ADAPTATION I

Fri., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

27 **19.1** Hypertrophic Signaling in Isolated Mature Muscle Fibers Induced by IGF-1 but Not by High Linear Strain. **R. Jaspers, J, Testerink, R. Krishnan, C. Offringa, C. Bagowski and W. van der Laarse.** *VU Univ. of Amsterdam, Harvard Sch. of Public Hlth. and Univ. of Leiden, The Netherlands.*

28 **19.2** The Acute Effects of Heavy Resistance Exercise on the Local Inflammatory Response in Physically-Active, Post-Menopausal Women in the Absence of Hormone Replacement Therapy. **T. Buford, M. Cooke and D. Willoughby.** *Baylor Univ.*

29 **19.3** Age-Related Adaptation in Skeletal Muscle Characterized by Performance and Molecular Mechanisms. **B. Baker, J. Ensey, M. Kashon, M. Hollander and R. Cutlip.** *Natl. Inst. for Occupational Safety and Hlth., Morgantown.*

30 **19.4** Tissue Oxygenation of Limb and Respiratory Muscles During Progressive Inspiratory Loading. **W. D. Reid, B. Shadgan, J. A. Guenette and A. W. Sheel.** *Univ. of British Columbia.*

31 **19.5** Effect of Exercise on Protein Metabolism in the Muscle of Uremic Mice. **X. Wang.** *Emory Univ.*

32 **19.6** Changes in Basal and Inflammation-induced Hsp25 and αβ-crystallin in Mouse Skeletal Muscle Following Exercise Training. **K. Huey and B. Meador.** *Univ. of Illinois, Urbana.*

33 **19.7** Adaptation of the Rat's Soleus to Combined Aerobic Exercise Training and Heat Acclimation-Genomic Physiological Aspects. **E. Kodesh and M. Horowitz.** *Hebrew Univ.*

Board #

34 **19.8** Long Term Reliability of Muscle Function and Size in the Knee Extensors. **S. Cook and L. Ploutz-Snyder.** *Syracuse Univ.*

35 **19.9** Calcium Transients Contribute to the Contraction-induced Elevation of Heat Shock Protein 72 mRNA in Isolated Single Skeletal Muscle Fibers. **C. Stary, B. Walsh, A. Knapp, D. Brafman and M. Hogan.** *UCSD.*

36 **19.10** Low Glucose Enhances Oxidative Capacity of Rabbit Skeletal Muscle Cells in Culture. **N. Hanke, J. Meissner, R. Scheibe, V. Endeward, G. Gros and H-P. Kubis.** *Hannover Med. Sch. and Univ. of Wales.*

37 **19.11** Resveratrol Treatment in a Mouse Model of ALS. **C. D. Markert, D. Gifondorwa, C. Milligan and M. K. Childers.** *Wake Forest Univ.*

38 **19.12** Shift Towards Faster Gene Expression Pattern in Vastus Lateralis Muscle after Strength Training with Eccentric Overload in Athletes. **B. Friedmann-Bette, T. Bauer, R. Kinscherf, S. Vorwald, K. Klute, D. Bischoff, P. Baertsch and R. Billeter.** *Univ. Hosp. Heidelberg, Univ. of Heidelberg, and Univ. of Nottingham.*

39 **19.13** Nitric Oxide Synthase Inhibition Impairs Chronic Low-Frequency Stimulation-Induced Satellite Cell Activation and Prevents Skeletal Muscle Adaptation. **K. J. B. Martins, P. McDonald and C. T. Putman.** *Univ. of Alberta.*

40 **19.14** Chronic High Fat Feeding Attenuates the Surgically-induced Hypertrophy of Skeletal Muscle. **M. Sitnick, S. Bodine and J. C. Rutledge.** *Univ. of California, Davis.*

41 **19.15** Deletion of MuRF1 Results in Improved Fatigue Recovery in Skeletal Muscle. **S. Bodine and R. Carlsen.** *Univ. of California, Davis.*

42 **19.16** Carnosine Loading and Unloading in Human Skeletal Muscle. **A. Baguet, A. Pottier, I. Everaert, S. Callens, H. Reyngoudt, E. Achten and W. Derave.** *Univ. of Ghent, Belgium.*

43 **19.17** Mechanical Overload Induced Skeletal Muscle Plasticity in the Obese Zucker Rat. **C. E. Arnold, E. R. Blough, C. P. Ingalls, J. C. Rupp, S. Kakarla, A. Gutta and A. Doyle.** *Marshall Univ., and Georgia State Univ.*

Board #

44 **19.18** Effects of Hind Limb Ischemic Challenge on Vascular Responses in Low and High Capacity Endurance Running Rats. **E. Fontentot, C. Stang, S. Britton, L. Koch and R. Lust.** *East Carolina Univ. and Univ. of Michigan.*

45 **19.19** Effects of Hind Limb Ischemic Challenge on Fat Oxidation in Low and High Capacity Endurance Running Rats. **E. Fontentot, E. Granville, J. Price, T. Woodlief, S. Britton, L. Koch, R. Cortright and R. Lust.** *East Carolina Univ. and Univ. of Michigan.*

46 **19.20** The Role of Immune Cell Infiltration in Adaptation to Skeletal Muscle of Adult and Old Mice Following Exercise. **D. Harrison, F. McArdle, and A. McArdle.** *Univ. of Liverpool.*

47 **19.21** Trade-off Between Force and Speed in Mammalian Muscle Fibers. **P. Reiser and S. Bicer.** *Ohio State Univ.*

48 **19.22** Inhibiting Contraction Causes Temperature-Dependent Increase in Km and Vmax of ADP-Stimulated Mitochondrial Respiration in Permeabilized Skeletal Myofibers. **D. Kane, E. Anderson, C-T. Lin and P. D. Neufer.** *East Carolina Univ.*

49 **19.23** The Time Course of Muscle Hypertrophy, Strength, and Muscle Activation with Intense Eccentric Training. **J. Krentz and J. Farthing.** *Univ. of Saskatchewan.*

50 **19.24** Stress Responsive miR-23a Attenuates Skeletal Muscle Atrophy by Targeting MAFbx/Atrogin-1. **S. Wada, Y. Kato, M. Okutsu, S. Miyaki, K. Suzuki, H. Asahara, T. Ushida and T. Akimoto.** *Univ. of Tokyo, Natl. Inst. of Advanced Indust. Sci. and Tech., Duke NUS, Natl. Res. Inst. for Child Hlth. and Development and Waseda Univ., Japan.*

51 **19.25** Human Single Fiber Contractile Function Differs Between Vastus Lateralis and Soleus Muscles. **N. Luden, T. A. Trappe, K. Minchev, E. Hayes, E. Louis and S. Trappe.** *Ball State Univ.*

52 **19.26** Skeletal Muscle Mitochondrial Membrane Phospholipid Fatty Acid Composition. **L. Stefanyk, N. Coverdale, B. Roy, S. Peters and P. LeBlanc.** *Brock Univ., Ontario.*

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

53 **19.27** The PIF-pocket Domain of PDK1 is Required for Activation of S6K1 and S6 Following an Acute Bout of Resistance Exercise. **M. MacKenzie, L. Hamilton, J. Hickman, J. Bayascas and K. Baar.** *Univ. of Dundee and Univ. of Autònoma de Barcelona, Spain.*

54 **19.28** The Impact of ACTN3 Gene Polymorphism on Progression of Disease in Chronic Heart Failure. **B. Norman, C. Sylvén, B. Andersson and E. Jansson.** *Karolinska Univ., and Gothenburg Univ.*

55 **19.29** Increased Fiber Size and Intramyocellular Lipid Accumulation in Skeletal Muscles of Ossabaw Miniature Swine with Metabolic Syndrome. **T. Kostrominova, B. Clark, D. del Rosario, M. Alloosh, J. Wenzel and M. Sturek.** *Indiana Univ. Sch. of Med.*

56 **19.30** No Association Between ACTN3-genotype and Muscle Fibre Type Composition in Non-athletes. **H. Rundqvist, M. Esbjörnsson and B. Norman.** *Karolinska Univ.*

57 **19.31** Inhibition of C2C12 Cell Differentiation in the Presence of a Sulfated Polysaccharide. **K. Ball and B. Smith.** *Alma Col.*

58 **19.32** Pyruvate-induced Shift Towards Lipid Metabolism in C2C12 Myotubes. **A. Philp, J. Perez, K. Brogan and K. Baar.** *Univ. of Dundee.*

59 **19.33** Training Increases Skeletal Muscle Fatty Acid Transport Proteins on the Sarcolemma and Mitochondria in Women. **J. Talanian, L. Snook, G. Heigenhauser, A. Bonen and L. Spriet.** *Univ. of Guelph and McMaster Univ.*

60 **19.34** The Effect of Short Term Training on Vascular Endothelial Growth Factor Expressions in Red and White Gastrocnemius Muscles. **D. Tekin, A. D. Dursun and H. Ficicilar.** *Ankara Univ., Turkey.*

61 **19.35** Voluntary Wheel Running Attenuates Cancer Cachexia. **G. Diffee, D. McCarthy and H. Piepmeyer.** *Univ. of Wisconsin, Madison and Ohio State Univ.*

62 **19.36** Myostatin Knockout Mice Respond Normally To Endurance Training But have Lower Exercise Capacity. **K. Savage, J. Portas and A. McPherron.** *NIDDK, NIH.*

Board #

63 **19.37** Evidence for High Fat Diet Induced Peroxisomal Activity in Skeletal Muscle from Low and High Capacity Endurance Running Rats. **R. Cortright, R. Noland, T. Woodlief, H-B. Kwak, J. Price, S. Britton, L. Koch and R. Lust.** *East Carolina Univ. and Univ. of Michigan.*

64 **19.38** Withdrawn.

64A **19.39** HIF-1 Specific Prolyl Hydroxylases in Elite Athletes. **C. Sundberg, M. Klintberg, J. Norrbom, T. Gustafsson and H. Rundqvist.** *Karolinska Inst.*

Poster Session

20.0 COMPARATIVE PHYSIOLOGY

Fri., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

65 **20.1** Muscle Fiber Types in Ghost Crabs: Implications for Running Performance. **S. Medler.** *Univ. of Buffalo.*

66 **20.2** Malignant Hyperthermia in Kansas City 1965-1985. **M. G. Zukaitis, G. P. Hoech, Jr. (ret.), J. D. Robison and C. H. Williams (ret.).** *Private Practice, Gastonia, NC, and Shawnee Mission Med. Ctr.*

67 **20.3** Incidence of Malignant Hyperthermia in Greater Kansas City 1996-2006. **C. H. Williams and G. P. Hoech, Jr. (ret.).** *Sunrise Beach, MO, and Kansas City.*

68 **20.4** Comparison of Maximal Aerobic Speed and Physiological Transition Thresholds Assessed in Laboratory and Field Conditions in Endurance Runners. **G. Vieira, K. Souza, M. Baldi, L. Guglielmo and F. De Oliveira.** *Fed. Univ. of Santa Catarina and Fed. Univ. of Lavras, Brazil.*

69 **20.5** Cardiac Function During Exercise and Temperature Change: Matching Metabolic Rates to Separate Increased Oxygen Consumption VS Physical Affects Using a Poikilothermic Model. **C. Reiber.** *Univ. of Nevada.*

70 **20.6** Single Muscle Fiber Contractile Function of the Black Bear. **E. Hayes, K. Minchev, D. Riley, V. Vogel, M. Gappa, B. Kohn, D. Costill and S. Trappe.** *Ball State Univ., Med. Col. of Wisconsin, Wildlife Re-Creations and Wisconsin DNR.*

71 **20.7** Aplasticity of Skeletal Muscle in *Varanus exanthematicus* Following Compensatory Overload. **A. Szucsik, B. Rourke and J. Hicks.** *Univ. of California, Irvine.*

Poster Session

21.0 OXIDANT/ANTIOXIDANT EFFECTS

Fri., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

72 **21.1** Oxidant/Antioxidant and Metabolic Response in Mice During a Long Duration Swim. **A. Kormanovski, E. Lara-Padilla, F. Santana and B. Gutierrez.** *Escuela Superior de Medicina, Mexico.*

73 **21.2** Effects of Antioxidant Supplementation and Exercise Training on Skeletal Muscle Antioxidant Enzymes and Mitochondrial Biogenesis. **N. A. Strobel, J. M. Peake, A. Matsumoto, S. A. Marsh, J. S. Coombes and G. D. Wadley.** *Univ. of Queensland, Univ. of Alabama at Birmingham, and Univ. of Melbourne.*

74 **21.3** Antioxidant Supplementation Enhances Muscle Recovery from Contusion Injury in Rats. **M. Kruger, C. Smith, R. Smith, K. H. Myburgh.** *Stellenbosch Univ., South Africa.*

75 **21.4** Oxidative Stress and Antioxidant Mechanisms at the Transition to an Aerobically Intensive Lifestyle in Honey Bees **S. Roberts, J. Williams and M. Elekonich.** *Univ. of Nevada.*

76 **21.5** Weekly Heat Therapy Restores Glucose Uptake in Insulin-resistant Skeletal Muscle: Role of Heat Shock Proteins and Stress Kinases. **A. A. Gupte, G. L. Bomhoff and P. C. Geiger.** *Univ. of Kansas Med. Ctr.*

77 **21.6** High Fat Diet Influences CNS Oxidative Capacity and Decreases Striatal Dopamine Turnover: Implications for Diabetes and Parkinson's Disease. **J. K. Morris, A. A. Gupte, G. L. Bomhoff, J. A. Stanford and P. C. Geiger.** *Univ. of Kansas Med. Ctr.*

78 **21.7** Uncoupling Protein-3 Inversely Correlates with Anaerobic Threshold in Fit Young Men. **L. Edwards, N. Knight, C. Holloway, P. Robbins and K. Clarke.** *Univ. of Oxford.*

Poster Session

22.0 CHO/LIPID METABOLISM

Fri., 11:00 AM - 3:00 PM Archer/Barnwell Ballroom.

Board #

79 **22.1** Substrate Oxidation During 5h of Treadmill Walking with Ingestion of 13C-labelled Starch. **J. Tremblay, F. Péronnet, D. Massicotte and C. Lavoie.** *Univ. of Montréal, Univ. of Québec at Montréal and Univ. of Québec at Trois-Riviéres.*

80 **22.2** Evidence for the Mitochondrial Lactate Oxidation Complex in Rat Neurons: Crucial Component for a Brain Lactate Shuttle. **G. Brooks, T. Hashimoto, R. Hussien, H-S. Cho and D. Kaufer.** *Univ. of California, Berkeley.*

Board #

81 **22.3** Can the Addition of L-Arginine or L-Glutamine to Exercise Energy-hydration Beverages Facilitate Glucose and Fluid Delivery? **D. Rowlands, M. Thorburn, R. Thorp and J. Clarke.** *Massey Univ., New Zealand.*

82 **22.4** Even in Athletes, Exercise does not Increase 24 h Fat Oxidation. **E. Melanson, W. Gonzansky, D. Barry, P. MacLean and J. Hill.** *Univ. of Colorado, Denver.*

83 **22.5** Skeletal Muscle Mitochondrial Oxidative Capacity and Metabolic Responses to a High Fat Diet or Aging in Rats Bred for High and Low Aerobic Capacity. **S. Borengasser, S. Naples, R. S. Rector, C. Mikus, G. Uptergrove, E. M. Morris, L. Koch, S. Britton, J. Ibdah and J. Thyfault.** *Univ. of Missouri, Columbia.*

84 **22.6** Evidence for the Involvement of CaMKKβ in the Regulation of Glucose Uptake in Perfused Rat Muscle. **M. J. Abbott and L. P. Turcotte.** *Univ. of Southern California.*

85 **22.7** Nitric Oxide and ROS Regulate Skeletal Muscle Glucose Uptake During Contraction Independent of AMPK α2. **T. Merry, G. Steinberg, G. Lynch and G. McConell.** *Univ. of Melbourne.*

86 **22.8** The Effects of Endogenous and Exogenous Carbohydrate Availability on Training-induced Oxidative Enzyme Adaptation of Human Skeletal Muscle. **B. Drust, M. James, L. Croft, B. Jonathan, D. MacLaren, A. McArdle and T. Reilly.** *Liverpool John Moores Univ. and Univ. of Liverpool.*

87 **22.9** Developmental Changes of MCTs in Thoroughbreds. **Y. Kitaoka, D. Hoshino, K. Mukai, A. Hiraga and H. Hatta.** *Univ. of Tokyo, and Japan Racing Assn.*

88 **22.10** Subcellular Localization of Muscle Glycogen–Fiber-to-fiber Heterogeneity and Effect of Fasting. **J. Nielsen, H. D. Schrøder and N. Ørtenblad.** *Univ. of Southern Denmark.*

89 **22.11** Role of Local Muscle Contractile Activity in the Exercise-induced Increase in NR4A Receptors mRNA Expression. **E. Kawasaki, F. Hokari, M. Sasaki, A. Sakai, K. Koshinaka and K. Kawasaki.** *Niigata Univ. of Hlth. and Welfare, Japan.*

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

90 **22.12** Hyperglycemia During Maximal Exercise Occurs in Trained, but is Prevented in Untrained Individuals by the Direct Effect of Insulin on Liver. **C. Yeckel, M. Gosselin, B. Gulanski, R. McCrimmon and R. Sherwin.** *John B. Pierce Lab. and Yale Med. Sch.*

91 **22.13** Post-game Cycling does not Enhance Blood Lactate Removal in Collegiate Hockey Players. **J. Durocher, D. Bustos, C. Schwartz and J. Carter.** *Michigan Tech. Univ.*

92 **22.14** Ceramide Content in Human Muscle Fibers. **J. Helge, P. Nordby, D. Kristensen, K. Ekroos, F. Dela and C. Prats.** *Univ. of Copenhagen and Astra Zeneca R&D, Mölndal.*

93 **22.15** Evidence for Metabolic Inflexibility in Response to Dietary Lipid with Obesity. **K. Boyle, J. Canham, L. Consitt, D. Zheng and J. Houmard.** *East Carolina Univ.*

94 **22.16** Estrogen Receptor alpha: A Potential Player in Glucose Regulation. **B. Gorres, G. L. Bomhoff, A. A. Gupte and P. C. Geiger.** *Univ. of Kansas Med. Ctr.*

95 **22.17** Dehydration Elevates Muscle Temperature During Exercise and Muscle Glycogenolysis. **E. Coyle.** *Univ. of Texas at Austin.*

96 **22.18** Metabolic and Cardiovascular Responses to the Ingestion of Fructose. **A. J. Bidwell, M. E. Holmstrup, R. P. Doyle and T. J. Fairchild.** *Syracuse Univ.*

97 **22.19** The Effects of Oral Acetate Supplementation After Prolonged Moderate Intensity on Acetate Metabolism and Muscle Glycogen Resynthesis in Horses. **A. Waller, R. Geor and M. Lindinger.** *Univ. of Guelph and Michigan State Univ.*

98 **22.20** Fluid and Electrolyte Supplementation After Prolonged Moderate Intensity Exercise Enhances Muscle Glycogen Resynthesis in Standardbred Horses. **A. Waller and M. Lindinger.** *Univ. of Guelph.*

99 **22.21** Reducing Dietary Fat from Meals After Exercise Enhances Muscle Glycogen Resynthesis in Unfit Adults. **S. Newsom, K. Thomas, S. Schenk, M. Harber, N. Smith, N. Goldenberg and J. Horowitz.** *Univ. of Michigan.*

Board #

100 **22.22** Insulin Sensitivity Increases in Lean but Not Obese Young Women After 7 Weeks of Progressive Resistance Training. **K. Hinnerichs, B. Echtenkamp, S. Malin, T. Evetovich, D. Conley, B. Braun and B. Engebretsen.** *Wayne State Col.*

101 **22.23** Metformin Treatment Decreases Fat Utilization After Exercise. **S. Malin, B. Stephens, C. Sharoff, S. Chipkin and B. Braun.** *Univ. of Massachusetts.*

102 **22.24** Stride Length does not Influence Substrate Oxidation During Walking with Altered Kinematics in Obese Women. **E. Russell, B. Braun and J. Hamill.** *Univ. of Massachusetts.*

103 **22.25** Alterations in Lipid Metabolism After One Day of Overeating are Reversed by a Single Session of Exercise. **A. Cornford, M. Li, S. Schenk, M. Harber and J. Horowitz.** *Univ.of Michigan.*

Poster Session

23.0 REGENERATION

Fri., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

104 **23.1** Effects of Unloading on Protein Expression During the Regeneration of Injured Soleus Muscle of Mice. **K. Goto, Y. Matsuba, Y. Ohno, T. Sugiura, N. Hashimoto, Y. Ohira and T, Yoshioka.** *Toyohashi Sozo Univ., St. Marianna Univ. Sch. of Med. Yamaguchi Univ., Natl. Inst for Longevity Sci., Osaka Univ. and Hirosaki Gakuin Univ., Japan.*

105 **23.2** Intense Training and Physical Exercise does not Modify Human Skeletal Muscle Regeneration. **G. Butler-Browne, V. Renault, A. Klein, V. Mouly and L-E. Thornell.** *UPMC, Inserm, Paris, France, and Univ. of Umeå.*

106 **23.3** Notch and Wnt Temporal Relationship Following Downhill Running. **S. Tsivitse, M. Peters, A. Stoy, G. Hixenbaugh and E. Bergman.** *Univ. of North Carolina, Charlotte.*

107 **23.4** The Impaired Inflammatory Response to Muscle Damage Contributes to the Impaired Muscle Regenerative Capacity and to Increased Muscle Adiposity with Aging. **S. Machida and T. Okamoto.** *Tokai Univ., Kanagawa and Waseda Univ.*

108 **23.5** Treadmill Training Enhances Axon Regeneration in Cut Peripheral Nerves without Affecting Topographic Specificity of Reinnervating Motoneurons. **M. Sabatier, M. Kaufman, D. Cucoranu, A. Mulligan and A. English.** *Emory Univ.*

Board #

109 **23.6** Vasculogenesis, an Exercise-induced Process? **A. Strömberg, E. Rullman, E. Jansson and T. Gustafsson.** *Karolinska Univ.*

110 **23.7** Withdrawn.

111 **23.8** Swimming Exercise Reverses Tactile Stimulus-induced Hypersensitivity Following Peripheral Nerve Injury. **M. Benedetti, R. Merino, S. Zanon, G. Lucas, R. Maia and G. Silva.** *Univ. of São Paulo.*

112 **23.9** Simvastatin Reduces Human Primary Satellite Cell Proliferation in Culture. **A. Thalacker-Mercer, M. Baker, C. Calderon and M. Bamman.** *Univ. of Alabama at Birmingham.*

113 **23.10** O-linked-Beta-N-acetylglucosamine Modification Affects C2C12 Cell Cycle Regulation and Differentiation. **C. Calderon, A. Thalacker-Mercer, M. Baker, D. Mayhew and M. Bamman.** *Univ. of Alabama at Birmingham.*

Don't forget…..
Pick up your Banquet Ticket by 10:00 AM on Thursday

This banquet is free but you MUST have a ticket for entry

Symposium VII

24.0 REACTIVE OXYGEN SPECIES: CONSEQUENCES ON CELLULAR METABOLISM

Fri., 3:00 - 5:00 PM, Calibogue Ballroom.

Chair: **Michael B. Reid,** *Univ. of Kentucky Med. Ctr.*

3:00 PM **24.1** Introduction. **Michael B. Reid.** *Univ. of Kentucky Med. Ctr.*

3:05 PM **24.2** Disruption of Mitochondrial Redox Circuitry in Oxidative Stress. **Dean P. Jones.** *Emory Univ. Sch. of Med.*

3:35 PM **24.3** Linking Mitochondrial ROS to Insulin Resistance. **P. Darrell Neufer.** *East Carolina Univ. Sch. of Med.*

4:05 PM **24.4** How Does Exercise Affect ROS and RNS in Skeletal Muscle? **Malcolm Jackson.** *Univ. of Liverpool.*

4:35 PM **24.5** Exercise Training and Antioxidant Therapy as Treatment of Insulin Resistance and Type II Diabetes. **Erik J. Henriksen,** *Univ. of Arizona.*

Symposium VIII

25.0 **REMODELING OF THE EXTRACELLULAR MATRIX OF TENDON AND SKELETAL MUSCLE IN RESPONSE TO EXERCISE**
Fri., 3:00 - 5:00 PM, Danner Ballroom.

Chair: **Benjamin F. Miller,** *Colorado State Univ.*

3:00 PM **25.1** Introduction. **Benjamin F. Miller.** *Colorado State Univ.*

3:05 PM **25.2** Extracellular Matrix Adaptation of Tendon and Skeletal Muscle to Exercise. **Michael Kjaer.** *Univ. of Copenhangen.*

3:35 PM **25.3** Effects of Muscle Disuse on Tendon and Muscle Extracellular Matrix Collagen Expression. **Keith Baar.** *Univ. of Dundee.*

4:05 PM **25.4** Role of the Matrix Metalloproteinases in Exercise-induced Muscle Damage, Repair and Hypertrophy. **David L. Allen.** *Univ. of Colorado, Boulder.*

4:35 PM **25.5** Influence of Aging, Unloading, Exercise, and Gender on the Extracellular Matrix in Skeletal Muscle and Tendon of Humans. **Todd A. Trappe.** *Ball State Univ.*

APS Education Session

WRITING YOUR FIRST PAPER: THE *INS* AND *OUTS* OF AUTHORSHIP
Fri., 5:30 - 6:30 PM, Calibogue Ballroom.

Presented by **Michael Strurek.** *Indiana Univ. Sch. of Med.*

Ancillary Session

NSBRI RESEARCH INFORMATION FORUM
Fri., 5:30 - 6:30 PM, Danner Ballroom.

Presented by **Susan Bloomfield,** *NSBRI Musculoskeletal Alterations Team Associate Leader, and* **Greg R. Adams,** *NSBRI funded Investigator.*

SATURDAY, SEPTEMBER 27, 2008

Symposium IX

26.0 **SIGNALING MECHANISMS REGULATING METABOLIC AND TRANSCIPTION PROCESSES IN SKELETAL MUSCLE**
Sat., 8:30 - 11:00 AM, Calibogue Ballroom.

Chair: **Eva R. Chin,** *Univ. of Maryland.*

8:30 AM **26.1** Introduction. **Eva R. Chin.** *Univ. of Maryland.*

8:35 AM **26.2** Signaling Machanisms Mediating Lipid Metabolism. **Debra M. Muoio.** *Duke Univ. Med. Ctr.*

9:10 AM **26.3** Signals Controlling Glucose Transport in Contracting Muscle. **Laurie J. Goodyear.** *Harvard Med. Ctr.*

9:45 AM **26.4** Molecular Signaling Mechanisms Leading to Exercise-induced Changes in Transcription. **Mark Hargreaves.** *Univ. of Melbourne.*

10:20 AM **26.5** Signaling Mechanisms Controlling Post-exercise Insulin Sensitivity in Contracting Human Skeletal Muscle. **Jorgen Wojtaszewski.** *Univ. of Copenhagen.*

Symposium X

27.0 **ROLES OF BIOMECHANNICAL SIGNALING IN CARDIAC AND SKELETAL MUSCLE**
Sat., 8:30 - 11:00 AM, Danner Ballroom.

Chairs: **Tara Haas,** *York Univ. and* **Ronald L. Terjung,** *Univ. of Missouri, Columbia.*

8:30 AM **27.1** Introduction. **Tara Haas.** *York Univ.*

8:35 AM **27.2** Deciphering the Mechanisms of Actin Filament Architecture in Cardiac Myocytes. **Carol Gregorio.** *Univ. of Arizona.*

9:10 AM **27.3** Mechano-sensing from within the Z-disc of Cardiac Myocytes. **Samuel Boateng.** *Univ. of Illinois, Chicago.*

9:45 AM **27.4** Mechanical Regulation of Stem Cells. **Song Li.** *Univ. of California, Berkeley.*

10:20 AM **27.5** At the Interface Between Blood and Myofibers: Divergent Biomechanical Signal Pathways in Endothelial Cells. **Tara Haas.** *York Univ.*

Poster Session

28.0 **SIGNALING**
Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

1 **28.1** The Role of PI3K/PKB and Phosphatidic Acid in the Activation of mTOR Signaling Following Resistance Exercise. **T. Hornberger and Tyriina O'Neil.** *Univ. Wisconsin, Madison.*

2 **28.2** Higher Leucine Content in an Essential Amino Acid Solution Enhances mTOR Signaling in Human Skeletal Muscle. **E. L. Glynn, C. S. Fry, M. J. Drummond, S. Dhanani, K. L. Timmerman, E. Volpi and B. B. Rasmussen.** *Univ. of Texas Med. Branch.*

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

3 **28.3** Exercise Training does not Reverse and Even Promotes the Unfolded Protein Response Induced by a High-fat Diet in Mice Skeletal Muscle. **L. Deldicque, P. D. Cani, J-M. Raymackers, N. M. Delzenne and M. Francaux.** *Univ. Catholic of Louvain, Belgium.*

4 **28.4** Neuregulin Signaling in Skeletal Muscle Following Denervation-induced Inactivity. **N. Hellyer, H. Argadine, C. Mantilla, W-Z. Zhan and G. Sieck.** *Mayo Clinic.*

5 **28.5** Rapamycin Prevents the Post-exercise Increase in Protein Synthesis in Human Skeletal Muscle. **M. Drummond, C. Fry, E. Glynn, H. Dreyer, S. Dhanani, K. Timmerman, E. Volpi and B. Rasmussen.** *Univ. of Texas Med. Branch.*

6 **28.6** Characterization of Oxidative Capacity in Primary Human Skeletal Muscle Cells: A Sststem for Studying Metabolic Disease. **J. Schaefer, M. Banker, J. Hadcock and Y. Will.** *Pfizer Gobal R&D.*

7 **28.7** The Impact of Ovarian Hormone Status on Functional and Cellular Characteristics of Skeletal Muscle. **L. Wohlers, S. Sweeney, R. Lovering, C. Ward and E. Spangenburg.** *Univ. of Maryland, College Park and Baltimore.*

8 **28.8** Hsp27 Overexpression is Sufficient to Inhibit NF-κB Activation During Skeletal Muscle Disuse. **B. Hain, S. Dodd and A. Judge.** *Univ. of Florida, Gainesville.*

9 **28.9** Hsp70 Inhibits Foxo3a-dependent Transcription of Atrophy Genes in Skeletal Muscle. **S. Senf, S. Dodd, B. Gagnon and A. Judge.** *Univ. of Florida, Gainesville.*

10 **28.10** Caffeine Activates p38 MAPK via a Ca^{2+} Independent Pathway. **T. Kohn and E. Ojuka.** *Univ. of Cape Town.*

11 **28.11** Glucocorticoids Activate Ubiquitin Transcription in Muscle By Suppressing PI3-Kinase: Implications for Muscle Atrophy. **R. Price and B. Zheng.** *Emory Univ.*

12 **28.12** Alterations in Akt-FOXO3a Signaling Before and After 12 Weeks of Resistance Exercise in Young (24 yr) and Old Women (85 yr). **D. Williamson, U. Raue and S. Trappe.** *Ball State Univ.*

13 **28.13** FoxO1 Inhibits Skeletal Muscle Hypertrophy. **A. D. DeLong, Z. Brinkman, B. Renwand, S. Smith, Y. Kamei, S. Muira, O. Ezaki and T. J. McLoughlin.** *Univ. of Toledo, Tokyo Med. & Dental Univ. and NIHN, Tokyo.*

Board #

14 **28.14** Endurance Training, Independent of Weight Loss, Improves Mitochondrial Oxidative Capacity and Enhances Insulin Signal Transduction in Lean and Obese Men. **I. A. Samjoo, M. J. Hamadeh and M. A. Tarnopolsky.** *McMaster Univ., and York Univ.*

15 **28.15** RhoA Regulation is Transcriptionally Active in Skeletal Muscle Following Acute Eccentric Exercise. **L. MacNeil, S. Melov, A. Hubbard, S. K. Baker and M. A. Tarnopolsky.** *McMaster Univ., Buck Inst. for Age Res., Novato, CA, Univ. of California, Berkeley.*

16 **28.16** Multiple Signaling Pathways Regulate the Contractile Activity-mediated Induction of PGC-1α Transcription in Skeletal Muscle Cells. **V. Ljubicic, I. Irrcher, K. Singh and D. A. Hood.** *York Univ.*

17 **28.17** MARK4 Is A Novel CaMKKα- and Contraction-Regulated Kinase in Mouse Skeletal Muscle. **C. Witczak, T. Toyoda, K. Rockl, M. Hirshman, H-J. Koh and L. Goodyear.** *Joslin Diabetes Ctr.*

18 **28.18** Time Course and Dose Responses of Myofibrillar Protein Synthesis and Intracellular Signalling to Resistance Exercise Between 20 and 90% 1 Repetition Maximum in Young and Elderly Men in the Post-absorptive State. **V. Kumar, P. Atherton, A. Selby, R. Patel, D. Rankin, J. Williams, W. Hildebrandt, K. Smith and M. Rennie.** *Univ. of Nottingham and Derby Natl. Hlth. Service Trust.*

19 **28.19** p70S6k Signaling Induces eIF2B-epsilon Protein Expression in Response to Mechanical Load. **D. Mayhew and M. Bamman.** *Univ. of Alabama at Birmingham.*

20 **28.29** The Effect of Heat Shock on Acute Hypertrophic Signaling Following Skeletal Muscle Damage. **C. Touchberry, A. A. Gupte, G. L. Bomhoff, P. C. Geiger and P. Gallagher.** *Univ. of Kansas.*

Poster Session

29.0 FATIGUE

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

21 **29.1** Immobilization-induced Increases in Fatigue Resistance is not Explained by Changes in the Muscle Metaboreflex. **B. Clark, R. Hoffman and D. Russ.** *Ohio Univ.*

Board #

22 **29.2** Relationship Between Mood Profiles and Plasma Tryptophan Ratio During the Competition Period in Elite Female Wrestler. **T. Murakami, R. Sakamoto, S. Sugiyama, K. Sakae, A. Kitagawa, T. Higuchi, K. Hamada and S. Mori.** *Chukyo Women's Univ. and Otsuka Pharmaceutical Co. Ltd., Japan.*

23 **29.3** Glycogen has a Structural Role in Maintaining Normal EC Coupling in Elite Cross Country Skiers, by Modulating SR $Ca2^{+}$ Release Rate. **N. Ortenblad, J. Nielsen, B. Saltin and H-C. Holmberg.** *Univ. of Southern Denmark, The Copenhagen Muscle Res. Ctr. and Mid Sweden Univ.*

24 **29.4** Fatigue Alters *in vivo* Function Within and Between Limb Muscles During Running. **T. Higham and A. Biewener.** *Harvard Univ.*

25 **29.5** Fatigue in a Hill-based Muscle Model of Human Tibialis Anterior. **R. Miller, G. Caldwell and J. Kent-Braun.** *Univ. of Massachusetts.*

Poster Session

30.0 MECHANOTRANSDUCTION

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

26 **30.1** Fundamental Characteristics of the Mechano-Sensing Machinery in Skeletal Muscle. **T. Hornberger, J. Frey, E. Farley and T. O'Neil.** *Univ. of Wisconsin, Madison.*

27 **30.2** Costameres are Nodal Points of Myofibre Differentiation and Force Transmission *in vivo*. **M. Flueck, A-C. Durieux, G. D'Antona, R. Bottinelli, D. Desplanches, D. Freyssenet and M-N. Giraud.** *Manchester Metro. Univ., Univ. of Berne, Univ. of Pavia, Univ. of Lyon, Univ. Jean Monnet, St. Etienne and Univ. Hosp. of Berne.*

28 **30.3** Depolarization of Muscle Cells Following Eccentric Contractions can be Reversed. **T. McBride and E. Spangenburg.** *California State Univ. and Univ. of Maryland, College Park.*

Poster Session

31.0 GENOMICS/PROTEOMICS

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

29 **31.1** FTO Genotype is Associated with Exercise Training-induced Change in Adiposity: The HERITAGE Family Study. **T. Rankinen, T. Rice, M. Teran-Garcia, D. C. Rao and C. Bouchard.** *Pennington Biomed. Res. Ctr. and Washington Univ. Sch. of Med.*

Board #

30 **31.2** Mechanisms of Decreased Fatty Acid Oxidation in Skeletal Muscle of Morbidly Obese Individuals. **M. Hubal, J. Berggren, E. Hoffman and J. Houmard.** *Children's Natl. Med. Ctr., Washington, DC. and East Carolina Univ.*

31 **31.3** Phosphorylation of Heat Shock Protein 20 at Serine 16 is Induced in the Rat Heart in Response to Endurance Exercise. **J. Burniston.** *Liverpool John Moores Univ.*

32 **31.4** Proteomic Identification of Sex-specific Differences in Muscle Heat Shock Protein Expression in Response to Interval Training. **J. Burniston, K. Holloway, T. Cable and D. Goldspink.** *Liverpool John Moores Univ.*

33 **31.5** Skeletal Muscle Capillarity and Exercise Capacity is Increased in Thrombospondin-1 Knock-out Mice. **M. Olfert and M. Malek.** *UCSD.*

34 **31.6** Relationships Between Changes in Circulating Metabolic Intermediates and Insulin Sensitivity with Six Months of Aerobic Exercise Training or Inactivity. **K. Huffman, C. Slentz, S. Shah, R. Stevens, J. Bain, M. Muehlbauer, C. Tanner, M. Kuchibhatla, J. Houmard and W. Kraus.** *Duke Univ. Med. Ctr. and East Carolina Univ.*

35 **31.7** Analysis of the Effect of High Protein-carbohydrate Nutrition on Global mRNA Expression in Skeletal Muscle During Recovery from High-intensity Endurance Exercise. **D. Rowlands, J. Thomson, B. Timmons, F. Raymond, R. Mansourian, S. Metairon, A. Fuerholz, T. Stellingwerff and M. A. Tarnopolsky.** *Massey Univ., New Zealand, McMaster Univ and Nestle Res. Ctr., Lusanne.*

36 **31.8** Does DNA Methylation of the Myosin Heavy Chain IIb Gene Promoter Reguate Expression During Skeletal Muscle Differentiation? **A. Ludlow, M. Auriemma, P. Nadendla, K. Y. Ngai, E. Spangenberg and S. Roth.** *Univ. of Maryland, College Park.*

37 **31.9** miRNA-mediated Regulation of Metabolic Control and Muscle Differentiation Following Acute Endurance Exercise. **A. Safdar, M. Akhtar, B. Hettinga and M. A. Tarnopolsky.** *McMaster Univ.*

Don't forget to visit the exhibits from 11:00 AM – 3:00 PM

Board #

38 **31.10** Effects of Dietary Folate Intake and Physical Activity on the Interaction Between the Plasma Homocysteine and MTHFR Genotype. **H. Murakami, M. Iemitsu, K. Yamamoto, H. Kawano, Y. Gando, Y. Omori, K. Sanada and M. Miyachi.** *Natl. Inst. For Hlth and Nutrition, Tokyo, Internatl. Pacific Univ. and Waseda Univ.*

39 **31.11** Plasma Metabolic Profiling of Acute Exercise in Humans. **G. D. Lewis, M. E. Martinovic, L. A. Farrell, A. Asnani, X. Shi, S. A. Carr and R. E. Gerszten.** *Massachusetts Gen. Hosp.*

40 **31.12** The Arg16Gly Polymorphism of the Beta-2 Adrenergic Receptor and Muscular Efficiency During Exercise. **N. Cassuto, S. Lalande, T. Olson, B. Johnson and E. Snyder.** *Univ. of Arizona and Mayo Clinic.*

41 **31.13** Exercise Proteomics: Alterations in the Human Vastus Lateralis Muscle Proteome After Eccentric Exercise. **C. Malm and L. Frängsmyr.** *Umeå Univ.*

Poster Session

32.0 MOLECULAR REGULATORY MECHANISMS

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

42 **32.1** CAMK Activation by Caffeine Increases NRF-1 Binding to the mef2a Promoter and the Expression of both MEF2A and GLUT4 in C2C12 Myotubes. **E. Mukwevho and E. Ojuka.** *Univ. of Cape Town.*

43 **32.2** Functional Interaction of Regulatory Factors with the Pgc-1α Promoter in Response to Exercise by *in vivo* Imaging. **T. Akimoto, P. Li and Z. Yan.** *Univ. of Tokyo and Duke Univ. Med. Ctr.*

44 **32.3** Endurance Exercise Affects Transcription of Ubiquitin Proteasome Pathway Components. **M. Urso, J. McClung, H. McClung, G. Cloutier, R. Fielding, M. Pikosky and A. Young.** *USARIEM, Natick, Tufts Univ. and Natl. Dairy Council, Rosemont, Il.*

45 **32.4** Apoptosis Resistance of Differentiated Myotubes is Associated with Enhanced Anti-death Mechanisms. **R. Xiao and E. Dupont-Versteegden.** *Univ. of Kentucky.*

46 **32.5** High Active C57L/J Mice have Different Dopaminergic Profiles Compared to Low Active C3H/HeJ Mice. **A. Knab, R. Bowen, A. Hamilton, A. Gulldge and J. T. Lightfoot.** *Univ. of North Carolina, Charlotte.*

Board #

47 **32.6** Rapid Increases in Skeletal Muscle PGC-1α and PPAR Contents Precede Increases in Mitochondrial Enzymes During High-intensity Interval Training in Men. **C. G. R. Perry, G. P. Hollaway, G. J. F. Heigenhauser, A. Bonen and L. L. Spriet.** *Univ. of Guelph and McMaster Univ.*

48 **32.7** Tumor Suppressor p53 Determines Aerobic Exercise Capacity. **J. Y. Park, T. Matsumoto, H. J. Sung, J. W. Choi, W. Ma, J-G. Kang and P. M. Hwang.** *NHLBI, NIH.*

49 **32.8** Activity of the Antisense Beta Myosin Heavy Chain Gene Promoter Depends on the NF1/CTF1 Binding Site in Rat Hearts. **J. Giger, F. Haddad, P. Bodell and K. Baldwin.** *Univ. of California, Irvine.*

50 **32.9** Possible Involvement of Lipin-1 in Mitochondrial Enzyme Adaptations to Endurance Exercise in Rat Skeletal Muscle. **K. Higashida, M. Higuchi and S. Terada.** *Waseda Univ., Japan.*

51 **32.10** Exercise Induces Hyperacetylation of Histones at the MEF2 Binding Site on the glut4 Promoter by a CaMK-dependent Mechanism. **E. Ojuka.** *Univ. of Cape Town.*

52 **32.11** Withdrawn.

53 **32.12** Influence of a Cyclooxygenase-2 Inhibitor on Cyclooxygenase mRNA Expression After Resistance Exercise in Humans: Implications for Muscle Protein Synthesis. **J. M. Dickinson, N. A. Burd, J. K. LeMoine, C. C. Carroll, J. M. Haus, B. Jemiolo, S. Trappe, G. M. Hughes, C. E. Sanders, Jr. and T. A. Trappe.** *Ball State Univ.*

54 **32.13** FoxO1 Induces Apoptosis in Skeletal Myotubes. **S. Smith, K. Esser, T. Unterman and T. McLoughlin.** *Univ. of Toledo, Univ. of Kentucky and Univ. of Illinois at Chicago.*

55 **32.14** Inhibition of Caseine Kinase Iα Increases Nuclear NFAT in C2C12 cells. **E. R. Chin, and J. F. Schaefer.** *Pfizer Gobal R&D.*

56 **32.15** Amino Acid Infusion Alters Growth Related Gene Expression in Human Skeletal Muscle. **A. Konopka, J. Crane, B. Jemiolo, T. A. Trappe, S. Trappe and M. Harber.** *Ball State Univ.*

Poster Session

33.0 INFLAMMATION

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

57 **33.1** Withdrawn.

58 **33.2** Eicosapentaenoic Acid is More Effective Than Docosahexaenoic Acid in Inhibiting Pro-inflammatory Mediator Production and Transcription from LPS-induced Human Asthmatic Alveolar Macrophage Cells. **M. Lindley, S. Tecklenburg, G. Montgomery and T. Mickleborough.** *Loughborough Univ., UK., and Indiana Univ.*

59 **33.3** β2 Integrins Contribute to Skeletal Muscle Hypertrophy in Mice. **C. Dearth, J. Marino, B. Tausch, M. Manacci, T. McLoughlin, S. Rakyta, M. Linsenmayer and F. Pizza.** *Univ. of Toledo.*

60 **33.4** Exercise Induces a Cardioprotective, Anti-inflammatory Phenotype in the Rat Heart that is Blocked by Delta Opioid Receptor Antagonists. **G. Denning, L. Ackermann, P. Ludwig, L. Stoll and E. Dickson.** *Univ. of Iowa.*

61 **33.5** The Effect of Combined Statin Therapy and Exercise Training on Mediators of Inflammation. **P. Coen, M. Flynn, M. Markofski, B. Pence, A. Carrillo, J. Bell and R. Hannemann.** *Univ. of Pittsburgh and Purdue Univ.*

62 **33.6** Statin Plus Exercise Training: Markers of Inflammation, Liver Function, and Muscle Damage. **M. Markofski, M. Flynn, P. Coen and R. Hannemann.** *Purdue Univ.*

63 **33.7** Macrophage Depletion does not Affect mdx Mouse Total Body Strength. **M. Kostek.** *Univ. of South Carolina.*

Poster Session

34.0 AGING

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

64 **34.1** Six-Minute Walk Distance in Individuals with Parkinson Disease: A Regression Model. **M. Falvo and G. Earhart.** *Washington Univ.*

65 **34.2** Genetic Background Influences Daily Running Wheel Duration across the Lifespan in Three Generations of Mice. **M. Turner, S. Courtney, E. Grindstaff, A. El Masri, S. Kleeberger and T. Lighfoot.** *Univ. of North Carolina, Charlotte and NIEHS, NIH.*

66 **34.3** Are There Muscle-Specific Effects of Training Status or Old Age on Oxidative Capacity and Intramyocellular Lipids *in vivo*? **R. Larsen, D. Callahan, S. Foulis, D. Befroy and J. Kent-Braun.** *Univ. of Massachusetts and Yale Univ. Sch. of Med.*

Board #

67 **34.4** Aging Differentially Affects Human Skeletal Muscle MicroRNA Expression at Rest and Following a Protein Anabolic Stimulus. **M. Drummond, J. McCarthy, K. Esser and B. Rasmussen.** *Univ. of Texas Med. Branch and Univ. of Kentucky.*

68 **34.5** Effect of Resistance Exercise with Blood Flow Restriction on Muscle Protein Synthesis and mTOR Signaling in Older Men. **C. S. Fry, E. L. Glynn, M. J. Drummond, K. L. Timmerman, S. Fujita, T. Abe, Y. Sato, S. Dhanani, E. Volpi and B. Rasmussen.** *Univ. of Texas Med. Branch., and Univ. of Tokyo.*

69 **34.6** Skeletal Muscle Gene Expression is Strongly Correlated with Strength and Size Gains After Resistance Exercise Training in Elderly Adults. **R. Dennis, H. Zhu, P. Kortebein, H. Bush, J. Harvey, D. Sullivan and C. Peterson.** *Central Arkansas Vet. Healthcare Sys., Univ. of Kentucky and Univ. of Arkansas for Med. Sci.*

70 **34.7** Exogenous Antioxidants Mimic the Effects of Exercise Training on Endothelial Function in Arteries Perfusing Skeletal muscle of Aged Rats. **D. Trott and C. Woodman.** *Texas A&M Univ.*

71 **34.8** Effect of Exercise Capacity on Forearm Vascular Response to Sympathetic Activation in Healthy Middle-aged Subjects. **C. Notarius, B. Morris and J. Floras.** *Univ. of Toronto.*

72 **34.9** Running Performance by Aged Female Mice: Effects of Estradiol Treatment and Residual Ovarian Tissue. **S. Greising and D. Lowe.** *Univ. of Minnesota.*

73 **34.10** Reductions in GLUT4 Protein Content in Fast Twitch Muscle with Aging are Prevented by Exercise Training. **A. Betik, D. Wright, L. Sutherland, M. Thomas and R. Hepple.** *Univ. of Calgary, and Univ. of Alberta.*

74 **34.11** Age-related Changes in the Energy Cost of Twitch Contractions in Human Skeletal Muscle *in vivo*. **M. Tevald, S. Foulis, I. Lanza and J. Kent-Braun.** *Univ. of Massachusetts and Mayo Clinic.*

75 **34.12** Changes in Exercise Tolerance and Physical Performance in Myostatin Transgenic Mice. **S. Porszasz-Reisz, A. Abraham and J. Porszasz.** *Charles Drew Univ. of Med. and Science., Los Angeles, and Los Angeles Biomed. Res. Ctr.*

Board #

76 **34.13** Exercise-induced Shear Stress is Associated with Plasma VWF in Older Humans. **J. Gonzales, B. Thompson, J. Thistlethwaite and B. Scheuermann.** *Univ. of Toledo.*

77 **34.14** The Angiogenic Response to Aerobic Exercise Training is Preserved in Aged Compared to Young Women. **T. Gavin, R. Kraus, J. Carrithers, C. Evans, R. Ruster, D. Knapp, J. McCartney, J. Garry and R. Hickner.** *East Carolina Univ.*

78 **34.15** Exercise Training-induced Improvements in Antibody Responses to Influenza Vaccination in Older Adults are Related to Changes in Cardiovascular Fitness. **S. Mar-tin, B. Pence, V. Vieira, E. McAuley and J. Woods.** *Univ. of Illinois, Urbana.*

79 **34.16** Fiber-type Specific Expression and Aging-related Decline of Skeletal Muscle Nampt. **J. Brandauer, L. W. S. Finley, C. A. Witczak, M. Haigis and L. J. Goodyear.** *Joslin Diabetes Ctr.*

Poster Session

35.0 MUSCLE FUNCTION AND ADAPTATION II

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

80 **35.1** Endurance Training Redistributes Intramyocellular Lipids from the Subsarcolemmal to the Intramyofibrillar Region in Skeletal Muscle of Lean and Obese Men. **I. A. Samjoo, M. J. Hamadeh, A. W. Glover, N. J. Mocellin and M. A. Tarnopolsky.** *McMaster Univ., and York Univ.*

81 **35.2** PGC-1α Promotes Antioxidant Enzyme Expression and Prevents Muscle Atrophy in Chronic Heart Failure. **T. Geng, P. Li, X. Yin and Z. Yan.** *Duke Univ. Med. Ctr.*

82 **35.3** Hypergravity Resistance Training on a Human Powered Centrifuge. **J. Blank, M. Baker, A. Kreitenberg, G. Adams, K. Baldwin and V. Caiozzo.** *Univ. of California, Irvine.*

83 **35.4** PGC-1α and β Slow Muscle Atrophy by Inhibiting Protein Degradation and the Induction of Atrophy-specific Ubiquitin Ligases, Atrogin1 and MuRF1. **J. Brault, J. Jespersen and A. Goldberg.** *Harvard Med. Sch.*

84 **35.5** Assessment of Cumulative FSR Over a 24h Period with Hindlimb Unloading and Intermittent Reloading in Rats. **M. Wiggs, H. Gasier, S. Previs and J. Fluckey.** *Texas A&M Univ. and Case Western Res. Univ.*

Board #

85 **35.6** A Comparison of 2H2O and Phenylalanine Flooding Dose Methodologies to Investigate Protein Fractional Synthesis Rates in Skeletal Muscle of Rats. **H. Gasier, T. Lee, V. Chen, M. Wiggs, S. Riechman, S. Previs and J. Fluckey.** *Texas A&M Univ. and Case Western Res. Univ.*

86 **35.7** Muscle Damage or Myofibrillar Remodeling in Human Muscle after Eccentric Exercise. **L. Carlsson, G. Faulkner, D. O. Fürst and L-E. Thornell.** *Umeå Univ., Internatl. Ctr. of Genetic Eng. & Biotech., Trieste and Univ. of Bonn.*

87 **35.8** Mouse Skeletal Muscle Volume Regulation by the Na^+,K^+,2Cl- Cotransporter During Exposure to Hypertonic and Hypotonic Solutions. **M. Lindinger and B. Stephenson.** *Univ. of Guelph.*

88 **35.9** Skeletal Muscle Volume Regulation by the Na^+,K^+,2Cl- Cotransporter is Impaired in mdx Mice During Hypertonic Stress. **M. Lindinger, B. Stephenson and R. Grange.** *Univ. of Guelph and Virginia Tech.*

89 **35.10** Strength Training, Ovariectomy and MMP-2 in Skeletal Muscle. **J. Prestes, R. Leite, R. Marqueti, G. Pereira, G. Shiguemoto, J. P. Botero, F. Ferreira, H. Sobreiro Selistre de Araújo, R. Magosso, V. Baldissera and S. Eduardo de Andrade Perez.** *Fed. Univ. of São Carlos, Brazil.*

90 **35.11** Effects of High-intensity Cycling Training on Phosphocreatine Recovery Kinetics. **S. Forbes, J. Slade and R. Meyer.** *Michigan State Univ.*

91 **35.12** Autophagic Protein Expression in Denervated Skeletal Muscle. **M. O'Leary and D. Hood.** *York Univ.*

92 **35.13** Elevations in Endogenous Anabolic Hormones do not Enhance Muscle Hypertrophy or Strength of the Elbow Flexors Following Resistance Training in Young Men. **D. West, N. Burd, D. Moore, J. Tang, A. Holwerda, S. Baker and S. Phillips.** *McMaster Univ.*

93 **35.14** Influence of Resistance Training Alone or Combined with Cyclooxygenase Inhibitor Consumption on Skeletal Muscle Proteolysis in Older Humans. **C. Carroll, J. LeMoine, J. Dickinson, J. Haus, E. Weinheimer, J. Lee, B. Sullivan, C. Hollon and T. A. Trappe.** *Ball State Univ.*

Board #

94 **35.15** Short Term, Progressive-resistance Wheel Running by C57BL/10 Mice is not Sufficient to Mimic a Resistance Exercise. **J. Call, K. Baltgalvis and D. Lowe.** *Univ. of Minnesota.*

95 **35.16** Chronic Hypoxia Increases Glucose Uptake in Skeletal Muscle after Insulin Stimulation. **J. Gamboa and F. Andrade.** *Univ. of Kentucky.*

96 **35.17** Differential Stimulation of Myofibrillar and Sarcoplasmic Protein Synthesis with Protein Ingestion at Rest and after Resistance Exercise. **D. Moore, J. Tang, T. Rerecich, A. Josee, Y. Yang, N. Burd and S. Phillips.** *McMaster Univ.*

97 **35.18** Growth Response to Resistance Exercise: Influence of Exercise Device. **T. Conley, M. Harber, J. Dickinson, J. Crane, U. Raue, N. Luden, E. Louis, E. Hayes, B. Jemiolo, T. A. Trappe and S. Trappe.** *Ball State Univ.*

98 **35.19** Effect of Amino Acid Supplementation on Myogenic and Proteolytic Gene Expression following Resistance Exercise. **T. Conley, M. Harber, Y. Yang, U. Raue, E. Louis, B. Jemiolo, T. Trappe and S. Trappe.** *Ball State Univ.*

99 **35.20** Mitochondrial Adaptations Following Exercise Training in Dystrophic Mouse Skeletal Muscle. **K. Baltgalvis, A. Kosir, J. Call and D. Lowe.** *Univ. of Minnesota.*

100 **35.21** Whey Protein Stimulates a Greater Increase in Mixed Muscle Protein Synthesis than Casein or Soy at Rest and after Resistance Exercise in Young Men. **J. Tang, D. Moore, G. Kujbida and S. Phillips.** *McMaster Univ.*

101 **35.22** Early Changes in Myosin Heavy Chain Isoform Expression After Spinal Cord Transection in Adult Rats. **R. Talmadge, Y. Rotratsirikun, D. Su and H. Castellon.** *California Poly., Pomona.*

102 **35.23** Aerobic Endurance Running Phenotype Influences Adipose Fatty Acid Transport Protein in Response to High Fat Diet. **E. Granville, E. Fontentot, T. Nolan, L. Koch, S. Britton and R. Lust.** *East Carolina Univ. and Univ. of Michigan.*

103 **35.24** Lactate Stimulates the Pgc-1α Transciption by Reducing the NAD^+/NADH Redox State and Repressing SIRT1 Histone Deacetylase. **Z. Yan, Y. Luo, R-P. Dai and Y. Li.** *Duke—NUS Grad. Med. Sch., Singapore, Duke Univ. Med. Ctr. and Inst. of Molec. and Cell Biol., Singapore.*

Board #

104 **35.25** Anabolic Steroids Withdrawal in Strength Trained Athletes: How Does it Affect Skeletal Muscles? **A. Eriksson, F. Kadi, C. Malm, P. Bonnerud and L-E. Thornell.** *Umeå Univ., Luleå Univ. of Tech. and Örebro Univ.*

Poster Session

36.0 MUSCLE INJURY

Sat., 11:00 AM - 3:00 PM, Archer/Barnwell Ballroom.

Board #

105 **36.1** MRI Imaging of Skeletal Muscle Injury in the Tibialis Anterior Muscle of Live Rats. **R. Cutlip, M. Hollander, B. Baker, A. Johnson, B. Johnson and S. Friend.** *Natl. Inst. for Occupational Safety and Hlth., Morgantown and Duke Univ.*

106 **36.2** Evidence of Muscle Damage in Electrically Stimulated Human Skeletal Muscle in an Isometric Position. **A. Mackey, J. Bojsen-Moller, K. Qvortrup, H. Lang-berg, C. Suetta, M. Kjaer and S. P. Magnusson.** *Univ. of Copenhagen.*

107 **36.3** The effect of Elevated Muscle Fluid Volume on Indices of Muscle Damage Following an Acute Bout of Eccentric Exercise. **B. Roy, P. LeBlanc, S. Peters, M. A. Tarnopolsky and R. Harrison.** *Brock Univ., Ontario and McMaster Univ.*

108 **36.4** Protease-Activated Receptor-Mediated Ca^{2+} Signaling and Cytokine Production in Cultured C2C12 Skeletal Muscle Cells. **A. Bakker, K. Burlinson and G. Pinniger.** *Univ. of Western Australia, Perth.*

109 **36.5** Characterization of MMP-3 and TIMP-1 Protein Expression in Response to Skeletal Muscle Injury in Mice. **E. Szelenyi, M. Urso, R. Nicholson and B. Barnes.** *USARIEM, Natick.*

110 **36.6** Nitric Oxide Synthase Inhibition Exacerbates Isolated EDL Muscle Force Deficits During and Immediately After Performing Eccentric Contractions. **B. T. Corona and C. P. Ingalls.** *Georgia State Univ.*

111 **36.7** NFκB Functions as an Inhibitor of Myogenesis During Post-natal Development. **J. M. Dahlman and D. C. Guttridge.** *Ohio State Univ.*

Symposium XI

37.0 ROLE OF INFLAMMATION IN HEALTHY, DISEASED AND AGED MUSCLES

Sat., 3:00 - 5:00 PM, Calibogue Ballroom.

Chairs: **James G. Tidball,** *UCLA.* **Robert W. Grange,** *Virginia Tech.*

3:00 PM **37.1** Introduction. **James G. Tidball.** *UCLA.*

3:05 PM **37.2** Impact of Exercise on Inflammation in Acutely and Chronically-injured Skeletal Muscle. **Gordon L. Warren.** *Georgia State Univ.*

3:35 PM **37.3** Impact on Exercise on Inflammation in Diseased Muscle. **Michele Wehling-Henricks.** *UCLA.*

4:05 PM **37.4** Regulatuion of NFkB by Exercise and Lessons Learned from Myogenesis and Muscle Wasting. **Denis C. Guttridge.** *Ohio State Univ.*

4:35 PM **37.5** Impact of Exercise on Inflammation in Sarcopenia. **Anne McArdle.** *Univ. of Liverpool.*

Symposium XII

38.0 SARCOLEMMAL, T-TUBULE AND INTRACELLULAR DETERMINANTS OF CONTRACTILE FUNCTION IN SKELETAL MUSCLE

Sat., 3:00 - 5:00 PM, Danner Ballroom.

Chairs: **Michael Lindinger,** *Univ. of Guelph,* **Scott Trappe,** *Ball State Univ.*

3:00 PM **38.1** Introduction. **Michael Lindinger.** *Univ. of Guelph.*

3:05 PM **38.2** Determinants of Excitability of the Sarcolemma and T-Tubule System. **Michael Fauler.** *Ulm Univ. Germany.*

3:35 PM **38.3** Functional Roles of SR, Myoplasmic and Extracellular Calcium in Determining Force Generation. **Eva Chin.** *Univ. of Maryland.*

4:05 PM **38.4** Contractile Protein—Cytoskeletal Mechanical Link. **Dawn Lowe.** *Univ. of Minnesota.*

4:35 PM **38.5** Structural and Functional Adaptations within Human Myocytes in Response to Altered Loading. **Scott Trappe.** *Ball State Univ.*

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

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NOTES

2008 APS Intersociety Meeting
The Integrative Biology of Exercise - V

Abstracts of Invited and Contributed Presentations

Thursday, September 25

Friday, September 26

Saturday, September 27

1.0: REGULATION OF PERIPHERAL VASCULAR RESISTANCE

1.2

COORDINATION OF ARTERIOLAR DILATION WITH MUSCLE FIBRE CONTRACTION

Coral Murrant[1]
[1]Human Health and Nutritional Science, University of Guelph, 12 Stone Road East, Guelph, Ontario, N1G2W1, Canada.

It is a well known phenomena that blood flow increases to skeletal muscle upon the initiation of skeletal muscle contraction and that the increase in blood flow experienced by the muscle is related to the metabolism of the working skeletal muscle cells. Blood flow has been shown to be directed to the working skeletal muscle fibres themselves. The increase in blood flow to contracting skeletal muscles is in part due to decreasing the vascular resistance within the working muscle. A decrease in vascular resistance is achieved by increasing vascular radius but which vascular radius is changing? The microvasculature contains multiple branch orders of small arteries and arterioles, therefore which radius is being changed? If blood flow is to be directed to capillaries feeding active skeletal muscle cells then only very specific arteries and arterioles must have to change their radius. Contracting skeletal muscle fibres can stimulate capillaries and arterioles to induce upstream dilations that are directional and coordinated in order increase red blood cell flux through the stimulated capillaries. This presentation will explore old and new ideas regarding how skeletal muscle cells stimulate the vasculature in order to coordinates arteriolar dilation to direct blood flow to capillaries feeding active skeletal muscle fibres.

1.3

THE ROLE OF INTEGRINS IN THE CONTROL OF SKELETAL MUSCLE ARTERIOLAR DIAMETER

Luis Martinez-Lemus[1], Zhe Sun[2], Michael Hill[1], Gerald Meininger[1]
[1]Dalton Cardiovascular Research Center and Department of Medical Pharmacology and Physiology, University of Missouri-Columbia, 134 Research Park Drive, Columbia, MO, 65211, [2]Dalton Cardiovascular Research Center, University of Missouri-Columbia, 134 Research Park Drive, Columbia, MO, 65211.

Integrins are the best-characterized cellular receptors for extracellular matrix (ECM) proteins. They consist of two noncovalently linked subunits that connect ECM with the cytoskeleton. In skeletal muscle arterioles, integrins provide cell adhesion, conduct signals in both directions across the cell membrane, and participate in controlling tone and structure. Acutely, integrins take part in mechanotransduction processes that transform pressure and flow signals into changes in vascular tone, whereas chronically, integrins are part of the remodeling process that changes arteriolar structural diameter. Vascular smooth muscle $\alpha5\beta1$ and $\alpha v\beta3$ integrins have been clearly identified as modulators of calcium conductance and necessary components of pressure-induced (myogenic) tone. The involvement of integrins in flow-mediated responses is less clear and has not been studied in skeletal muscle arterioles. Results from other vascular beds, however, suggest endothelial $\alpha1\beta1$, $\alpha5\beta1$ and $\alpha v\beta3$ integrins are involved in flow-dependent production of vasoactive autacoids. In remodeling, $\alpha v\beta3$ integrins are needed for the structural reduction of arteriolar diameter that occurs in response to prolonged vasoconstriction. Whether exercise affects any, or all, of these integrin-dependent processes remains largely unknown, but a wealth of data indicates integrins are active participants in the acute and chronic control of arteriolar diameter in skeletal muscle. (Funded by AHA0530031N and NIH HL58960).

1.4

MICROVASCULAR ADAPTATIONS TO OBESITY AND THE METABOLIC SYNDROME

Jefferson Frisbee[1], Adam Goodwill[1], Milinda James[1], Randy Bryner[2], Stephanie Frisbee[1]
[1]Center for Interdisciplinary Research in Cardiovascular Sciences, West Virginia University HSC, 1 Medical Center Drive, Morgantown, WV, 26506, [2]Exercise Physiology, West Virginia University HSC, 1 Medical Center Drive, Morgantown, WV, 26506.

The combined presentation of obesity with other CVD risk factors (e.g., dyslipidemia, insulin resistance) represents a profound public health challenge. Combined, these pathologies are defined as the metabolic syndrome, which is associated with increased risk for poor vascular outcomes. The obese Zucker rat (OZR) possesses a dysfunctional leptin receptor, causing hyperphagia-induced metabolic syndrome and poor vascular outcomes, including alterations to reactivity and microvascular density (MVD). Prior studies suggest that reductions in skeletal muscle MVD in OZR are best predicted by insulin resistance severity, and are associated with a progressive reduction in vascular nitric oxide (NO) bioavailability. Interventions against elements of the metabolic syndrome (pharmacological) or against the syndrome itself (exercise) improved MVD, dependent on increased NO bioavailability. Also identified were improvements to inflammation associated with reductions to MVD and NO bioavailability. Of these, the earliest to demonstrate a significant change from baseline in OZR is TNF-*f*Ñ, preceding alterations to MVD or NO bioavailability. Chronic inhibition of TNF-*f*Ñ improved NO bioavailability and blunted reduced MVD in OZR. Taken together, these results suggest that microvessel loss in the metabolic syndrome may represent a multi-factorial process where patterns of peripheral inflammation integrate to reduce NO bioavailability. It may be that this loss in NO bioavailability alters angiogenic/angiostatic growth factors resulting in reduced MVD. (NIH DK64668; AHA 0740129N).

1.5

EXERCISE VERSUS AGING IN MICROVASCULAR CONTROL: ROLE OF REACTIVE OXYGEN SPECIES

Zoltan Ungvari[1], Anna Csiszar[1]
[1]Dept. of Physiology, New York Medical College, BSB A12, Valhalla, NY, 10595.

Previous studies have shown that flow-induced vasodilation is attenuated with old age in rat coronary arterioles1 and skeletal muscle microvessels2, as well as in human conduit arteries3 due to an increased oxidative stress, which may contribute to exercise intolerance with age. Here we will overview the evidence implicating NAD(P)H oxidase and other cytplasmic sources of ROS in endothelial dysfunction in aging. We also present evidence that in endothelial cells of aged vessels there is an increased mitochondria-derived production of ROS. Mitochondrial biogenesis is involved in the control of cell metabolism, signal transduction and regulation of mitochondrial ROS production. We recently found that in the endothelial cells of rat vessels a decline in mitochondrial biogenesis occurs with aging. In aged vessels expression of the mitochondrial biogenesis factors (including PGC1á) is decreased. Among the components of the electron transport chain cytochrome C oxidase (COX) expression/activity exhibit the greatest age-related decline. In cultured coronary arterial endothelial cells partial knockdown of COX (by siRNA) significantly increased mtROS production. We posit that impaired mitochondrial biogenesis and down-regulation of COX may contribute to increased mitochondrial oxidative stress contributing to endothelial dysfunction in aging. Exercise is known to affect mitochondrial biogenesis in the skeletal muscle, but further studies are needed to elucidate its effect on mtROS in endothelial cells. 1) Csiszar A et al. Circ Res. 2002;90(11):1159.; 2) Spier SA et al. Am J Physiol 2007;292:H3119; 3) Eskurza I et al. J Physiol. 2004;556:315.

2.0: CONTROL OF RIBOSOMAL BIOGENESIS IN MUSCLE HYPERTROPHY

2.3

RIBOSOME BIOGENEIS AND CARDIAC MYOCYTE HYPERTROPHY

R.D. Hannan (1,2) H. Chan (3,4), and W.G. Thomas (4).
(1) Research Division, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia; (2) Department of Biochemistry and Molecular Biology, Melbourne University, Parkville, VIC Australia; (3) Department of Pharmacology, Melbourne University, Parkville, VIC Australia; (4) Department of Physiology, School of Biomedical Sciences, University of Queensland, Australia.

None of the current therapies successfully prevent the transition from left ventricular hypertrophy (LVH) to the onset of heart failure. Redundancy is one reason, as is the likely requirement for input from multiple effectors. Based on these considerations, we have developed a new approach to target the development of LVH. Regardless of the initiating cause, cardiomyocyte growth requires increased rates of protein synthesis and this, in turn, requires more ribosomes. Accordingly, methods that prevent the increase in ribosome synthesis should reduce the cardiac enlargement prevalent in all forms of cardiac hypertrophic disease. This obviates the need to resolve the exact aetiology of the disease or the complex signal transduction pathways involved. The major limiting step for the synthesis of ribosomes is the transcription of the ribosomal genes (rDNA) and a key rDNA specific transcription factor termed UBF. We have demonstrated that activation of UBF is both necessary and sufficient to drive hypertrophic growth of cultured cardiomyocytes through effects on rRNA. Our current work focuses on the hypothesis that G protein couple receptors regulate UBF expression and ribosome biogenesis through trans-activation of the type 4 EGFR receptor (Her4) and subsequent activation of c-MYC, a key regulator of LVH.

2.5

MTOR AND THE INTEGRATION EXERCISE AND AMINO ACID NUTRIENT STATUS IN THE REGULATION OF TRANSLATION

Scot Kimball[1]
[1]Physiology, Penn State College of Medicine, 500 University Drive, Hershey, PA, 17033.

The serine/threonine protein kinase known as the mammalian target of rapamycin (mTOR) is often referred to as a master regulator of cell growth. The reference has its origin in studies showing that signaling through mTOR is increased in response to a variety of growth-promoting stimuli, and that inhibition of the kinase using the selective inhibitor, rapamycin, both decreases cell size and represses hypertrophic growth. The stimulation of cell growth associated with mTOR activation is due in part to its ability to phosphorylate S6K1 and 4E-BP1, two proteins involved in the regulation of mRNA translation. This effect is mediated by the mTOR complex 1 (mTORC1) which, in addition to containing mTOR, also contains proteins such as raptor and LST8. A ras homolog, Rheb, reversibly associates with mTORC1. Previous studies have shown that, compared to mTORC1 lacking Rheb, the binding of either Rheb•GDP or Rheb•GTP to the complex increases mTORC1 signaling. However, Rheb•GTP is significantly more potent than Rheb•GDP in increasing mTORC1 signaling. Recent studies suggest that amino acids stimulate mTORC1 signaling by increasing the association of mTORC1 with Rheb. In contrast, hormones, e.g. insulin or IGF-1, stimulate mTORC1 signaling in part by increasing the proportion of Rheb in the GTP-bound form. The relevance of these mechanisms to exercise-mediated changes in mTORC1 signaling will be discussed.

3.0: CARDIOVASCULAR

3.1

SYMPATHETIC AND CARDIOVASCULAR RESPONSES DURING LOCAL SALINE INFUSION

Jian Cui[1], Patrick McQuillan[2], Raman Moradkhan[1], Charles Pagana[1], Lawrence I. Sinoway[1]
[1]Medicine, Penn State Heart & Vascular Institute, 500 University Drive, Hershey, PA, 17033, [2]Anesthesia, Penn State College of Medicine, 500 University Drive, Hershey, PA, 17033.

The intravenous regional anesthesia (Bier block) technique has been employed to locally administer drugs for basic human experiments. However, the sympathetic responses to this procedure per se are unclear. The aim of this study was to examine the hypothesis that the Bier block procedure itself evokes sympathetic activation. Blood pressure, heart rate, and muscle sympathetic nerve activity (MSNA) responses were assessed in 12 young healthy subjects during local infusion of 40 ml saline into an arm with the Bier block procedure. From the baseline (11.4 ± 1.5 bursts/min), MSNA increased significantly during the period of limb exsanguination and the saline infusion (19.2 ± 2.4 bursts/min, $P < 0.03$), and during the last 2 minutes of 20 min cuff occlusion (22.2 ± 3.0 bursts/min, $P < 0.001$). MSNA remained elevated just after cuff deflation (21.8 ± 2.3 bursts/min, $P < 0.001$). The blood pressure rose during the limb exsanguination and was maintained at the higher level throughout the period of tourniquet application (all $P < 0.05$). We conclude that the Bier block procedure itself induces sympathetic activation. The effects of the sympathetic activation and the cardiovascular responses during the procedure should be considered when utilizing the Bier block method. Supported by AHA 0635245N (Cui) and P01 HL077670 (Sinoway).

3.2

ARTERIAL PRESSURE AND HEART RATE ALTERATIONS IN EXERCISE TRAINED RATS SUBMITTED TO ORTHOSTATIC STRESS

Marli Martins-Pinge[1], Sérgio Borghi[1]
[1]Physiological Sciences, State University of Londrina, campus universitário s/n, Londrina, 86051-990, Brazil.

The main objective of this work was to examine the arterial pressure and heart rate alterations of orthostatic stress ("head up tilt") in conscious rats submitted prior to physical training. Adult male Wistar rats (200-220g) were submitted to a swimming training protocol (1 hour/day; 5 days/week, 4 weeks).One day after training, control (C) or trained (T) rats were anesthetized for catheter implantation in the femoral artery and vein, for recording of mean arterial pressure (MAP) and drugs injection. 24 hours later, after baseline parameters, C or T rats were placed in a plastic tube positioned over the tilt board. The tilt test was conducted by raising the head side of the tilt board from horizontal position to 75 degrees head up position for 15 min. The baseline

parameters between C or T groups had shown differences in the average MAP (C=106±2 mmHg, n=12; T=115±3 mmHg, n=7) and in the heart rate (HR) were observed a bradycardia at rest in the T group (C=359±5 bpm; T=335±5 bpm, p<0,05). During restraint rats presented an increase in MAP and HR. After tilt it was observed in the first 5 minutes a decrease in MAP for both groups, with a tendency to be accentuated in the trained animals (ΔMAPC= -8±5; ΔMAPT= -16±7mmHg). Heart rate parameters did not change at this point, but during the tilt the trained rats presented bradycardia instead of tachycardia observed in the control. Our data suggest that exercise training may induce orthostatic intolerance in healthy individuals.

3.3

MODERATE-INTENSITY RESISTANCE TRAINING AND COMBINED RESISTANCE AND AEROBIC TRAINING IMPROVE REACTIVE HYPEREMIA

Hiroshi Kawano[1], Motohiko Miyachi[2], Mitsuru Higuchi[1]
[1]Faculty of Sport Sciences, Waseda University, 2-579-15 Mikajima, Tokorozawa, 359-1192, Japan, [2]Program for Health Promotion, 2. National Institute of Health and Nutrition, 1-23-1, Toyama, Shinjuku, 169-8636, Japan.

Background: Reduced response to reactive hyperemia (RH) in forearm or leg reflects impaired endothelium-dependent dilation of microvasculature. The aim of the present study was to determine whether the resistance training and the combined aerobic and resistance training increase the endothelial vasodilation of forearm assessed by using RH. Methods: A total of 39 young men were assigned into either high- (HIR; 6 type of exercises, 80%1RM x 10 reps x 3 sets, n=14) and moderate-(MIR; 6 type of exercises, 50%1RM x 16 reps x 3 sets, n=14) intensity resistance training and combined high-intensity resistance training and moderate-intensity endurance training (COMBO; HIR and 60%HRmax x 30 min, n=11) groups. We measured forearm blood flow response to RH before and after 4 months of exercise intervention. Results: All training groups increased maximal strength in all muscle groups tested (all P<0.05). After 4 months of training, the maximal forearm blood flow during RH increased significantly in MIR and COMBO groups, from 57±4 to 66±7 mL/min per 100 mL tissue and from 59±6 to 74±8 mL/min per 100 mL tissue, respectively (both P<0.05). There was no change of the response to RH in HIR groups. Conclusions: We concluded that both moderate-intensity resistance training and combined resistance and endurance training improve the endothelial function of microvasculature in forearm.

3.4

OPTIMUM AEROBIC CAPACITY IMPROVEMENT

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Challenging the oxidative metabolism of the component that limits the aerobic exercise capacity safely stimulates the maximum rate of O_2 metabolism improvement. This 58-year-old man had such severe generalized arteriosclerosis of the myocardial vessels he suffered 2 cardiac arrests and was proclaimed ineligible for surgical treatment. He was unable to walk more than 30 seconds at 0.5 mph for more than 30 seconds due to the development of severe angina and ST segment depression. His PaO_2 was 62 mmHg. Hyperthermia 30 min. per day In the sauna while in the supine position with nasal O_2 and dipyridamole 50 mg TID increased the PaO_2 to 82 mmHg in 1 Month. Then he was able to walk on the treadmill without developing angina or ST depression. Walking on the treadmill for 15 min. was then added to his treatment. That enabled his heart metabolism to improved enough within one month such that the metabolic capacity of the skeletal muscles became the limiting component. The treadmill exercise thereafter was adjusted so that he was exercising at the maximum pulse rate that did not demonstrate a threshold phenomenon in order to challenge the oxidative metabolic capacity of the working muscles. After a total of three months treatment his aerobic exercise capacity improved enough that he was able to return to work supervising the welding operations in a shipyard for three years. Before he left the shipyard he was descending and assending 50 to 60 ft. vertical ladders in the holds of ships without difficulty. He worked the next 2 years on steel erection of an atomic energy power plant including that at 300 ft. high. Conclusion; challenging the oxidative metabolism of the limiting component can safely and rapidly improve sustained aerobic activity capacity.

3.5

MITOCHONDRIAL KATP CHANNEL INHIBITION BLUNTS ARRHYTHMIA PROTECTION IN ISCHEMIC EXERCISED HEARTS

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In this investigation the mitochondrial ATP sensitive potassium channel (Mito KATP) was investigated as a mechanism of exercise-induced cardioprotection against arrhythmias produced during ischemia reperfusion (IR). Male Sprague Dawley rats performed treadmill exercise at 70% maximal aerobic capacity for 60 minutes on 3 consecutive days. 24 hours following the final exercise bout, sedated rats received a surgically induced IR (I = 20 min, R = 30 min) challenge to induce arrhythmias. Two separate groups of rats, exposed to identical exercise and IR treatments, received pharmacologic inhibitors to either the Mito KATP channel (5HD) or the sarcolemmal ATP sensitive potassium channel (HMR-1098). Electrocardiographic recordings from exercised rats were compared with those from sedentary rats receiving an identical IR challenge. The frequency of preventricular contractions (PVC), ventricular tachycardia (VT), and ventricular fibrillation (VF) were quantified and analyzed by one-way ANOVA. Arrhythmia variables were further evaluated in aggregate using an established arrhythmia scale. Findings reveal that IR induced a significant arrhythmic load ($P < 0.001$) and that exercise prevented much of the arrhythmic response to IR. Further, exercised animals treated with 5HD did not exhibit arrhythmic cardioprotection while exercised animals receiving HMR-1098 were protected. These data indicate the Mito KATP channel in exercised hearts is a mediator of cardioprotection against IR induced arrhythmia. Supported by App State Univ Research Council and the National Institute of Health (NHLBI; JCQ - 1R15HL087256-01).

3.6

INTERACTION BETWEEN FLEXIBILITY AND CARDIORESPIRATORY FITNESS ON ARTERIAL STIFFNESS

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PURPOSE: Cardiorespiratory fitness (CF) has been identified as determinants of arterial stiffness. Although the flexibility is one of the components of fitness, the relationship between flexibility and arterial stiffness remains unknown. Using the cross-sectional study design, we examined the relationships among flexibility, CF, and arterial stiffness. METHODS: We studied a total of 227 adults (aged 40 to 77 years; 54 +/- 9 years). Subjects were grouped into either low-CF or high-CF on the basis of peak oxygen uptake during incremental cycle exercise test. In each CF group, they were categorized into either low-flexibility or high-flexibility on the basis of sit-and-reach test. The arterial stiffness was assessed by brachial-ankle pulse wave velocity (baPWV). RESULTS: Age did not differ among four groups. In high-CF group, baPWV did not differ between two flexibility groups (low- vs high-flexibility: 1259 +/- 143 vs 1236 +/- 134 cm/s). In low-CF group, baPWV was higher in low-flexibility than in high-flexibility peers (1394 +/- 234 vs 1263 +/- 188 cm/s, P<0.01). The difference remained significant after normalizing baPWV for age and sex when analyzed by ANCOVA. CONCLUSION: These results suggest that in determining the arterial stiffness, the flexibility interacts with the CF. When both the flexibility and CF are poor, the cardiovascular risk may increase.

3.7

PHYSICAL ACTIVITY ESTIMATED BY TRIAXIAL ACCELEROMETER IS AN INDEPENDENT PREDICTOR OF ARTERIAL STIFFENING

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PURPOSE: Poor cardiorespiratory fitness has been identified as determinants of arterial stiffness. However, effect of amount of physical activity on arterial stiffening is less convincing. The aim of this study was to evaluate the relations between cardiorespiratory fitness, amount of physical activity assessed by an accelerometer, and arterial stiffness. METHODS: The study population consisted of 149 healthy subjects (mean+/-SD age, 48+/-11 years). All subjects wore an accelerometer to measure the number of steps as well as the amount of physical activity calculated by intensity and duration. They performed an incremental cycle exercise test to assess cardiorespiratory fitness. The arterial stiffness was measured by brachial-ankle pulse wave velocity (baPWV). RESULTS: The arterial stiffness values of poor and high fitness group were 1280 +/- 208 and 1190 +/- 142 cm/sec (P<0.01), and low and high physical activity level (METs*h; Mets multiplied by hours spent in physical activity) groups were 1312 +/- 218 and 1203 +/- 157 cm/sec (P<0.001). However, there was no significant difference between low and high step counts group. Stepwise logistic regression analysis showed age, systolic blood pressure, amount of physical activity, and BMI to be significant predictor of baPWV. CONCLUSION: We concluded that the amount of physical activity calculated by the intensity and duration is identified as an independent predictor of arterial stiffening.

3.8

CD34+/KDR+ ENDOTHELIAL PROGENITOR CELLS AND VASCULAR HEALTH: EXERCISE AND DETRAINING

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Regular physical activity may improve the number of endothelial progenitor cells (EPCs), bone derived CD34+/KDR+ cells that contribute to vessel re-endothelialization. The purpose of this study was to determine the effect of long-term exercise training and 10-days of training cessation on EPC number and endothelial function. Forearm blood flow (FBF) response to reactive hyperemia assessed endothelial function. EPCs were quantified with flow cytometry. Measures were repeated following 10-days of detraining. 10 healthy male long-term exercisers and 11 low-active age- and BMI-matched individuals participated in the study. EPC number was not different between groups (p=0.23). EPCs tended to decrease (p=0.11) following detraining. The percent change in EPCs was positively correlated with the change in FBF response to reactive hyperemia (p=0.02). The detraining response was characterized by individuals who decreased (responders) and those who had no decrease (non-responders) in EPC number. Compared with non-responders, the responders had greater EPC number at baseline (p = 0.008) and a greater percentage decrease in EPC number with detraining (p=0.006). Baseline FBF and peak FBF prior to detraining was significantly different between the responders and non-responders (p = 0.02) but not after detraining. EPC number is closely related to endothelial function. Regular acute exercise bouts appear to be important for some individuals to preserve endothelial function.

3.9

LOW DOSE ESTROGEN THERAPY DOES NOT CHANGE HEMODYNAMICS AND NEURAL RESPONSES TO STATIC EXERCISE IN POSTMENOPAUSAL WOMEN

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The aim of the study was to evaluate whether estrogen therapy alters the hemodynamics and neural responses to static exercise in postmenopausal women. Twenty two women received oral estrogen (n=12, 1mg/day) or placebo (n=10) for six months prior to the study. Then, they underwent an experimental session where the muscle sympathetic nerve activity (MSNA, microneurography), mean blood pressure (MBP, oscillometry), heart rate (HR, ECG), and forearm blood flow (FBF, plethysmography) were measured and forearm vascular resistance (FVR) was calculated (FVR= FBF/MBP) during a 3-min baseline period and a 3-min static handgrip exercise performed at 30% of maximal voluntary contraction, followed by a 2-min of posthangrip circulatory arrest. Data were analyzed by a two-way ANOVA. Estrogen therapy did not affect the hemodynamic and neural responses to static exercise compared to placebo. For both groups MSNA, MBP and HR increased during static exercise (P<0.01 for all v baseline). During circulatory arrest MSNA remained elevated (P<0.01 v. baseline), HR reduced to baseline values and MBP had a slight decrease but it remained higher than baseline (P<0.01). FBF and FVR did not change during static exercise or circulatory arrest compared to baseline. In conclusion oral estrogen therapy did not change MSNA, MBP, HR FBF and FVR responses to

static exercise in healthy postmenopausal women. Static exercise enhanced MSNA, MBP and HR, but did not affect FBF and FVR.

3.10

SINGLE AND MULTIPLE SPRINT EXERCISE ACUTELY STIFFENS THE CENTRAL ARTERIES OF YOUNG HEALTHY MALES

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Peripheral arterial distensibility is improved with sprint interval training in healthy males (Rakobowchuk et al AJP 2008). To better understand the mechanisms contributing to these chronic effects we examined the acute vascular responses to sprint interval exercise. Following 60 min of rest 10 (20.1 ± 1.2 y) males completed either a single 30s "all-out" sprint (Wingate) or a sprint interval session (4 Wingates tests each separated by 4.5 min of recovery). At 2, 15, 30, 45, and 60 min of recovery, peripheral arterial distensibility was measured at the superficial femoral artery using ultrasound imaging and continuous central and peripheral pulsewave velocity (PWV) was acquired every minute. Heart rate was significantly elevated throughout recovery following both the sprint sessions ($p<0.05$), while central artery PWV was increased until 20 minutes of recovery ($p<0.05$) and lower extremity PWV was decreased until ~45 minutes ($p<0.05$). Although blood pressure was increased immediately post exercise, central stiffness persisted beyond the time when arterial pressure returned to baseline levels. These results indicate that brief (30s) extremely high intensity exercise acutely increases central artery stiffness, likely through high adrenergic sympathetic tone. Further, functional sympatholysis likely reduces peripheral stiffness well into recovery potentially contributing to chronic alterations of stiffness through altered vessel wall protein expression. Supported by CIHR and NSERC.

3.11

THE EFFECTS OF ACUTE ISOMETRIC HANDGRIP ON AUTONOMIC MODULATION

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Isometric handgrip (IHG) training has been shown to reduce resting arterial blood pressure. These reductions are hypothesized to be associated with alterations in sympathovagal balance. This study examined whether acute IHG is sufficient to alter autonomic modulation, as assessed by the 4-second exercise test (4sET), a pharmacologically validated procedure used to evaluate cardiac vagal tone (CVT). In a sample of eighteen older (72 ± 4 years), unmedicated normotensives (systolic: 125 ± 3 mmHg; diastolic: 67 ± 2 mmHg), participants completed two 4sET protocols separated by either IHG exercise (four 2-min isometric contractions at 30% MVC) or a control rest period. CVT and non-linear dynamics of heart rate complexity (Sample Entropy) were determined pre- and post- IHG and time-matched control conditions. In the IHG condition, CVT increased (1.24 ± 0.03 to 1.29 ± 0.03, $p<0.01$) and heart rate complexity increased (1.28 ± 0.03 to 1.40 ± 0.05, $p<0.001$) pre-to-post. In the control condition, CVT decreased pre-to-post (1.26 ± 0.02 to 1.22 ± 0.03, $p<0.01$) as did heart rate complexity (1.26 ± 0.04 to 1.11 ± 0.04, $p<0.001$). This evidence of improved cardiac autonomic modulation following acute IHG may be mechanistically linked to the observed attenuations in resting arterial blood pressure seen in previous IHG training studies. These acute effects may also have clinical applications and require further investigation.

3.12

HEMODYNAMIC RESPONSES AND CARDIOVASCULAR AUTONOMIC REGULATION FOLLOWING SUPRAMAXIMAL EXERCISE

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PURPOSE: To evaluate hemodynamic responses and cardiovascular autonomic control following supramaximal exercise. METHODS: Continuous ECG and beat-to-beat arterial pressure (AP), cardiac output (CO) and total peripheral resistance (TPR) were recorded before and 5 min after a Wingate test in 11 males aged 21 yr. Analysis of HR and AP variability was used to estimate cardiac and vasomotor autonomic control. The high frequency (HF) power of the HR variability spectrum was used as an index of cardiac vagal activity and the ratio of the low frequency (LF) to HF power (LF/HF) was used as an index of cardiac sympathovagal balance. The LF power of the systolic AP spectrum (LF_{SAP}) was used as an index of sympathetic vasomotor tone. RESULTS: Post-exercise blood pressure did not significantly differ from pre-exercise ($p>0.05$). Recovery HR and CO were significantly greater than pre-exercise, whereas TPR was significantly reduced during recovery ($p<0.05$). Post-exercise HF (0.2 ± 0.1 msec^2) was lower than pre-exercise (0.7 ± 0.2 msec^2), whereas LF/HF (4.2 ± 0.6) and LF_{SAP} (0.7 ± 0.2 mmHg^2) were greater than pre-exercise (LF/HF: 3.4 ± 0.8 and LF_{SAP}: 0.5 ± 0.2 mmHg^2), $p<0.05$. CONCLUSION: Cardiac and vasomotor sympathetic activity remained elevated, whereas peripheral vasodilation was pronounced during the recovery period from a Wingate test. A 30-sec supramaximal exercise test poses significant stress to the cardiovascular system as manifested by elevated hemodynamics following exercise.

3.13

THE EFFECT OF EXERCISE INTENSITY ON ENDOTHELIAL FUNCTION IN HEALTHY YOUNG ADULTS

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Endothelial dysfunction is an important early marker of increased risk of atherosclerosis and cardiovascular disease. Exercise has been suggested as an intervention for improving endothelial function. We examined the effects of exercise intensity on the acute time course of changes in endothelial function measured by brachial artery flow-mediated dilation (FMD). Eleven healthy lean young adults completed a cycle ergometry lactate threshold (LT)/VO_2peak test. Subjects were studied during 3 randomized admissions [control (C, no exercise), moderate (M, @ LT) and high (H, > LT) intensity cycle ergometer exercise (30 min)]. FMD was assessed by high-resolution Doppler ultrasound at baseline and at 1, 2, and 4 h post-exercise. FMD increased over time in all conditions, including C. A condition effect was observed for absolute increase in FMD above baseline ($P < 0.05$), with H having the greatest effect (from 6.6 to 10.1%). Similar results were observed for relative increases in FMD, with H resulting in a 71% increase above baseline (vs. 31% and 24% for C and M, respectively). FMD increased over the first 2 h after H, and remained elevated at 4 h. We conclude that in healthy young adults, high intensity exercise enhances systemic endothelial function more than moderate intensity exercise of the same duration, and that this effect of acute exercise persists for at least 4 h. This study was supported in part by an NIH grant funding the General Clinical Research Center (RR00847).

3.14

MULTIPLE SPRINT EXERCISE ACUTELY DECREASES STROKE VOLUME DURING RECOVERY IN YOUNG HEALTHY MALES

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Although the acute cardiovascular responses to a single Wingate have been fully characterized, the acute cardiovascular recovery pattern in response to multiple Wingate exercise bouts performed in an interval pattern have yet to be described. Ten recreationally active males aged 19.8 ± 1.2 years performed a sprint interval session (4 Wingate tests each separated by 4.5 minutes of recovery). Heart rate (HR), blood pressure (BP), stroke volume (SV), and cardiac output (CO) were measured prior to exercise (PRIOR), at two-minutes of recovery (R2) and then at 15-minute intervals until 120 minutes (R120). HR was elevated at R2 compared to PRIOR, and remained elevated at R120. SV was significantly decreased from 87.3 ± 5.7 mL PRIOR to 60.0 ± 5.6 mL at R2. CO was increased at R2 (7.4 ± 0.9 L/min) compared to PRIOR (5.1 ± 0.5L/min), and continued to increase to a maximum value of 8.1 ± 0.7 L/min at R15. At R2 SBP, DBP, and MAP were all elevated compared to PRIOR (155 ± 3 vs. 122 ± 3, 73 ± 2 vs. 67 ± 2, and 100 ± 3 vs 85 ± 2 mmHg respectively). Although SBP and MAP returned to resting values at R15, DBP continued to decrease, resulting in relative hypotension from R15 and R30. These results indicate that the recovery time is longer after multiple Wingate exercise, than after a single Wingate bout. This type of supramaximal exercise may pose a risk to untrained individuals by temporarily reducing SV in recovery. Supported by NSERC.

3.15

THE EFFECTS OF SHORT-TERM ENDURANCE EXERCISE TRAINING ON VASCULAR FUNCTION IN YOUNG MALES

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We investigated the effects of a short-term model of endurance exercise training (6 consecutive days, 2 hours/day at 65% VO2peak) on arterial stiffness and vascular conductance (VC) in young males. Fourteen healthy males (<2 hours of low-moderate physical activity/week) with a mean age ($\pm$ SD) of 25 $\pm$ 4 years were recruited. Measures of peak oxygen consumption (VO2peak), arterial stiffness and VC were obtained prior to and two days following the cessation of the training program. VO2peak was directly measured during a graded exercise test on a cycle ergometer. Indices of arterial stiffness were obtained by applanation tonometry using a commercial system to determine aortic augmentation index normalized to a heart rate of 75bpm (AIx@75bpm), and central and peripheral pulse wave velocity (CPWV; PPWV). Resting and maximal calf VC were calculated from concurrent measures of blood pressure and calf blood flow using venous occlusion strain-gauge plethysmography. Following training, there was a significant increase in VO2peak (42.8 ± 6.0 ml•kg^{-1}•min^{-1} vs. 44.1 ± 5.5 ml•kg^{-1}•min^{-1}, $p<0.05$). Both the CPWV (5.9 ± 0.8 m/s vs. 5.4 ± 0.8 m/s) and PPWV (9.7 ± 0.8 m/s vs. 8.9 ± 1.3 m/s) were significantly reduced following training ($p<0.05$). No significant changes were observed for the AIx@75bpm or in maximal VC following training. These data indicate that favorable changes in arterial stiffness can be achieved in healthy young males following only six days of intensive endurance exercise.

3.16

HEART RATE RESPONSES TO TRANSITIONS FROM LOW AND HIGH WORKRATES BEFORE AND AFTER SPRINT INTERVAL TRAINING

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Endurance exercise training reduces steady-state exercise heart rate and speeds oxygen uptake kinetics in previously sedentary individuals (Phillips et al. J. Appl. Physiol. 1995). Sprint interval training (SIT) increases VO_{2peak} and exercise performance (Burgomaster et al. J. Physiol. 2008). The effects of SIT on steady-state heart rate (HR) and the kinetic HR responses have not been evaluated. Eight young healthy individuals (4 males) (age: 22.8 ± 0.78 y, H: 1.7 ± 0.03 m, 68.9 ± 3.6 kg) completed 6 wks of SIT consisting of four to six 30-s "all-out" sprints separated by 4.5 min of recovery on a cycle ergometer, 3 d/wk. Before and after training, participants completed 3 trials of a step transition from a low (2 min) to high intensity (5 min) on an electrically braked kicking ergometer. Kicking exercise trials were separated by 10 min. ECG was recorded continuously throughout these transitions. HR during low intensity kicking was decreased following training (98 ± 5 vs. 94 ± 5 bpm; $p<0.04$). As well, end exercise HR was decreased following training (147 ± 9 vs. 141 ± 8 bpm; $p<0.02$). HR drift as determined by the difference between HR at the 3rd and 5th minutes was not significantly altered with training (7 ± 1 vs. 5 ± 1 bpm; $p=0.14$). These results indicate that steady state submaxmal HRs during both low and high intensity kicking exercise are lowered with SIT. This suggests cardiac performance is enhanced and more efficient. Supported by CIHR and NSERC.

3.17

MODELING STUDY OF MUSCLE PUMP, STARLING RESISTOR AND HEART RATE DURING EXERCISE

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To analyze the changes in distribution of blood flow during exercise and effects of muscle contractions we developed a dynamic computational model of the circulation. The model consisted of a series of elastic chambers representing venous and arterial circulations and the heart and included parallel systemic compartments; one with a slow time constant (Tau) of venous drainage (splanchnic bed) and a fast Tau (muscle bed). For the initial simulation of peak exercise, we distributed 90% of Q to muscle, decreased venous resistance by 50%, and increased stressed volume by 15 ml/kg (decreased capacitance) (Magder, 2002, 80, 971-9). We then investigated the role of an arterial Starling resistor (Pc), a muscle pump and changes in heart rate. Results: Muscle contractions (simulated by time varying elastance, duty cycle 1/4, contraction rate = 100/min) increased Q from 19 to 23 l/min with no change at higher rates and elastance > 1 mmHg/ml. There was a marked transfer of muscle blood volume centrally. The initial Pc was 30 mmHg. Values above and below the initial Pc of 30 mmHg slightly increased Q during muscle contraction. Q was higher with Pc =10 at high elastance and conversely higher with Pc = 50 at low elastance. Failure to adequately increase heart rate resulted in a marked increase in pulmonary venous pressure. Conclusion: muscle contractions decrease local venous pressure and

shift volume centrally. This decompresses the muscle vessels and moderately increases in Q. Similarly, an increase in heart rate decompresses pulmonary capillary vessels.

4.0: INTEGRATIVE EXERCISE RESPONSE

4.1

CHANGED EXPRESSION OF EXTRACELLULAR MATRIX MRNA IN JOINT CAPSULE AND PATELLA TENDON AFTER ACUTE LOW-INTENSITY TREADMILL EXERCISE

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In order to investigate whether expression of genes related to water concent, stiffness and elasticity in connective tissues of joint capsule and patella tendon changes with mild exercise, we used an acute low-intensity treadmill running protocol in rats at 55-60% VO_2max (18 m/min, 5°) for 30 min. We confirmed changes of gene expression of hyaluronic acid synthase (HAS), core protein of versican (PG-M) and splicing variants of PG-M, matrix metalloproteinase 3 (MMP3), collagen type I and III, HSP27, and HSP47 using RT-PCR analysis and the level of hyaluronic acid (HA) in joint capsule and patella tendon 1, 6, 12, and 24 hours of recovery from the exercise. Expression of each HAS mRNA was elevated with exercise after 6 hour of the exercise. Expression of total PG-M gene was elevated significantly and all splicing variant except V3 increased significantly after 6h of recovery. Significant increase of gene-expression of type III collagen in treadmill groups was also found compared with control groups at 12h and 24h of recovery. However, expression of type I collagen mRNA did not change during recovery. Expression of HSP27 mRNA was increased with exercise at 24h recovery. We concluded that treadmill exercise alters mechanical properties of knee joint by increasing water contents and elasticity of the connective tissue induced by the increased expression of HA and other related genes.

4.2

RELATIVE SAFETY AND EFFICACY OF BLOOD FLOW RESTRICTED RESISTANCE EXERCISE

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Blood flow restricted resistance exercise (BFRE) increases muscle mass and strength, however little is known about its safety despite theoretical concerns. In the present study, 12 healthy subjects had their nerve conduction velocity (NCV), prothrombin time (PT) pulse wave velocity (PWV, index of arterial stiffness), ankle-brachial index (ABI) and isometric and 1-repetition maximum (1-RM) strength assessed before and after 4-weeks of BFRE knee extension training (n=7; intensity=20% of strength) or high intensity resistance exercise (HIRE) training (n=5; intensity=80% of strength). Training was performed 3 days/wk (3 sets). During BFRE a cuff was inflated to 30% above systolic blood pressure. Isometric strength increased similarly in both groups (BFRE: 9.8±5.0% and HIRE: 6.0±1.1%), although 1-RM increased more with HIRE (12.6±3.6% vs 3.0±0.1%). PT and ABI values did not change in either group (p=0.87 and 0.43), and all subjects remained within the normal lab values for both outcomes (PT range 0.9-1.2; ABI range (0.91-1.25). NCV did not change in either group with training (BFRE: 0.8±1.3%% and HIRE: -2.1+2.7%) (p=0.67) nor did PWV (BFRE: 9.07±0.05 to 8.71±0.04 m/sec and HIRE: 7.95±0.03 to 8.05±0.06 m/sec). These findings indicate that BFRE induces similar gains in isometric strength as HIRE, and that neither protocol significantly alters the assessed neurovascular outcome measures. Future studies using longer training durations and special populations are warranted.

4.3

INTERMITTENT HYPOXIA CONDITIONING IMPROVES EXERCISE PERFORMANCE, HEMODYNAMICS, AND VENTILATION OF HEALTHY SENIOR MEN WHO AVOID EXERCISE

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Impact of exercise on the hemodynamic effects of intermittent hypoxia conditioning (IHC) was investigated in healthy, 60-74 yr men. Fourteen men (Gr 1) who exercised daily were compared with 21 (Gr 2) who avoided exercise. Before and after 10 days of IHC, the ventilatory response to sustained hypoxia (SH, 12% O_2 for 10 min), work capacity, and forearm cutaneous perfusion were determined. IHC (normobaric rebreathing for 5 min) was administered to reduce FiO_2 to 12%; during the remaining 3.5-4 min of IHC, O_2 and CO_2 were added to maintain FiO_2 at 12% and $PetCO_2$ at its pre-hypoxia value. SaO_2 was reduced to 85-86%. Four periods of hypoxia were separated by three 5-min periods of room air inspiration. No pathological ECG changes were observed, and ventilatory response to SH was unaltered by IHC. In Gr 1, IHC produced no changes in hemodynamic indices and work capacity. In Gr 2, IHC decreased BP by 7.9±3.1 mm Hg*, increased submaximal work by 11.3%*, and increased anaerobic threshold by 12.7%*. The increase in HR and BP caused by a 55 W work load was reduced by 5% and 6.5%, respectively*. Cutaneous perfusion increased by 0.06±0.04 ml/min/100 g in Gr 1 and by 0.11±0.04 ml/min/100 g in Gr 2*. Hyperaemia recovery time increased significantly by 15.3±4.6 s in Gr 1 and by 25.2±11.2 s in Gr 2. Thus, IHC was well tolerated by healthy senior men. IHC had greater positive effects on hemodynamics, microvascular endothelial function, and work capacity in men who avoided exercise. *P<0.05.

4.4

EXERCISE AND OSTEOPATHIC LYMPHATIC PUMP TREATMENT INCREASE LYMPH FLOW IN CONSCIOUS DOGS WITH NORMAL AND EXPANDED EXTRACELLULAR FLUID VOLUME

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Exercise, expansion of the extracellular fluid volume (ECE), and osteopathic lymphatic pump treatment (LPT) have previously been demonstrated to increase lymph flow. Interactions among these interventions were investigated in eight conscious dogs instrumented with an aortic catheter and an ultrasonic flow transducer implanted on the thoracic lymph duct. LPT and moderate treadmill exercise (3 mi/hr, 0% grade) were performed for 8 min before and after ECE with normal saline, iv, 4.4±0.3% body weight. Before ECE, LPT increased lymph flow from 1.7±0.5 to 5.0±1.1 ml/min at 1 min. Following ECE, LPT increased lymph flow from 4.8±0.6 to 9.9±1.1 ml/min at 1 min. Lymph flow remained significantly above pre-treatment baseline for 4 min before and after ECE. The net increase in lymph flow produced by LPT was 15.4±1.1 ml before ECE and 18.3±3.8 ml after ECE. Moderate treadmill exercise increased lymph flow from 1.0±0.3 to 8.9±1.9 ml/min at 1 min before ECE and from 4.0±0.3 to 15.2±3.0 ml/min at 1 min after ECE. Lymph flow during exercise remained significantly above baseline for 4 min before and for 6 min after ECE. The net increase in lymph flow produced by exercise was 24.9±5.5 ml before ECE and 39.6±5.1 ml after ECE (P<0.05 vs LPT). Expansion of the extracellular fluid volume produced large increases in thoracic duct lymph flow, which were further augmented by lymphatic pump treatment and more so by moderate treadmill exercise. (NIH grant U19 AT002023).

4.5

EFFECTS OF ESTROGENS AND PROGESTERONE ON AVP SECRETION, THIRST AND SERUM SODIUM CONCENTRATION

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We hypothesized that an early osmotic threshold for arginine vasopressin (AVP) release contributes to exercise-associated hyponatremia (EAH) in women and estradiol (E) and progesterone (P) influence this association. Six women with prior hyponatremia [EAH, 24(4) y, 21.4(2.4) kg/m^2] and 8 controls [NC, 24(4) y, 24.1(0.8) kg/m^2] took a gonadotropin releasing hormone antagonist (G, 16 days), G+E (E, 0.2 mg/d, 11 days) and G+E+P (E/P, 200 mg/d, 4 days). Under each hormone condition, subjects cycled (35°C) at 65%VO_{2peak} for 60 min, then at 60% VO_{2peak} for 120 min (8 ml/kg water intake every 30 min over the final 120 min). Blood was collected at 15 and urine at 60 min intervals. $S[Na+]$ fell by 5.9, 4.7, and 5.6 mEq/L with drinking in G, E, and E/P in EAH, with little fall in NC despite similar weight change. P_{Osm} threshold for AVP release (intercept of linear $P_{[AVP]}$-P_{Osm} relationship in first 60 min of exercise) was lower in EAH vs NC during G. During E, the threshold fell in NC [278(7), 273(8) and 277(7) mOsmol/kg H_2O, P<0.05] but increased in EAH [273(8), 279(4) and 275(5) mOsmol/kg H_2O, in G, E and E/P, P<0.05]. The P_{Osm}-thirst threshold was lower in NC [279(4), 276(11) and 273(7)] vs EAH [284(4), 283(5) and 278(4) mOsmol/kg H_2O, in G, E and E/P, P<0.05]. The osmotic AVP operating point shifted lower in women at risk for EAH but increased with E. However free water clearance was similar across groups and treatments arguing against a role for AVP in EAH.(Support by GSSI).

4.6

MUSCLE VOLUME DECREASES WITH WHOLE BODY DEHYDRATION

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While performance decrements associated with dehydration are well described, the underlying changes in water content across tissues are not known. Here we sought to investigate changes in muscle volume associated with whole body dehydration. To this end, twelve active, heat acclimated subjects (5F;7M) were required to cycle in the heat (38 C, 33% humidity, 13 kph wind) on 2 test days (one dehydration one with fluid replacement). Each test day included evaluation of body weight, quadriceps femoris (QF) muscle volume using MRI and blood sampling for blood osmolality. Subjects were evaluated 3 times on each test day; rest and again at 3% and 5% of estimated total body water (TBW) loss. Upon attaining the 3% and 5% loss of TBW, subjects were removed from the heat and rested in the supine position for 45 min. Blood samples and MRI scans were obtained 1 hour after the end of each exercise bout (to allow for fluid redistribution). Right side QF volume decreased (p<0.01) on the dehydration day (rest=1.53±0.48 L; 3%=1.47±0.46 L; 5%=1.42±0.42 L) with no change (p>0.05) on the fluid replacement day (1.49±0.44 L; 1.48±0.44 L; 1.48±0.44 L). QF volume decreased by 3.6% and 6.6% when the concurrent estimated loss of TBW reached 3% and 5% respectively. This suggests muscle volume/water reflects changes in TBW and therefore, the measurement of muscle volume/water content could potentially be used as a surrogate for evaluation of whole body dehydration. Funding: DOD and IAI.

4.7

HIGH INTENSITY INTERMITTENT EXERCISE TRAINING IN RODENTS: IMPACT ON PLASMA VOLUME AND HEPATIC ALBUMIN MRNA EXPRESSION

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We tested the ability of a 12-day high intensity intermittent exercise protocol to induce plasma volume (PV) expansion and increased hepatic albumin gene expression in rodents. 40 adult male Sprague-Dawley rats weighing between 245-350 grams were randomly assigned to one of four groups: cage control (CC); sham exercise 10 min/day at 48% VO_2max (SHAM); continuous exercise training, 60 min /day at 72% VO_2max (MI); and high intensity, intermittent exercise training, 8 bouts of 4 min at 98% VO_2max followed by 5 min at 48% VO_2max (HI). 24 hours after the last training session the rats were anesthetized and PV determined by dilution of a labeled-albumin molecule (Texas Red albumin). The liver and red quadriceps (RQ) muscle tissue was then removed, flash frozen, and stored for later analysis. HI produced a significant increase in RQ citrate synthase activity ($p < 0.05$). PV averaged 23.6 ± 2.7 ml•kg^{-1} body mass in the CC group and 26.6 ± 1.3 ml•kg^{-1} body mass in the HI group. The increase in PV following exercise training was a function of exercise volume (meters per day) ($p<0.05$, $r=0.98$). Albumin mRNA expression determined by real time polymerase chain reaction (PCR) increased 2.2 ± 0.1 and 2.9 ± 0.2 fold following MI and HI exercise training, respectively. These data support the hypothesis that during exercise-induced PV expansion albumin gene expression is increased and contributes to an increase in plasma albumin content and PV expansion.

4.8

OPIOID-MEDIATED MUSCLE AFFERENTS INHIBIT CENTRAL MOTOR DRIVE AND LIMIT PERIPHERAL MUSCLE FATIGUE TOLERANCE IN EXERCISING HUMANS

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We investigated the role of somatosensory feedback from locomotor muscles on central motor drive (CMD) and the development of peripheral fatigue during high-intensity endurance exercise. In a double-blind, placebo-controlled design, 8 cyclists randomly performed 5km time-trials: placebo ($5K_P$, interspinous saline, L3-L4) and intrathecal fentanyl ($5K_F$, L3-L4) to impair cortical projection of opioid-mediated muscle afferents. Quadriceps fatigue was assessed via changes in force output pre vs post exercise in response to magnetic nerve stimulation (ΔQ_{tw}). CMD during the time-trials was estimated via quadriceps EMG (iEMG). Fentanyl had no effect on quadriceps strength. Impairing neural feedback from the locomotor muscles increased iEMG during the 1st half of $5K_F$ vs $5K_P$ by 12% ($P<0.05$); during the 2nd half iEMG was similar between trials. Power output was 6% higher during the 1st and 11% lower during the 2nd half of $5K_F$ vs $5K_P$ ($P<0.05$). Capillary blood lactate was higher (16 vs 13 mmol/L) and arterial HbO_2 saturation was lower (89 vs 94%) following $5K_F$ vs $5K_P$. Exercise-induced ΔQ_{tw} was greater following $5K_F$ vs $5K_P$ (-46 vs -33%, $P<0.01$). Our results emphasize the critical role of neural feedback from working muscles on the determination of CMD and force output. Attenuated afferent feedback from exercising locomotor muscles results in an overshoot in CMD and power output normally chosen by the athlete, thereby causing more muscle metabolites and excessive peripheral muscle fatigue.

4.9

REVERSE LACTATE THRESHOLD - A PILOT STUDY OF A HIGH-RESOLUTION, SINGLE-SESSION, ANAEROBIC-THRESHOLD TEST

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Background: Existing single-session, anaerobic-threshold (AnT) tests show unsatisfactory validity, reliability and resolution, while the main shortcoming of the accepted 'gold standard', the multi-session Maximal Lactate (La) Steady-State (MLSS) test, is its prohibitive impracticality. Purpose: To introduce the 'Reverse Lactate Threshold' test (RLT) – a single-session AnT test that identifies La's highest equilibrium in the blood by progressively approaching it, in reverse, from higher rather than from lower exercise intensities. Subjects & Methods: Four athletes of different sports (rowing, cycling, running) and training levels completed all RLT and MLSS-verification tests. Accepted MLSS determination standards were used as the verification criterion. One athlete was retested after 2.5 months of endurance training to gauge RLT's sensitivity to fitness changes. Results: RLT–MLSS agreement to within 1 watt (<0.5%) or <0.1 mph (~1%) was shown in all 4 subjects. Full post-training RLT–MLSS agreement at the 1 watt resolution was shown at a markedly higher level in the re-tested athlete. Conclusions: The RLT precisely predicted MLSS intensity in all subjects. Its single-session attribute makes it highly practical for routine athletic testing. Based on the present pilot data, the RLT appears to at least match the MLSS test's resolution in estimating true AnT exercise intensity and in reflecting AnT changes with training. [Funding: Brock University].

4.10

EFFECTS OF A 12-WEEK RESISTANCE TRAINING PROGRAM ON MUSCLE GROWTH AND BASAL GENE EXPRESSION IN YOUNG AND OLD WOMEN

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The purpose of this study was to measure whole muscle adaptations and basal level anabolic and catabolic gene expression (GE) before and after 12 weeks of progressive resistance training (PRT). Eight young women (YW; 23±2 y, 67±5 kg) and 6 old women (OW; 85±1 y, 67±4 kg) performed 3 x 10 knee extensions at 70% of 1-RM, 3 days/week for 12 weeks. Vastus lateralis muscle biopsies were obtained in the resting state before and after 12 wks of PRT. mRNA levels of MyoD, MRF4, myogenin, MGF, IGF-1, myostatin, MuRF-1, atrogin-1 and FOXO3A were measured using real-time RT PCR. As a result of PRT, YW had an increase ($p<0.05$) in whole muscle size (5%) and 1-RM strength (36%). OW increased ($p<0.05$) 1-RM strength (26%), but did not hypertrophy. In YW basal level GE decreased ($p<0.05$): IGF-1 (35%), myostatin (52%), MuRF-1 (29%), and FOXO3A (37%, $p=0.08$). In OW basal level GE increased ($p<0.05$): IGF-1 (48%, $p=0.06$), MGF (328%), and myostatin (34%). After PRT, OW expressed higher ($p<0.05$) mRNA levels of MyoD, myogenin, IGF-1, myostatin, MuRF-1, and FOXO3A compared to YW. These data suggest that in YW a decrease in catabolic markers myostatin, MuRF-1 and FOXO3A mRNA levels may play an integral role in the whole muscle adaptations observed with PRT. Whole muscle adaptations were blunted in OW, and although MGF and IGF-1 mRNA increased, it may have been negated by the failure to decrease already high age-related mRNA levels of catabolic markers. Supported by NIH grant AG18409.

4.11

THE EFFECTS OF INTRINSIC AEROBIC CAPACITY AND DIET ON INSULIN SIGNALING AND IKK-BETA ACTIVITY IN RATS

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Physical activity results in many beneficial effects, including improved insulin sensitivity and signaling in skeletal muscle. The use of low (LCR) and high-capacity endurance running (HCR) rats provides a model wherein genetic differences can be explored without a confounding effect of training. To explore the mechanisms that may explain the contrast in insulin sensitivity between animals that differ in inherent aerobic capacity, LCR and HCR rats were fed either chow or high-fat diet (HFD) in the untrained state. We measured IKK-beta activity and IRS-1 pSer307 in MG after 12 wk of feeding. OGTT-AUC revealed greater glucose and insulin levels in the LCR rats on HFD vs HCR rats and insulin values were higher in LCR vs HCR rats on both diets. IkappaB-alpha levels, an inverse indicator of IKK-beta activity, were 13% lower in LCR vs HCR chow-fed rats and this disparity increased to 47% on the HFD. In contrast to the HCR rats, IkappaB-alpha levels in the LCR rats on the HFD were 28% lower vs those fed chow. Also, pSer307 levels in the LCR rats increased 31% on the HFD vs chow. From these data we conclude that the differences in insulin sensitivity between LCR and HCR rats are partly explained by differences in IKK-beta activity and pSer307 levels and that, unlike LCR rats, HCR rats are resistant to the signaling defects that accompany a HFD. This work was supported by NIH Grants DK046121 and DK061314.

4.12

HIGH INTENSITY EXERCISE INDUCES IMMUNE SUPPRESSION THROUGH ENDOCANNABINOID INCREASE

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The main scope of this research was to characterize experimentally the precise nature of endocannabinoid response to exercise, specifically the relative importance of intensity and duration, and alterations in the immune system response via the endocannabinoids, a result suggestive of a new possible explanation for immunological and psychological changes. 60 male rats were categorized randomly into 3 groups labelled as; (a) Control (b) moderate and (c) endurance type of exercise groups. Experimental procedures are set forth in the Declaration of Helsinki and the APS " Guiding Principals in the Care and Use of Animals". Rats were exercised 5 days per week for 16 weeks. Blood samples were collected immediately after the last bout of exercise. Anandamid (ANA) and 2-Arachidonylglycerol (2-AG) serum levels were determined with Affinity Chromatography and HPLC; whereas alterations in immune cells (T cells, B cells, NK cells) were determined quantitatively by Flow Cytometry. One way ANOVA test followed by Tukey posthoc tests showed that endurance type of exercise would increase plasma ANA and 2-AG levels, and lower immune effector cell counts, on the average, more than the moderate type of exercise group and control group. Correlation coefficients were computed among immunity effector cells and endocannabinoids and Bonferroni Approach was used to control for Type I Error. The results showed statistically significant negative correlations between ANA and WBC (r= -.80, p< .001), B cells (r= -.53, p= .005), T cells (r= -.50, p= .009) , whereas 2-AG was significantly correlated with WBC (r= -.52, p= .004)cells. It can be concluded that both ANA and 2-AG increase as a response to exercise,there by giving rise to immune system alterations.

4.13

ACUTE RESPONSES TO BLOOD FLOW RESTRICTED EXERCISE

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Blood flow restriction (BFR) during low intensity exercise results in a potent muscle growth response in humans. However, there may be serious side effects due to the restriction of blood flow. Therefore, we evaluated the acute cardiovascular and blood coagulation responses to knee extension exercise performed at 20% of maximal strength with BFR in comparison to a free-flow (FF) bout performed at 80% of maximal strength. Five healthy subjects aged 29-39 years reported to the laboratory between 7 and 9 AM on two separate occasions in a fasted condition. During BFR exercise, a 10 cm wide tourniquet cuff was placed around the upper thigh at 1.5 systolic blood pressure immediately before exercise and remained inflated (~15 minutes). Subjects reported greater peak pain levels on a 0 to 10 scale during the 20% BFR (7.8 ± 1.8) compared to the 80% FF (5.5 ± 2.8) condition. Peak heart rate showed similar responses to both conditions (BFR: 83.8 ± 12.4 vs. FF: 84.8 ± 6.7). Peak systolic blood pressure (BFR: 148.8 ± 12.9 vs. FF: 139.0 ± 15.6) and diastolic blood pressure (BFR: 102.6 ± 4.3 vs. FF: 96.4 ± 12.0) was slightly, but not statistically higher during BFR exercise. D-dimer, a degradation product of crosslinked fibrin showed no change 30 min post exercise for either condition. In conclusion, resistance exercise performed at low intensity with BFR has similar cardiovascular and blood coagulation alterations when compared to FF resistance exercise performed at high intensity.

4.14

LOCOMOTOR COMPENSATION IN A MOUSE MODEL OF MUSCULOSKELETAL DEGENERATION

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Osteoarthritis (OA) is a degenerative joint disease that causes pain and impaired mobility and may contribute to physical inactivity. To better understand how animals with OA adapt their locomotor behavior to accommodate joint-loading induced pain, we examined the spontaneous activity levels and gait patterns in collagen type IX knock-out (KO) mice. We hypothesized that KO mice would alter their gait to reduce the magnitude of joint loading and decrease their spontaneous locomotor activity to reduce the daily frequency of joint loading. To test this, we quantified changes in joint loading patterns and spontaneous activity levels during low intensity (over-ground) and high intensity (wheel) locomotion in 5 WT and 5 KO 15 month-old mice. High-speed video data were used to calculate stride frequency and duty factor during wheel and speed-matched treadmill running, and knee OA scores were determined by histological analysis. At matched speeds, KO mice used the same stride frequencies and duty factors for both treadmill and wheel running, suggesting that joint loading patterns are not significantly altered. Rather, KO mice alter the frequency of daily joint loading. Cartilage structural degeneration was negatively correlated with over-ground and wheel running distance. Furthermore, KO mice had greatly reduced high intensity (wheel) but not low intensity (over-ground) running distances and speeds, consistent with recent human OA studies. Funding support from NIH AR051672, AR50245, AR047442, and the Arthritis Foundation.

4.15

THE RELATIONSHIP BETWEEN AEROBIC CAPACITY, BODY COMPOSITION, AND PHYSICAL ACTIVITY AMONG ETHNIC GROUPS

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Whether aerobic capacity (VO2max) is associated with physical activity levels or whether these are two distinct phenotypes – as is the case in rodents - is unknown. The purpose of this study was to examine the relationship between VO2max, body composition, and physical activity levels in various ethnic groups. Sixty healthy, non-smoking men and women completed a maximal treadmill test, body composition testing (BOD POD), and wore an accelerometer (Actigraph) for seven days to measure physical activity. African Americans (AA: 24.7±6.2 years, 74.4±15.1 kgs) had significantly ($p>0.05$) lower VO2max than European Americans (EA: 24.2±5.4 years, 68.4±17.6 kgs) and Hispanics (27.5±6.45 years, 60.7±3.7 kgs). AA and Asian Americans (ASA: 21±1.7 years, 62.7±18.3 kgs) had lower mean steps per day (MSPD) than EA (23% difference). ASA had significantly lower percent body fat (BF) than the other groups (21.5±4.8% vs 27.8±10.3%). All associations were similar regardless of ethnic group. These results support previous research that there are ethnic differences in these measures and that physical activity, age and body composition are associated with VO2max.

4.16

EFFECTS OF EXERCISE AND WEIGHT LOSS ON SKELETAL MUSCLE ADIPOSE TISSUE TRIGLYCERIDE LIPASE

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Adipose Tissue Triglyceride Lipase (ATGL) is a protein recently discovered in adipose tissue reported to promote triglyceride lipolysis. Its function in skeletal muscle has not been elucidated. The purpose of this study was to examine the effects of calorie restriction-induced weight loss and moderate exercise on ATGL protein expression in human skeletal muscle. Skeletal muscle ATGL protein content determined by Western blot analyses in six overweight to obese (BMI=30.5±1.6kg/m^2) subjects increased (P<0.05) with 16 weeks of moderate aerobic exercise with or without diet-induced weight loss. ATGL was not related, however, to improvements in insulin sensitivity determined by the glucose clamp. In conclusion, these novel data are the first to suggest that ATGL protein can be modulated in human skeletal muscle by exercise and weight loss. Further investigations are needed to determine whether changes in ATGL are implicated in alterations in storage or utilization of lipids within skeletal muscle. Moreover, these data warrant further investigation into the differential effects of exercise and weight loss on several other, as of yet, uncharacterized lipid droplet proteins within skeletal muscle.

4.17

HYDROGEN ION THRESHOLD DIFFERS BETWEEN THE THIGH AND CALF MUSCLES DURING LOCOMOTION

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An exercise-induced hydrogen ion (H^+) threshold can be detected in the vastus lateralis (VL) using near infrared spectroscopy (NIRS) and is correlated with lactate threshold. Different levels of work in upper and lower leg muscle during locomotion may result in dissimilar rates of H^+ accumulation and perhaps influence the onset of local fatigue. We hypothesized that the H^+ threshold in the lateral gastrocnemius (LG) would precede the H^+ threshold in the VL because of the predominant role of the LG in stance and propulsion during locomotion. Nine healthy subjects exercised on a motorized treadmill at 3.2 km·h^{-1} for 3 min, increasing 1.6 km·h^{-1} each 3 min until reaching 85% of predicted maximal heart rate. NIRS sensors were secured over the VL and LG. Whole-body oxygen consumption (VO_2) was measured using a standard metabolic cart. H^+ threshold was defined as the VO_2 at which the slope of [H^+] increased with work rate as determined by a simultaneous bilinear regression (R^2>0.68). Paired t-tests were used to detect differences in H^+ threshold between muscles. The H^+ threshold occurred at a lower VO_2 in the LG (1.00±0.26 l·min^{-1}; mean ±SD) than in the VL (1.26±0.40 l·min^{-1}, p=.003), which corresponded to a lower treadmill speed (LG: 5.6±0.9; VL: 6.6±1.3 km·h^{-1}, p=.01). The lower H^+ threshold of the LG, compared to the VL, may lead to an earlier onset of LG fatigue during higher treadmill walking speeds, potentially influencing the walk-to-run transition. Supported by NSBRI.

4.18

PHARMACOLOGICAL BLOCKADE OF THE TRPV1 RECEPTOR IN SKELETAL MUSCLE ATTENUATES THE EXERCISE PRESSOR REFLEX IN RATS

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The skeletal muscle exercise pressor reflex (EPR) contributes importantly to increases in heart rate (HR) and mean arterial pressure (MAP) during physical activity. This reflex is activated during contraction by stimulation of afferent fibers responsive to mechanical distortion and/or the metabolic by-products of muscle work. However, the receptors responsible for activating these afferent fibers have yet to be precisely identified. It has been reported that pharmacological stimulation of the transient receptor potential vanilloid 1 (TRPv1) receptor within skeletal muscle (localized to unmyelinated afferent fibers) elicits increases in MAP and HR similar to those generated by the EPR. Thus, we hypothesized that stimulation of the TRPv1 receptor during muscle contraction contributes to the activation of the EPR. The EPR was stimulated by electrically-induced static muscle contraction in Sprague-Dawley rats before and after the administration of the TRPv1 receptor antagonists, capsazepine (Capz; 100 µg/100 µl) and iodoresinaferatoxin (IRTX; 1µg/100 µl). Muscle contraction induced increases in both HR (8±2 bpm) and MAP (21±3 mmHg). The HR and MAP responses to contraction were significantly lower (P<0.05) after the administration of both Capz (2±1 bpm; 7±1 mmHg, respectively) and IRTX (3±2 bpm; 5±3 mmHg, respectively). The data suggests that the TRPv1 receptor contributes importantly to activation of the EPR during muscle contraction. Supported by HL-070242 and AHA-0735355N.

4.19

METABOLIC ADAPTATIONS TO VOLUNTARY WHEEL RUNNING IN HYPERTENSIVE HEART FAILURE PRONE RATS

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Heart failure (HF) is associated with a number of physiologic and metabolic abnormalities. Female Spontaneously Hypertensive Heart Failure (SHHF) and Wistar-Firth (WF) rats were housed with access to running wheels from 6-22 months of age. The wheels were connected to a Minimitter™ system using a magnetic sensor to record wheel rotations. At 22 months hindlimb muscles were obtained for metabolic measures that included mitochondrial enzyme function and expression, and muscle glycogen utilization. The SHHF rats exercised for longer periods than the WF (5.2±1.6 vs. 1.8±1.0 km•d-1, p<0.05; and 330±50 vs. 110±36 min•d-1, p<0.05), but not at a faster pace. Muscle citrate synthase gene and protein expression (EX: 0.038±0.05 vs. SED: 0.026±0.008 au; p<0.05; and 1.913±0.793 vs. SED: 0.764±0.120 au; p<0.05, respectively), citrate synthase activity (EX: 430.4±60.5 vs SED: 315.2±29.2 nmol•min-1•mg protein-1, p<0.05), and ß-hydroxyacyl-CoA dehydrogenase activity (EX: 83.6±3.8 vs. SED: 67.5±8.4 µmol•min-1•gwwt-1; p<0.05), were all increased with exercise in the WF, but not in the SHHF. The WF also experienced glycogen depletion (EX: 43.5±5.8 vs. SED: 90.2±7.5 µmol•gwwt-1; p<0.05) after exercise, but glycogen levels were similar for the SHHF exercise and sedentary groups. SHHF rats exposed to running wheels show no evidence of upregulation of metabolic pathways in skeletal muscle. Supported by NIH grants AG12834, HL62459, P20 RR017662, and P20 RR15576, and US NSF grant IOB-0448060.

4.20

INFLUENCE OF SHORT-TERM SPRINT-INTERVAL TRAINING ON INSULIN SENSITIVITY AND THERMOGENIC RESPONSE TO BETA-ADRENERGIC STIMULATION IN YOUNG ADULT HUMANS

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Sprint-interval training (SIT) and traditional endurance training may elicit similar physiological adaptations. From the perspective of metabolic regulation, hallmarks of endurance-trained adults include increased insulin sensitivity and augmented thermogenic response to beta-adrenergic (β-AR) stimulation, an important determinant of energy balance. Accordingly, we have investigated the hypotheses that short-term SIT will increase insulin sensitivity and augment β-AR metabolic function. 9 sedentary or recreationally active adults (19.8 < body mass index < 34.8 kg·m^{-2}) completed 6 sessions of repeated (4 to 7) 30-second bouts of very high-intensity cycle ergometer exercise over 14 days. Prior to and 72 hours following completion of SIT the following variables were quantified: Study 1 (n=4) insulin sensitivity (hyperinsulinemic euglycemic clamp); Study 2 (n=5) energy expenditure (EE: ventilated hood technique) at rest (REE) and during intravenous β-AR stimulation (isoproterenol: 24 ng·kg fat free mass^{-1}·min^{-1}). Compared with baseline, SIT increased insulin sensitivity (Glucose infusion rate: 5.7±1.9 vs. 8.3±2.2 mg·kg^{-1}·min^{-1}; mean±SE; P=0.099), did not affect REE (1275±145 vs. 1180±127 kcal·day^{-1}; P=0.20), and augmented the thermogenic response to β-AR stimulation (ΔEE: 23.9±3.6 vs. 34.0±4.2%; P=0.08). These preliminary data suggest short-term SIT may be a viable alternative to endurance training as a strategy for improving metabolic regulation. Support: NIH AG02205.

4.21

SKELETAL MUSCLE MITOCHONDRIAL DYSFUNCTION IN PULMONARY ARTERIAL HYPERTENSION

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STUDY OBJECTIVE: This laboratory has recently described blunted systemic oxygen extraction at maximum exercise in pulmonary arterial hypertension (PAH)*. The purpose of this study is to determine whether exercising limb skeletal muscle mitochondrial dysfunction is responsible. METHODS: Patients with PAH (n=6) defined by right-heart catheterization, and controls (n=5), underwent 3 minutes of isotonic quadriceps exercise at 0.5 Hz at 40% of MVC. ^{31}P-magnetic resonance spectroscopy of vastus medialis was performed in a 3T whole-body Siemens magnet. [Hb] < 10 mg/dl and exercise SpO_2 < 0.90 were excluded. Phosphocreatine (PCr) recovery following cessation of exercise was modeled monoexponentially, and tau (τPCr) was compared by unpaired t-test. RESULTS: Relative metabolic stress at cessation of exercise was similar for patients and controls, by end exercise intracellular pH (6.92±0.06 vs. 6.90±0.03) and ratio of PCr/Pi (1.37±0.27 vs. 2.19±0.56, p>0.05 for both). τPCr was slowed in PAH vs. controls (57.4±6.3 vs. 33.5±2.7 s, p<0.02). CONCLUSIONS: Delayed limb skeletal muscle PCr recovery following submaximal exercise with normal arterial O_2 content suggests an intrinsic abnormality of mitochondrial ATP synthesis and that PAH is more of a systemic disease than previously recognized. * Tolle JJ, et al. Med Sci Sports Exerc. 2008; 40:3-8.

4.22

CHANGES IN MOOD AND CORTISOL WITH EXERCISE AND REST

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Moderate exercise yields many benefits, including stress relief. However, cortisol, often used as a measure of stress, can be released both in response to psychological stress and as a normal physical response to exercise. We assessed the effects of 30 minutes of inactivity, very light exercise, or moderate exercise, including 30-minute rest period following treatments to monitor delayed changes in cortisol or mood. Cortisol levels dropped significantly for all treatments (2-way repeated-measures ANOVA, p=.007), with a similar pattern for inactivity and low intensity exercise. Cortisol levels were still elevated after moderate exercise, followed by a significant drop after 30 minutes of rest (t-test, p<.05). All participants exhibited a drop in Beck Anxiety Inventory scores with time, but the change was greatest for moderate exercise (2-way repeated-measures ANOVA, n=23, p<0.05). Changes in the Feeling Scale indicated an improvement in mood regardless of treatment (2-way repeated-measures ANOVA, n=20, p=0.018). There was a larger change for moderate exercise than for inactivity, and low-intensity exercise did not differ significantly from either. Relaxation may be as effective as moderate exercise in improving mood in individuals who are not anxious, but moderate exercise may be more effective in reducing anxiety than very light exercise or inactivity.

4.23

IMPAIRED CARDIAC CYCLE TIMING EVENTS POST-MARATHON AS DETECTED USING DIGITAL BALLISTOCARDIOGRAPHY

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Non-invasive dBG records timing of events and forces of contraction of the heart during the cardiac cycle. We hypothesized that the timing events would be altered after exertional exercise, and thus used dBG to observe whether functional disturbances can occur in the cardiac cycle before and after the 2008 Boston Marathon. In a single case study (female, 40 yr) pre- and post-marathon (Day1, Day2, Day3, Day7) resting dBG measurements were taken simultaneous with ECG. All dBG data was corrected to 60 bpm. The results showed, in comparison to pre-marathon values that there was a significant (p<0.05) reduction in the diastolic timing parameters including: atrial systole to mitral valve close on D1 (24%), D2 (30%), D3 (17%), D7 (17%), and mitral valve open to E-wave on D2 (12%) and D7 (8%), but E-wave to A-wave increased significantly on D1 (14%), D2 (29%), D3 (16%), D7 (14%). The systolic parameter aortic valve open to aortic valve close decreased (p<0.05) on D1 (11%), D2 (26%), D3 (15%), D7 (13%), as was aortic valve open to the rapid ejection period on D1 (11%), D2 (19%), D3 (13%), D7 (16%). Taken together, these results showed: 1) D2 post-marathon illustrated the most significant impairment in cardiac cycle timing and remained affected until D7, 2) alterations in systole and diastole could be related to exertional myocardial ischemia as a result of myocyte damage, and 3) dBG can be used to evaluate the dynamic alterations of the heart following intensive exercise performance Support: NSERC, Heart Force Medical.

4.24

GENDER COMPARISON OF MUSCLE GENE EXPRESSION IN RESPONSE TO RESISTANCE EXERCISE

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Generally, females do not accrue the same absolute amount of muscle mass in response to chronic resistance exercise (RE) training. However, the underlying molecular program governing these differences is poorly understood. The aim of this investigation was to compare myogenic (MyoD, myogenin, MRF4), proteolytic (atrogin-1, MuRF-1), myostatin, and myokine (IL-6, -8, -15) gene expression (GE) between male and female vastus lateralis (VL) muscles in response to RE. Biopsies from the VL of 7 males (26±3 y, 75±8 kg) and 7 females (25±3 y, 59±5 kg) were obtained before, and 2 and 6 h after 4 x 7 squat exercise at maximal effort using inertial ergometry. After exercise, both genders increased ($p<0.05$) myogenic GE (MRF4, myogenin). For proteolytic GE, both genders increased MuRF-1 initially ($p<0.05$), with females also increasing atrogin-1 ($p<0.05$) and myostatin ($p<0.05$) post-RE. In contrast, males decreased ($p<0.05$) MuRF-1 and atrogin-1 to below basal levels at the 6 h time point. Furthermore, females had a greater myokine response than males ($p<0.05$). These findings indicate that in response to an acute bout of RE, there are gender-related gene expression differences of genes involved in the regulation of muscle remodeling and growth. Specifically, these data suggest males have a more favorable molecular program to promote growth in response to RE when compared to females. Supported by NASA grant NNJ06HF59G.

4.25

GENE EXPRESSION DIFFERS IN HUMAN VASTUS LATERALIS AND SOLEUS MUSCLES IN RESPONSE TO RESISTANCE EXERCISE

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Research has indicated that the soleus (SOL) does not have the same growth response to resistance exercise (RE) as the vastus lateralis (VL). The underlying genetic basis for this disparity is unknown. The aim of this study was to compare myogenic (MyoD, myogenin, MRF4), proteolytic (atrogin-1, MuRF-1), myostatin, and myokine (IL-6, -8, -15) gene expression (GE) of the VL and SOL muscles in response to an acute bout of RE. Muscle biopsies from the VL and SOL of 7 males (26±3 y, 75±8 kg) were obtained before, and 2 and 6 h post 4 x 7 squat, and 4 x 14 calf-press exercises at maximal effort using inertial ergometry. More calf-press exercises were performed in order to equalize the muscle time-under-tension. After exercise, both muscles increased ($p<0.05$) myogenic GE (MyoD, myogenin, MRF4), with myogenin increasing more in the VL ($p<0.05$). For proteolytic GE, 2 h post-RE both muscles increased ($p<0.05$) MuRF-1 similarly, whereas 6 h post-RE proteolytic GE was suppressed in the VL ($p<0.05$) but not in the SOL. The SOL had a reduction in myostatin GE ($p<0.05$), and a more robust myokine response compared to the VL ($p<0.05$). These data show muscle-specific differences in molecular markers associated with the regulation of muscle remodeling in response to RE. Specifically, the larger induction of myogenic genes and suppression of proteolytic genes in the VL indicate a more favorable anabolic response to RE compared to the SOL. Supported by NASA grant NNJ06HF59G.

4.26

ADAPTATION OF EXERCISE VENTILATION FOLLOWING PASSIVE HEAT ACCLIMATION

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The study's objective was to assess if exercise ventilation would adapt similarly following acclimation to a hot environment as the main human heat loss response of eccrine sweating. Six males performed 2 incremental maximal exercise tests from rest to exhaustion on a cycle ergometer separated by a 10-day passive heat acclimation. Acclimation was completed at 50°C and 20% RH where participants remained seated at rest for 2 hr·day^{-1} for 10 consecutive days with their rectal temperature maintained at 38.5-39.0°C. The study was approved by the SFU Office of Research Ethics and conforms to the Declaration of Helsinki. Acclimation was confirmed by significant decreases in both resting esophageal temperature (T_{ES}) from 37.70±0.19 (mean ± SD) to 37.31±0.11°C ($p=0.001$) and during exercise in the T_{ES} thresholds for eccrine sweating from 37.68±0.20 to 37.30±0.12°C ($p=0.005$). Acclimation significantly increased exercise ventilation ($p<0.02$) and decreased T_{ES} thresholds for the ventilatory equivalents for oxygen from 38.25±0.16 to 37.85±0.14°C ($p=0.001$) and likewise for carbon dioxide from 38.28 ± 0.19 to 37.94±0.14°C ($p=0.004$). In conclusion, following passive heat acclimation, exercise ventilation during incremental tests from rest to exhaustion showed similar adaptations to eccrine sweating. This study was supported by grants from the Canadian Foundation for Innovation and from the Natural Sciences and Engineering Research Council of Canada.

4.27

ENERGETIC BALANCE RESPONSE TO PHYSICAL TRAINING DID NOT CHANGE BODY WEIGHT

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Objective: Body weight (BW) homestasis is determined by food intake (FI) and energy expenditure (EE) named energetic balance (EB). Aerobic physical training (PT) had been used to reduce BW due to increase EE, however the efficiency is dependent of EB. The aim of this study was investigate the influency of PT on EB and BW responses. Methods and Results: Male mice c57 were divided into sedentary (S, n=6) and trained (T, n=10) groups. During and after 4 weeks of swimming PT (2 session,1,5h, 5 days/week), were measured FI, BW, resting metabolic rate (RMR) by indirect calorimetry, exercise tolerance (ET) by treadmill, Lee index (LI), periepididymal (PF) and retroperitoneal (RF) fat pads and skeletal muscle soleus (MS) and gastrocnemio (MG) weight. Datas are showed as mean ± standart deviation. T group increased FI and ET significantly. BW after PT was higher in S group compared to BW before PT period (27,52±1,14 vs 29,80±1,69g), but did not change in T group (26,44±3,61 vs. 26,08±2,88g). RMR did not change in both group. LI (29,59± 0,38 vs. 28,65±1,02g$^{T/3}$/cm), PF (11,33± 2,44 vs. 11,59±2,98mg/g), RF (2,44± 0,93 vs. 2,80±0,93mg/g), MS (0,55± 0,04 vs. 0,50±0,05mg/g) and MG(10,25± 0,75 vs. 9,34±0,53mg/g) did not differ between S and T groups. Conclusion: Although PT increases EE, EB was maintened due to increased FI and inalterated RMR, which resulted in BW homeostasis. These datas showed the importance of caloric restriction association with PT to induce BW reduction efficiently.

4.28

RUNNING ALTERS THE EXPRESSION OF GROWTH RELATED GENES IN THE VASTUS LATERALIS AND SOLEUS MUSCLES

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The purpose of this investigation was to examine the muscle specific gene response to running in endurance-trained men. Eight males (26±2 yr; VO_2max 63±2 ml•kg^{-1}•min^{-1}) performed a 45-min treadmill run at 77±1% intensity. Muscle biopsies were obtained from the vastus lateralis (VL) and soleus (SOL) before, 4h and 24h post-exercise for the expression of myogenic (MRF4, myogenin, and MyoD), proteolytic (FOXO3A, MuRF-1, and atrogin-1), cytokine (IL-6, -8, -15), and myostatin mRNA using real time RT-PCR. At baseline, myostatin expression was ~2-fold higher ($P<0.05$) in SOL compared to VL while no other muscle specific differences were present. In response to running, myostatin expression was suppressed ($P<0.05$) in both muscles at 4h and rebounded to be higher ($P<0.05$) than baseline at 24h for VL only. For the myogenic genes, MRF4 was elevated ($P<0.05$) at 4h for both SOL and VL, MyoD was higher ($P<0.05$) at 4h in SOL only and myogenin expression was unaltered. For the proteolytic genes, FOXO3A was elevated ($P<0.05$) at 24h in SOL only, MuRF-1 was higher at 4h in VL only and atrogin-1 remained unchanged. IL-6 expression was elevated ($P<0.05$) at 24h in both muscles while IL-8 displayed a trend toward increasing ($P=0.06$) in both muscles. These data indicate that at the mRNA level, the soleus appears to be more responsive than the VL to run exercise. These subtle differences in gene expression may underlie muscle specific responses to chronic run training. NASA Grant NNJ06HF59G.

4.29

PROTEIN SYNTHESIS RESPONSE TO RUNNING IN HUMAN VASTUS LATERALIS AND SOLEUS MUSCLES

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The purpose of this study was to compare the anabolic response in two different leg muscles at rest and 24 hr post-exercise in endurance-trained men. Six male subjects (26±3 yr; VO_2max 63±2 ml•kg^{-1}•min^{-1}) performed a 45-min treadmill run at 77±1% intensity. Infusions of d_3-leucine were used to measure mixed muscle fractional synthetic rates (FSR) at rest and 24 hr post-exercise. An infusion of 10% amino acid solution was added to the post-exercise infusion to maximize the muscle anabolic response. Muscle biopsies were obtained from the vastus lateralis (VL) and soleus (SOL) muscles at 2 and 6 hr of the infusion for the measurement of isotope incorporation and the determination of FSR. Additional muscle biopsies were obtained prior to and 4 hr post-exercise for determination of muscle glycogen. No differences in FSR between the VL and SOL were present at rest. At 24 hr post-exercise, FSR was elevated ($p<0.05$) similarly in the VL (+0.023±0.007%/h) and SOL (+0.024±0.009%/h). Prior to exercise, glycogen concentration was higher in VL compared to SOL (413±43 vs. 351±54 mmol•kg^{-1} dw, $p<0.05$) and glycogen utilization (~115 mmol•kg^{-1} dw) was similar in both muscles during exercise. These data suggest that both the VL and SOL muscles are metabolically active during 45 min of level grade running. Furthermore, 24 hr post-exercise under fed conditions, protein synthesis is elevated in both muscles. NASA Grant NNJ06HF59G.

5.0: ENDOCRINE

5.1

SEX STEROID INFLUENCES ON RUNNING DISTANCE, DURATION, AND SPEED IN C57BL/6J MICE

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The regulatory mechanisms of physical activity are postulated to include environmental and genetic factors. Past rodent research has implicated several biological factors as potent regulators of voluntary activity. In particular, the sex steroids appear to have profound effects on wheel running distance (DST) in rodents. The purpose of this project was to investigate the effects of 17β-estradiol (E_2) and testosterone (T) on wheel running DST, duration (DUR), and speed (SPD). This study was approved by an institutional review board. Male and female C57BL/6J mice (N=46) were provided access to running wheels interfaced with computers to track running DST, DUR, and SPD. Activity was assessed in intact mice, after surgical gonadectomy, and supplemented with E_2 or T. An alpha level of 0.05 was deemed significant. Data are reported relative to baseline values. Upon removal of the gonads, running DST, DUR, and SPD were significantly reduced to 11, 16, and 56% in males and 33, 37, and 79% in females respectively. T recovered all activity to pre-surgical levels (88-113%) in both sexes. E_2 partially recovered DST (♂=69%, ♀=42%) and DUR (♂=44%, ♀=46%). E_2 treatment recovered SPD to 72 and 86% in males and females; in males the observed recovery rate was significantly less than intact and T treated mice. This study suggests that physical activity in mice is controlled by endogenous steroids and can be altered by exogenous steroid supplementation. Supported by: NIH Grant NIAMS AR050085.

5.2

EFFECT OF RESISTANCE EXERCISE ON MUSCLE STEROIDOGENESIS

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The purpose of this study was to examine the acute effect of heavy RE on intracrine muscle steroidogenesis. 15 young highly resistance trained men (n=8; 21±1 years, 175.3±6.7 cm, 90.8±11.6 kg) and women (n=7; 24±5 years, 164.6±6.7 cm, 76.4±15.6 kg) completed 6 sets of 10 repetitions of squats with 80% of their 1-repetition maximum. Before RE, and 10 min and 70 min after RE, muscle biopsies were obtained from the vastus lateralis. Before RE, after 3 and 6 sets of squats, and 5, 15, 30 and 70 min post-exercise blood samples were obtained from an anticubital vein. Muscle samples were analyzed for testosterone, 17β-hydroxysteroid dehydrogenase (HSD) type 3, and 3β-HSD type 1-2 content. Blood samples were analyzed for glucose and lactate concentrations. No changes were found for muscle testosterone, 3β-HSD1-2, and 17β-HSD3 concentrations between genders or pre- to post-exercise. However, a change in

protein migration in the Bis-Tris gel was observed for 17β-HSD3 post-exercise; this change in migration indicated an ~2.8 kd increase in molecular weight. These findings indicate that species differences in muscle testosterone production may exist between rats and humans. In humans, muscle testosterone concentrations do not appear to be affected by RE. This study expands on the current knowledge obtained from animal studies by examining resting and post-exercise concentrations of muscle testosterone and steroidogenic enzymes in humans.

5.3

EXERCISE STIMULATES LOCAL BIOACTIVE ANDROGEN METABOLISM IN SKELETAL MUSCLE

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Androgens, (i.e.testosterone) play important roles in increasing muscle strength and mass. Exercise-induced skeletal muscle adaptation occurs in both gender, although circulating testosterone levels are 10-fold higher in males than females. The testosterone is transformed into the bioactive androgen metabolite, dihydrotestosterone (DHT) by a steroidogegesis-related enzyme, 5alpha-reductase in local tissue. Here, we show that a single bout of exercise stimulates local bioactive androgen metabolism by increasing expression of 5alpha-reductase in the skeletal muscle. The gastrocnemius muscles of male and female rats (10 weeks old) were harvested at rest and after treadmill running (30 m/min,30 min). Dehydroepiandrosterone (DHEA), free testosterone, DHT, 5alpha-reductase and androgen receptor (AR) were measured by RT-PCR, Western blot and EIA in the skeletal muscle. Muscular bioactive androgen levels were increased after the exercise in both gender along with increased expression of 5alpha-reductase. These data suggest that local regulation of 5alpha-reductase by exercise plays a critical role in the process of skeletal muscle adaptation.

5.4

CHANGES IN LIVER GLUCAGON RECEPTOR DENSITY AND AFFINITY WITH EXERCISE AND POST-EXERCISE IN RATS

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The purpose of this study was to describe the effect of swimming exercise and post-exercise periods on liver glucagon receptor binding properties. Rats were randomly assigned to a rest control, a 180-min exercise and 180-min post-exercise groups. Plasma membranes were purified from liver and saturation kinetics were obtained by incubation (10 mg of proteins/150 mL) with (^{125})I-labelled glucagon at concentrations ranging from 0.15 to 3.0 nM for 30 min at 30°C. Saturating curves analysis indicated a significant higher glucagon receptor density after 180 minutes of exercise (8.19 ± 0.29 pmol/pg of proteins) and returned toward 3.09 ± 0.53 pmol/pg of proteins in liver from resting control after 180 minutes of post-exercise (4.46 ± 1.75 pmol/pg of proteins). Moderate changes in glucagon receptor affinity were also observed in the exercise and post-exercise groups compared to the control group (Kd = 0.46 ± 0.05 and 0.17 ± 0.01 vs 0.33 ± 0.05 nM in the control group). In conclusion, these preliminary results suggest that 180-min exercise and post-exercise episodes induced rapid modification in glucagon receptor binding properties. Funded by NSERC.

5.5

DIFFERENTIAL GENE RESPONSE TO GROWTH HORMONE TREATMENT

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Growth Hormone (GH) has been implicated in the regulatory and metabolic functions of muscle tissue. Our lab attempts to understand the genetic mechanism triggered by GH, and thus how it regulates the aforementioned functions. To do this, we treated 3T3-F442A pre-adipocytes, a cell line that is a sensitive model for GH response, with various dosages of GH. We incubated the cells using three time points (30 minutes, 4 hours, and 48 hours) and then measured gene expression using quantitative real-time polymerase chain reaction (QTPCR). Bioinformatic analysis had indicated genes that are likely to mediate the long-term effects of GH, specifically insulin resistance. Our experiment supported these conclusions. Each of the 5 genes that we probed for showed responsiveness to GH treatment that corresponded to the concentration of GH. SOCS2, IL6, ATF3 and c-fos all show heightened expression in response to GH while BCL-6 decreased in expression in response to GH. SOCS2 and IL6 are the two most likely genes to be involved in the genetic cascade leading to insulin resistance and possibly type-2 diabetes.

5.6

EFFECTS OF EXERCISE TRAINING AND ENERGY-RESTRICTION ON ADIPONECTIN SECRETION BY ADIPOSE TISSUE OF DIET-INDUCED OBESE RATS

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The present study examined the effects of exercise training and diet restriction on adiponectin (Adn) production by mesenteric (MEAT) and retroperitoneal (RPAT) adipose tissue explants. After 25 weeks of high fat (HF) diet, male Wistar rats were randomly assigned to either a sedentary (HFS, n = 8) or exercised (HFE, n = 8) groups. A number of HF diet animals were submitted to energy-restriction (ER) and divided into sedentary (ERS, n = 8) and exercised (ERE, n = 8) groups. Trained rats ran on a treadmill at 55% VO2peak for 60 min/day, 5 days/wk, for 8-10 wk. ER rats were fed a reduction (20%) of daily caloric ingestion (in relation to the control group), during 8-10 wk. Adn tissue levels (evaluated by ELISA) showed a significant increase in MEAT of HFS, when compared with the control group (standard laboratory diet, 3.9-fold, P<0.001).Trained rats (HFE) showed a reduction of 44% (P<0.05), when compared with HFS. ERS demonstrated a reduction of 47% (P<0.05) in MEAT levels with no effect of training in this group (interaction effect). In RPAT, no difference in Adn levels was found in response to training or energy-restriction. Both exercise training and diet restriction showed a similar restorative effect on Adn levels, suggesting a tissue-specific heterogeneous response.

6.0: CYTOKINES

6.1

INTERLEUKIN-6 INCREASES CAMP, ACTIVATES AMPK AND ALTERS SUBSTRATE METABOLISM IN AN ADRENERGIC MANNER

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Recent studies have reported that Interleukin (IL)-6 is released from skeletal muscle at the onset of physical activity. Previously we have shown that IL-6 can activate AMP-activated protein kinase (AMPK) in multiple tissues; however the mechanism by which it does so is unknown. We report here that in intact extensor digitorum longus (EDL), incubation with IL-6 alters cellular energy state, as shown by a nearly 3-fold increase in the AMP:ATP ratio; that coincided temporally with AMPK activation. Surprisingly, further studies revealed that AMPK activation by IL-6 can be inhibited by co-incubation with the β-adrenergic antagonist propranolol; suggesting IL-6 stimulates adrenergic signaling. In keeping with this notion, we found that IL-6 induced a transient increase in cAMP within the EDL and that incubation with an adenyl cyclase inhibitor, 2′5′-dideoxyadenosine, blocked the activation of AMPK by IL-6. Additional studies revealed that propranolol also blocked IL-6 induced changes in the AMP:ATP ratio. Finally, we found that IL-6, like other adrenergic stimuli, increases glycogen breakdown, lipolysis and palmitate oxidation in skeletal muscle. In conclusion, these studies demonstrate that IL-6, at concentrations that may be present in muscle during exercise, increases the concentration of cAMP, and secondarily, the AMP:ATP ratio and AMPK activity in skeletal muscle. They suggest that these changes increase both substrate availability and catabolism in order to assist the muscle cell in maintaining its energy state.

6.2

OVEREXPRESSION OF SUPPRESSOR OF CYTOKINE SIGNALING-3 ATTENUATES TNF-ALPHA INDUCED INHIBITION OF INSULIN SIGNALING IN CULTURED MYOTUBES

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We have shown that endurance exercise results in significant increases in SOCS-3 mRNA and protein expression in the soleus and plantaris muscle. The cellular role of the increased expression of SOCS-3 is unclear. Thus, it was hypothesized that increased SOCS-3 expression may provide protective effects to the skeletal muscle. C2C12 myoblasts were differentiated for 72 hrs until visible myotubes were readily apparent. The myotubes were subsequently exposed to TNF-alpha (10 ng/mL) for 24 hours. This exposure had no effects on SOCS-3 mRNA expression, although resulted in significant transcriptional activation of NF-kappaB suggesting that the TNF-alpha was used at an effective dose. These experiments were repeated, however upon completion of the 24 hr exposure the myotubes were exposed to insulin (100 nM) for 15 mins. TNF-alpha exposure resulted in significant inhibition of insulin-induced IRS-1 and Akt phosphorylation. Next, SOCS-3 cDNA was transfected in C2C12 myoblasts which were subsequently induced to differentiate for 72 hrs. The transfected myotubes were exposed to TNF-alpha for 24 hours and then exposed to insulin for 15 minutes. Overexpression of SOCS-3 preserved insulin-induced phosphorylation of Akt, but it did not prevent the inhibition of IRS-1 phosphorylation by TNF-alpha. These findings would suggest that increased expression of SOCS-3 may provide the muscle with a protected phenotype from pro-inflammatory cytokines. This work was supported by NIH Grant AR051396 (EES).

6.3

VOLUNTARY RUNNING IMPROVES HEAT STROKE RECOVERY IN MICE BY AN IL-6 INDEPENDENT MECHANISM

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High plasma levels of interleukin (IL)-6 correlate with heat stroke (HS) morbidity/mortality. Although exercise conditioning (EXC) has shown protection against HS mortality in animal models, the mechanism(s) of this effect is unknown. To determine if EXC protects against HS by an IL-6 dependent mechanism, we examined HS core temperature (T_c; radiotelemetry, ±0.1°C) responses in C57BL/6J (WT) and IL-6 knockout (KO) mice following 6 wk exposure to a sedentary or voluntary running (~3km/night) condition. To induce HS, mice were passively exposed to 39.5±0.2°C until T_c of 42.4°C (moderate HS) or 42.7°C (severe HS) was reached. T_c was monitored during 24 hours of recovery. During heat exposure, WT and IL-6 KO mice incurred similar thermal loads and body weight losses with no effect of EXC on these responses. Thus, EXC had no effect on thermoregulatory efficiency during heat exposure. EXC significantly improved cooling rates of WT and IL-6 KO mice during recovery from severe HS, which may be a mechanism of protection. Mice developed hypothermia during recovery, which was more pronounced in the severe (28.4±0.4°C) vs. moderate (31.1±0.5°C) HS condition. EXC attenuated hypothermia depth following severe HS in IL-6 KO, but not WT mice although improved recovery times were observed in both genotypes. In summary, our data support a protective effect of EXC against HS morbidity/mortality that (1) differs depending on the severity of the HS condition and (2) appears to be mediated by an IL-6 independent mechanism(s). Research supported by MRMC.

6.4

VOLUNTARY EXERCISE ATTENUATES PLASMA CYTOKINE EXPRESSION IN HEAT STROKED MICE

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Increased plasma cytokine levels correlate with heat stroke (HS) severity. Exercise influences plasma cytokine levels and the interaction of this response with HS severity is currently unknown. We hypothesized that exercise conditioning (EXC; 6 wk voluntary running, ~3 km/night) would influence the plasma cytokine profile of C57BL/6 mice and correlate with the core temperature (T_c; radiotelemetry, ±0.1°C) response to moderate (T_c=42.4°C) or severe

(T_c=42.7°C) HS. Plasma samples were collected at 24h in control and heat stroked mice for analysis of pro- and anti-inflammatory cytokines (Luminex FlowMetrix™ System) and corticosterone (RIA). At 24h of recovery, moderate HS mice in the sedentary (SED) condition had recovered T_c to baseline (35.6±0.3°C), which was not affected by EXC (36.0±0.8°C). With severe HS, SED mice remained hypothermic and EXC improved recovery to baseline T_c. Out of 14 cytokines measured, EXC had a significant effect on plasma levels of IL-6 and IL-10 in the severe HS condition only. That is, IL-6 and IL-10 plasma levels were inversely correlated with T_c in SED mice in the severe HS condition (P=0.01) and this response was mitigated with EXC. HPA axis sensitivity was also enhanced with EXC in the severe HS condition as corticosterone levels were inversely correlated with IL-6. Our data suggest that EXC improves severe HS tolerance through (1) the inhibition of IL-6 and (2) enhanced HPA axis sensitivity. Research supported by MRMC.

6.5

CIRCULATING ESTRADIOL & INTERLEUKIN-6 ACROSS THE PHARMACOLLOGICALLY CONTROLLED MENSTRUAL CYCLE: EFFECTS OF EXERCISE

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Estradiol (E_2) has been demonstrated to have anti-inflammatory and mediating effects on the immune system. Previously, interleukin-6 (IL-6) was shown to be downregulated by E_2 in cell cultures and bacterial stimulation experiments. IL-6 is no longer considered solely as a pro-inflammatory cytokine, but is considered to be an intercellular signaling mechanism involved in many physiological processes; one of which is alteration of substrate metabolism. IL-6 has been shown to increase in response to dynamic exercise under non-pathological conditions. There is little information investigating the effects of exercise on estradiol and IL-6, and their relationship to substrate metabolism in pre-menopausal females who menses were pharmacologically controlled. It was hypothesized that 1) IL-6 would be related to exercise & menstrual phase induced changes in E_2 2) fluctuations in IL-6 whether in response to phase or exercise, would be related to substrate level metabolism. Ten female subjects (24.0 ±3.2 yrs, 168.8 ±8.3 cm, 64.7 ±11.0 kg, 20.2 ±3.4 %BF, & 51.2 ±9.1 ml/kg/min) performed 60 minutes of treadmill exercise at 65% VO_{2peak} during the midfollicular (day 9±2d) and midluteal (day 20±2d) phases. E_2 & IL-6 were not different between phases, but did increase significantly in response to exercise. E_2 was not found to be related to IL-6 at rest, during, or post exercise. IL-6 was found to be positively related to indices of whole body fat metabolism. Subsequently, IL-6 was also found to be related to running economy. Based on the data from the current investigation, and known physiological redundancy of IL-6 as an intercellular signaling mechanism, future researchers should consider using other biomarkers of inflammation particularly during exercise.

6.6

CIRCUIT RESISTANCE TRAINING IN WOMEN: BODY COMPOSITION AND SERUM CYTOKINES LEVELS

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Exercise can elicit benefits or damage on the immunologic system. The aim of this study was to analyze the effects of circuit resistance training (CRT) on fat free mass (FFM), fat mass (FM) and cytokine responses in sedentary women, 39.71 ± 3.8 years old (n=14). The protocol consisted of 3 sessions/week of a circuit training of 9 stations with alternating muscle groups. In each session, the subjects performed the circuit 2 times with one set of 8-12 maximal repetitions (RM) in each station, during 10 weeks. The body composition was analyzed by DXA and, the inflammatory cytokines by flow cytometry (IL-1β; IL-6; IL-8; IL-10, IL-12p70 and TNF). Blood samples were collected from the antecubital vein in 8 moments: before the training; 5 min, 24h and 48h post-second session of training; and 5 min, 24, 48 and 96h post-last session of training. Student´s t and Wilcoxon test were applied for composition body and Friedman´s with Tukey post hoc tests for cytokines (α=0.05). There was an increase in the FFM and a decrease in the FM and no alterations of cytokines. The proposed CRT improved body composition and induced no pro-inflammatory effects in women. Key words: Circuit resistance training; body composition; cytokines; women.

6.7

RACIAL DIFFERENCES IN ANGIOGENESIS FACTORS AND CREATINE KINASE FOLLOWING ECCENTRICALLY-BIASED EXERCISE

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Objective: To determine if (a) eccentrically-biased exercise would alter selected angiogenesis factors as well as creatine kinase (CK), and (b) if the response would differ between racial groups. Methods: Venipuncture was performed on active, untrained Caucasian (n=8) and African (n=7) males before, immediately post and then at 3, 6, 9, 12, 24 h, 1, 2 and 3 weeks after 60 min of downhill running (-13.5%) at a speed eliciting 75% of their VO2max on a level grade. Serum concentrations of VEGF, bFGF, TNF-α, IL-8, MCP-1, IL-12, IFN-γ and CK were determined. Results were analysed using a repeated measures ANOVA. Results: There was a race effect for VEGF, TNF-α, IL-8, MCP-1, IL-12 and CK, with the concentrations significantly higher in the Africans. There was a time effect for MCP-1 with significantly elevated levels at 3 h (+44%), 6 h (+49%) and 9 h (+61%). CK also increased over time following the downhill run, peaking at 12 h for both groups. Conclusions: The elevation in MCP-1 may increase macrophage infiltration and vascular remodeling at tissue damage sites. The relative CK response to exercise in the Caucasians was higher, suggesting greater muscle damage. The racial disparity in angiogenesis factors may represent a genotype in the Africans that more consistently up-regulates angiogenesis. This has implications for performance including enhanced aerobic capacity and adaptation to tissue damage relating to training.

6.8

POST-EXERCISE ANTI- AND PRO-INFLAMMATORY RESPONSES TO MODERATE EXERCISE IN HEALTHY ADULTS

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Studies have shown that exhaustive exercise has immediate effects on pro-inflammatory cytokines, but studies of longer term effects of moderate exercise on immune profiles that include anti-inflammatory cytokines have been lacking. We examined short (0.5 hr) and longer term (8, 24 and 48 hr) effects of moderate exercise on serum levels of anti-inflammatory (IL-4, IL-10, IL-13) and pro-inflammatory (IL-1β, IL-2, and TNFα) cytokines. Healthy individuals (n = 17; mean age = 33 ± 11 yr) performed cycling at a work rate corresponding to 70% age-predicated maximal heart rate (pMHR) for 25 min. Work rate achieved at 70% pMHR was used to index fitness level. IL-10 was reduced at 0.5, 8, and 24 hours post-exercise ($p<.05$) and returned to baseline by 48 hr; IL-13 also tended to decrease at 0.5 and 8 hr ($p<.10$). No changes were observed for pro-inflammatory cytokines. At every time point significant correlations between IL-1β and TNFα were observed (r range = .59 to .89, $p<.05$) indicating consistency of pro-inflammatory responses within individuals. Significant correlations between absolute and relative work rate and anti-inflammatory cytokines were observed at all time points (IL-13 and work rate, r range = -.55 to -.62). At 48 hr post-exercise IL-10 correlated significantly with absolute work rate (r = .49, $p<.05$). These results indicate that moderate exercise did not result in significant pro-inflammatory responses and that anti-inflammatory cytokine responses decreased acutely and remained lower for at least 24 hrs post-exercise. The anti-inflammatory response is related to work rate, indicating that more fit individuals have lower IL-10 and IL-13 activity. Supported by NIH R21 NS057821.

6.9

CIRCUIT RESISTANCE TRAINING IN POSTMENOPAUSAL WOMEN: EFFECTS ON MUSCLE FORCE AND IL-6 SERUM LEVELS

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The aim of this study was evaluated the muscle force, and IL-6 serum levels after a 16 weeks circuit resistance training (CRT) in 30 postmenopausal women (58.03±5.33). CRT was performed into 12 exercises (6 of lower limb, 6 of superior limb), and the subjects realized 2 bouts of 10 repetitions of each exercise with 70% of 1RM. 1RM test was performed to evaluated muscle force: the first evaluation occurred at the beginning of the study, and the second 16 weeks after. Leg-Press, Bent Press, and Barbell Curls were the exercises elected to 1RM evaluation. Serum IL-6 was measured in the following periods: before the training session (rest), immediately, 24 and 48 hours after. Measurement of IL-6 in serum was made by ELISA. For 1RM was used paired t Student and for IL-6 was analyzed by one-way ANOVA with $p < 0,05$. Results showed significant increase in muscle force for Leg-Press (31.76%), Bent Press (22.58%), and Barbell Curls (10.09%). The serum levels of IL-6 did not have significant alterations in the concentrations in all periods assessed. In conclusion, the muscle force increased and the IL-6 levels sustained support that the Resistance Training does not suppress the immunological system. Key words: postmenopausal women, muscle force, IL-6, resistance training.

7.0: STEM CELLS

7.1

HEMATOPOIESIS : 1.ERYTHROGENESIS

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Introduction: 1. Believed that the blood is generated from the stem cell in the bone marrow. 2. The cause of sportsman anemia is not known. Neither is the process of self healing when the sportsmen cease their training. 3. Bone marrow theory come from the experimental research based on starved animals so it is not yet proved on normal feeding animals. Method: We have researched the increase or decrease of blood cells by M-H method ‡U which consist of culturing of the tissues with muscle, fat, bone marrow and cartilage, using the Costar Transwell. Filling the inner part with the sample tissues and RPMI-1640, the□@outer part with the same type blood of the tissue donor together□@with RPMI-1640, and counted the number of the cells every 24 hours. Results: 1. Muscle tissue: RBC increased, 2. Fat tissue: RBC increased, 3. Bone marrow: RBC increased, 4. Cartilage tissue: RBC decreased. Conclusion: The Costar□fs Transwell we used for this experiment holds a very thin filter with pore holes of 0.4*f*Êm. This filter only allows to pass the watery solution but not the cells. So Hematopoiesis have been done in the muscle, the fat tissue and bone marrow in the human living body.

7.2

HEMATOPOIESIS : 2. LEUCOGENESIS

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Method: 1. When the mixture of metamorphosed erythrocytes and leukocytes collected using New M-H Method is cultured in an incubator under the condition of 5%CO2 at 37□Ž, botryose proliferation of leukocytes can be observed in 3 to 5 hours after the start of incubation. 2. In the following two experiments also botryose proliferation of leukocytes can be observed in 6 to 8 hours after the start of incubation (using the leukocytes collected from the patients with atopic dermatitis, urticaria, cancer, hepatitis, etc.). (1) 1.5ml of frozen knee articular fluid collected from the patients with osteoarthritis or multiple articular rheumatism is dissolved in 1.5ml of RPMI-1640 containing the ULRBCs collected using M-H Method. Then the cellular components are changed to micro particles using an ultrasonic vibrating device and filtered using sterile filter. After U culture solution is added to the fluid, it is cultured in an incubator under the condition of 5%CO2 at 37□Ž.(2) Vitamin B6, Celestamine, etc. treated using N-MH Method are added to the upper layer of blood cells collected using MH Method and cultured in an incubator under the condition of 5%CO2 at 37□Ž. Thus, the phenomenon of leukocyte proliferation can be detected in both cases using articular fluid and certain sorts of drug. Discussion: According to the current hematopoiesis, it is concluded that blood is derived from retrogressive phenomenon. The bone marrow in elderly people has become yellow marrow; they, however, do not always suffer from anemia. I think the theory, where such lively activity as hematopoiesis is derived from retrogressive phenomenon, is extremely nonscientific. I believe that leucocytes are derived from leucocytes, just like erythrocytes.

7.3

HEMATOPOIESIS : 3. PROLIFERATION OF BLOOD PLATELET

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Actually blood platelets do not exist in blood flow. In blood flow, only substances like rice grain that rotate, glisten white or blacken. I call them gRice Grainsh. About Rice Grains and substances like Rice Grains (1)A bud-like part comes out of a red blood cell and the salience is getting longer and finally cut off at the root, resulting in a Rice Grain. (2) (a)When RBCs are exposed to RLB (hypotonic solution), they are destroyed and a large amount of the substances like Rice Grains appear. These are a little bigger than usual Rice Grains and characterized by sharp edges. (b)During incubation using MH Method, several white blood cells can cause a phenomenon like explosion together. In this case also the substances like Rice Grains appear; however, these are almost circular and usually big. (3)When Rice Grains in (1) and the substances like Rice Grains in (2) (a) and (b) stop movements, all of them create black aggregation. I believe that generally the Black Spot that can be detected when it stops its movement is called platelet in usual blood platelet examination. The electronography of platelet in medical textbook is precisely the image of this Black Spot. Thrombocytopenia includes the following conditions: 1.Decrease of Rice Grains, 2.Decrease of the substances like Rice Grains generated from red blood cells, 3.Decrease of the substances like Rice Grains generated from white blood cells, and 1+2, 1+3, 2+3, and 1+2+3; therefore thrombocytopenia has 7 sorts of conditions in total. Executive Summary of Part 1, 2 and 3 Red and white blood cells are made not from myeloid tissue cells but from red and white blood cells, respectively. It truly complies with the principle: cell from cell. Likewise, platelets are made not from myeloid tissue but from red blood cells and destroyed red/white blood cells.

7.4

SKELETAL MUSCLE-DERIVED MULTIPOTENT STEM CELLS ARE MULTI-MYOGENIC STEM CELLS THAT CAN GIVE RISE TO SKELETAL, SMOOTH AND CARDIAC MUSCLE CELLS

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Multi-myogenic differentiation into skeletal, smooth and cardiac muscle cells of skeletal muscle-derived CD34+/45- (Sk-34) and CD34-/45- (Sk-DN) cells were examined. Sk-34 and Sk-DN cells were isolated from green fluorescence protein (GFP) transgenic mice muscles using collagenase type-Ia and sorted by flowcytometry. Freshly isolated Sk-34 and 5-6 days cultured Sk-DN cells were then transplanted into severe-damaged model of skeletal muscle (wild-type mice) and cardiac muscle infarction model (nude rats). At 4 weeks after transplantation, implanted GFP+ cells gave rise to skeletal muscle cells, vascular cells (pericytes, smooth muscle and endothelial cells), and peripheral nerve cells (Schwann cells and perineurium) in the damaged skeletal muscle. In the cardiac infarction model, donor cells exhibited typical cardiomyocyte structure with formation of gap-junctions and desmosomes. These potentials were also confirmed by clonal cell transplantations of Sk-DN cells. Furthermore, multi-myogenic differentiation potential was also demonstrated by immunocytochemistry and expression of specific mRNAs after cell culture. These results clearly indicated that murine skeletal muscle-derived Sk-34 and Sk-DN cells were not only multipotent stem cells between mesodermal and ectodermal cell lineage, but also multi-myogenic stem cells that can give rise to skeletal, smooth, and cardiac muscle cells, and provide new insights into somatic stem cells with regard to myogenesis after birth.

7.5

MESENCHYMAL STEM CELL PROLIFERATION IS REDUCED BY STIFF MICRORODS IN 3D CULTURE

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Much has been learned recently about the importance of both stiffness and topography in regulation of fundamental functions such as cell division, apoptosis, migration, differentiation and phenotype. The hypothesis that stem cell regulation is also dependent upon physical cues of the microenvironment is tested. Mouse bone marrow stem cells (mBMSC) are plated in 1mm deep Matrigel with or without microrods made of SU8 (15µm diameter and 50 or 100 µm long). Phase contrast images show mBMSC migrate and aggregate around microrods of higher stiffness than the surrounding gel. mBMSC attached to microrods are flattened and elongated whereas in 3D gel alone they are stellate. Cell number is determined after 1 and 5 or 7 days of culture by the WST-1 assay using mean relative absorbance. By day 5, 100 µm microrods blunt mBMSC proliferation and by day 7, both 50 µm (17%, $p<0.05$) and 100 µm (33%, $p<0.001$) microrods in Matrigel blunt proliferation compared to cells cultured in Matrigel alone. The conclusion is that mBMSC proliferation is blunted most by the longer microrods and least by 3D gel alone. Optimization of the size and stiffness of these microrods may induce differentiation of the mBMSC along multiple lineages and be helpful in understanding how physical cues affect regeneration of various tissues. Supported by AHA 08155359 (JMC) and HL62426 (BR).

7.6

ACTIVITY AND PROLIFERTION OF CARDIOMYOCYTES DERIVED FROM MOUSE EMBRYONIC STEM CELLS IS REGULATED BY MICROPROJECTIONS

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The hypothesis is that physical properties of the microenvironment regulate activity and proliferation of the mouse embryonic stem cell (mESC) progeny. Microtopographic features were fabricated by photolithography to create 15µm high projections spaced 80 or 500µm apart tetragonally in poly-dimethyl-silicone (PDMS) membranes. mESC differentiation began in hanging drops, followed by suspension culture, before the resulting embryoid bodies were disassociated and plated on either flat or the microtextured surfaces. The number of heterogeneous SC derivatives observed with phase microscopy was 60 ± 20% (n=3) on the 80µm microprojections compared to flat PDMS. Similar results were seen for pure cardiomyocytes derived using a puromycin resistant cassette incorporated into the NCX1 promoter. Only 43 ±12% (n=3) and 75 ±16% (n=5) of the cardiomyocytes were found on the 80µm and 500µm spaced microprojections, respectively, compared to the flat PDMS. The beating rate per minute of the cardiomyocytes was recorded by video microscopy and was 1.8 ± 0.4 fold higher on the microprojections compared to the flat with surprising changes in coefficients of variance of 0.50 and 0.21 respectively (n=5). Results suggest that microtopography affects both expansion and beating characteristics of mESC progeny. T32HL007692 and HL 62426.

7.7

CHARACTERIZATION OF A SCA-1+CD45- STEM CELL POPULATION PREFERENTIALLY RECRUITED BY THE ALPHA7BETA1 INTEGRIN IN SKELETAL MUSCLE FOLLOWING ECCENTRIC EXERCISE

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The α7β1 integrin is a transmembrane receptor that maintains muscle structure and integrity. We recently demonstrated that eccentric exercise can promote the recruitment of Sca-1+CD45- stem cells to skeletal muscle in mice overexpressing the α7 integrin. PURPOSE: The purpose of this study was to provide in vitro characterization of Sca-1+CD45- stem cells recruited by the α7β1 integrin. METHODS: 5-wk old α7 integrin transgenic mice completed a single bout of downhill running exercise (-20°, 17 m/min, 30 min) and gastrocnemius-soleus complexes were collected 24h postexercise. Sca-1+CD45- cells were isolated and maintained in culture. On Day 5, cells were examined for expression of myosin heavy chain (MHC), α7 integrin, c-met, basic myelin protein (BMP), CD34, α-smooth muscle actin (α-SMA), CD133, and CD144. Cells were labeled with DiI and examined for their ability to differentiate into muscle. RESULTS: Immunofluorescence studies demonstrated that Sca-1+CD45- stem cells were negative for all markers except CD34 and α-SMA. Sca-1+CD45- cells were not able to spontaneously differentiate into myotubes. However, Sca-1+CD45- cells were capable of incorporating into muscle in myoblast co-cultures using DiI as an indicator. CONCLUSION: This study suggests that overexpression of the α7β1 integrin positively influences the appearance of Sca-1+CD34+CD45- stem cells and may provide a mechanism by which skeletal muscle regenerates following exercise-induced injury.

7.8

STIMULATION OF HUMAN SATELLITE CELLS WITH ERYTHROPOIETIN

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Erythropoietin (EPO) is a glycoprotein mainly produced by the cortex of the kidneys. It can also be produced locally in other tissues in response to metabolic or physical stress. EPO regulates erythrocyte production by inhibiting apoptosis via the erythropoietin receptor (EPOR). The EPOR is expressed on a variety of cells apart from the erythrocyte progenitors and activation has been shown to induce both cardio- and neuro protective effects, which include effects on tissue localized stem cells. The illegal use of EPO to improve performance among athletes indicates enhanced performance beyond expected from increased blood haemoglobin. This study aimed to evaluate if EPOR is present on human satellite cells (SaC) and if stimulation with EPO would have an effect on downstream signalling of the EPOR and SaC proliferation. To collect protein and RNA, human SaC from vastus lateralis were cultured with different concentrations of EPO. Immunofluorescence was used to detect the EPOR on the cells. The RNA and protein content were analysed with Real-time-PCR and Western Blot and proliferation with BrdU-ELISA. The SaC expressed EPOR. EPO administration increased EPOR protein expression and the proliferative capacity of the SaC. This study shows that satellite cells express EPOR and that EPO may enhance SaC proliferative capacity in vitro. However, the physiological relevance of EPO on SaC in vivo remains to be further investigated.

7.9

THE EXPRESSION OF SATELLITE CELL MARKERS IN HUMAN SKELETAL MUSCLE

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Human skeletal muscle growth, hypertrophy and repair are dependent on muscle satellite cells (SCs). To understand how SCs respond to exercise and/or other factors, it is important to use appropriate markers for their identification and quantification in quiescence and different stages of differentiation. Currently published results are highly variable. Previously we have examined muscle biopsies from strength trained power lifters (PL), strength trained athletes using anabolic steroids (PAS) and non athletes (C) (Kadi 2000; Eriksson 2006) with one marker for SCs. Now we have re-examined these biopsies using a new method based on multiple labelling, to further explore SC behaviour in response to training and anabolic steroids. With the new method the number of SCs per fiber area in PL and PAS was still higher than in C ($P<0,05$) however the numbers of SCs in PL and PAS was only half of the previously reported data. On the contrary the proportions of SCs per myonuclei were now equal for all groups. The majority of SCs identified by Pax7 and NCAM expressed both markers (95%). With the new method a more accurate identification of SCs was established. One marker is not enough to identify all SCs – the combination Pax7 and N-CAM is recommended together with additional markers for nuclei and the basal lamina. The latter allows delineation of what belongs to the muscle fiber. This is of utmost importance when dealing with muscles influenced by extensive exercise or muscle pathology.

7.10

LOW OXYGEN MAINTAINS HUMAN SATELLITE CELLS IN AN UNDIFFERENTIATED STATE AND INCREASES PROLIFERATION

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Two independent reports in mice and rat demonstrated that satellite cells (SaC) cultured under hypoxia (3-6% O_2) as compared to standard conditions (21% O_2) show a remarkable increase in proliferation and reduction in apoptosis. In the rats also an activation of PI3/Akt pathway and a down regulation of the cell cycle inhibitor $p27^{kip1}$ was found. Moreover, Gustafsson et al. demonstrated that hypoxia is required to maintain SaC in an undifferentiated state. If hypoxia is an effective tool to maintain the undifferentiated state and enhance proliferation in human SaC

has not been tested yet. Muscle biopsies were obtained from 6 males (3 healthy and 3 with heart failure). SaC were prepared. Desmin stains verified that satellite cells were isolated. The cells were cultured at 21% O_2 (standard) or at low O_2 (5%) in a proliferation medium. mRNA levels for beta actin and alpha actin were analyzed, where beta actin represents an undifferentiated and alpha actin a differentiated state. The results from both subjects groups show that the cells cultured at low O_2 had a higher expression of beta actin and lower expression of alpha actin. Thus, low O_2 better maintains the undifferentiated state during culturing of human SaC. Moreover, the proliferative activity as determined by BrdU-ELISA was higher at low O_2. Both the maintenance of an undifferentiated state and increased proliferation of SaC cultured under low O_2 may improve the efficacy of cell therapy. Nm.

7.11

FOXO DIFFERENTIALLY REGULATES P27^{KIP1} EXPRESSION IN RAT MUSCLE PRECURSOR CELLS

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Previous work from our lab has demonstrated that FOXO3a overexpression increased p27^{Kip1} promoter activity and protein expression, while it decreased proliferation in muscle precursor cells (MPCs). The objectives of the present study were to locate and identify FOXO responsive elements (REs) in the rat p27^{Kip1} promoter utilizing deletion analysis of a promoter/reporter construct and determine if age-related differences exist in FOXO-induced p27^{Kip1} expression. The full-length (-4.0 to +0.4 kb) rat p27^{Kip1} promoter construct revealed that both FOXO1 and FOXO3a induced an increase in reporter activity. Interestingly, MPCs isolated from old animals exhibited an increased FOXO3a-induced p27^{Kip1} promoter activity, compared to MPCs isolated from young animals. Deletion analysis revealed a significant decrease in the FoxO-induced p27^{Kip1} promoter in a 170-bp portion of the 5′ untranslated region (UTR). Mutation of a daf-16 family protein binding element (DBE) within this 170-bp portion of the 5′ UTR also demonstrated a decrease in FOXO-induced p27^{Kip1} promoter activity. These data suggest that a FOXO RE is located in the 5′ UTR of the rat p27^{Kip1} gene. Mutation of this RE affected the age-dependent differences in FOXO-dependent p27^{Kip1} promoter activity. These findings have implications for developing treatment strategies aimed at increasing proliferation of MPCs and regenerative capacity of aged skeletal muscle. Supported by RO1 AG18780.

8.0: MICROCIRCULATION

8.1

OXIDANT STRESS IS REQUIRED FOR ENDOTHELIUM-DEPENDENT DILATION IN SKELETAL MUSCLE ARTERIOLES

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The purpose of this study was to evaluate the effects exercise training and oxidant stress on endothelium-dependent dilation (EDD) in skeletal muscle arterioles from young and old rats. Young (3 mo) and old (22 mo) male rats were exercise trained (ET) or remained sedentary (SED) for 10 wks. To determine the impact of reactive oxygen species on EDD, vasodilatory responses to ACh were studied under control conditions and during the blockade of superoxide and/or hydrogen peroxide. Soleus 1A arterioles were isolated, cannulated and pressurized at 70 cm H20. EDD was assessed by exposure to ACh (1e-10 - 1e -4 M). Age decreased EDD to both flow and ACh. Exercise training restored flow- and ACh-induced EDD in arterioles from old rats, and improved flow-induced dilation in arterioles from young rats. Tempol, a scavenger of superoxide, reduced ACh-induced EDD in all groups of rats. Similarly, combined scavenging of superoxide and hydrogen peroxide by Tempol plus catalase impaired dilation in all groups. Apocynin, an inhibitor of superoxide production by NADPH oxidase eliminated dilation to ACh in all groups of rats. H202-induced vasodilation was preserved in young and old SED rats. These data indicate that 1) exercise training restores EDD in skeletal muscle arterioles of old rats, 2) hydrogen peroxide contributes to EDD in rat skeletal muscle arterioles regardless of age or exercise training status, and 3) superoxide is obligatory for ACh-induced dilation.

8.2

EFFECT OF ACETAZOLAMIDE ADMINISTRATION ON ENDOTHELIAL FUNCTION IN HUMANS

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Acetazolamide (ACZ) administration has been shown to increase vascular reactivity in cerebral arteries but little is known regarding the effect of ACZ on the peripheral vasculature. The purpose of this study was to determine if ACZ alters endothelial dependent flow-mediated dilation (FMD) of the brachial artery. Seven males underwent FMD tests during control (CON) and following ACZ administration (500 mg/d 3 d). Brachial artery diameter and velocities were measured continuously at rest and following 5 min of forearm cuff occlusion using Doppler ultrasound. FMD resulted in an increase in brachial artery diameter (CON 4.85 ± 0.59 mm; ACZ 4.79 ± 0.56 mm) compared to rest (CON 4.49 ± 0.51 mm; ACZ 4.60 ± 0.49 mm; p<0.05). When expressed as %FMD, ACZ was significantly reduced (4.11 ± 3.55%) compared to CON (7.98 ± 2.96%; p<0.05). This equates to a 48.5% difference in response between CON and ACZ conditions. Peak values for shear rate (SR) and shear stress (SS) were not significantly different between conditions (ACZ; SR 354.9 ± 98.2 s^{-1};SS 14.2 ± 3.9 dyn·cm^{-2} vs. CON; SR 295.2 ± 72.2 s^{-1};SS 11.8 ± 2.9 dyn·cm^{-2}. When FMD was normalized relative to shear rate (%FMD/SR), the ratio for ACZ (0.011 ± 0.010) was significantly lower (p<0.05) compared to CON (0.030 ± 0.005). These results indicate that the endothelial-dependent FMD response is attenuated following chronic ACZ administration even after normalizing for changes in shear stress.

8.3

MICROVASCULAR REMODELING AND DECREASED ANGIOGENIC FACTORS IN THE ATROPHIED RAT SOLEUS MUSCLE

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Microvascular complications occur during muscle atrophy. We describe the structural and functional changes of the capillary network and investigate the possible contribution of endothelial apoptosis and angiogenic factors in the soleus muscle of hindlimb unloaded (HU) rats. Contrast medium-injected sections were visualized with a confocal microscope to reconstruct the microvasculature in three-dimensions. The velocity of red blood cells (Vrbc) in soleus capillaries was determined using pencil-lens intravital microscopy. Apoptotic endothelial cells were identified by DNA fragmentation using immunofluorescent staining. VEGF, KDR, Flt-1, angiopoietin-1, 2, Tie-2, and HIF 1 alpha mRNAs were determined by real-time PCR. Mean capillary volume, luminal diameter, and number of anastomoses were significantly smaller and tortuosity lower in HU than control rats. Expression levels of all angiogenic factors, except HIF 1 alpha level, were lower in HU than control rats. TUNEL positive endothelial cells were observed only in HU rats, especially near anastomoses and/or tortuous capillaries. Vrbc in the capillaries was faster in HU than control rats. Thus HU results in reductions in capillary diameter and tortuosity with vascular endothelial cell apoptosis and a down-regulation of angiogenic factors. The increase in Vrbc after HU may reflect the decrease in capillary size and suggests less transit time for the delivery of oxygen and nutrients in the soleus of HU compared to control rats.

8.4

EFFECTS OF HINDLIMB UNWEIGHTING ON CONDUCTED VASODILATION OF RAT SOLEUS FEED ARTERIES

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The purpose of this study was to test the hypothesis that conducted dilation in rat soleus muscle feed arteries is impaired by hindlimb unweighting (HU). Male Sprague-Dawley rats were exposed to HU or weight-bearing control (Con) conditions for 14 days. Soleus feed arteries were isolated, cannulated, and exposed to constant pressure (90 cmH20). Body weights (Con=369.4±5.7, HU=316.2±5.5 g; p<0.05) and soleus weights (Con=217.0±6.9, HU=123.6±4.5 mg; p<0.05) differed whereas adrenal weights (Con=23.29±1.3, HU=26.0±0.8 mg; p>0.05) did not. While the mean internal maximal diameter for all locations measured (0, 500, 1000, 1500, 2000 µm) differed (Con=164.0±7.8, HU=139.9±4.2 µm; p<0.05) between groups, the mean internal diameters prior to microiontophoresis of acetylcholine (Con=65.1±9.0, HU=53.1±4.2 µm; p>0.05) and mean peak dilation were not different (Con=109.5±10.4, HU=92.0±4.6 µm; p>0.05). In addition the mean relative dilatory response (peak-baseline/max) was not different (p>0.05) between groups. Repeated measures ANOVA revealed no statistically significant main effects (p>0.05) of the conducted dilatory response between groups when expressed as percent dilation ([peak-baseline/max] x 100) or as a percent possible dilation ([peak-baseline)/(max-baseline)] x 100). Furthermore the degree of the dilation for each distal site measured (500, 1000, 1500, 2000) did not differ from the site of application (0) for either group (p>0.05). We conclude that ACh-induced conducted dilation of soleus feed arteries was preserved after 2 weeks of HU and the magnitude of the response of these arteries does not decay over the distances studied for either group. (NIH HL-36088).

9.0: PHYSICAL INACTIVITY AND CHRONIC DISEASE

9.1

MICRORNA EXPRESSION IS ALTERED DURING SKELETAL MUSCLE ATROPHY

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A new class of small, highly conserved, non-coding RNAs has been identified and these miRNAs (miR) have been shown to repress gene expression by a post-transcriptional mechanism. Given their emerging importance in striated muscle development, differentiation, regeneration, hypertrophy, and muscular dystrophy, the objectives of the present study were to identify those miRs expressed in the rat soleus muscle and determine if their expression was altered during muscle atrophy induced by hindlimb unloading (HU). We hypothesized that alterations in the expression of the known muscle-specific miRs would be involved in regulating slow-to-fast fiber type changes during HU. Microarray analysis showed that 162 miRs are expressed in soleus muscle of which 14 were significantly ($p < 0.05$) altered following HU, including the muscle-specific miR-499. Real time RT-PCR confirmed that expression of miR-499, as well as miR-107 and -221, were downregulated following seven days of HU. Following four weeks of HU, downregulation of miR-499 was associated with increased gene expression of Sox6 and Purβ, established transcriptional repressors of slow myosin heavy chain gene expression that are known targets of miR-499. In summary, skeletal muscle atrophy is associated with changes in miRs consistent with the proposed MyomiR network controlling fiber types. The role of miRs in loss of muscle mass is currently under study. Supported by AR47577 (CAP), AG028925 (EED), AR053641 (JJM) and AR45617 (KAE).

9.2

THE RELATIONSHIP BETWEEN BLOOD CELLS AND DRUGS

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The ability of blood cells in the upper layer is mainly dependent upon drugs during suffering diseases. Therefore, it is most important to prescribe proper drugs based on the relationship between drug and blood cell. For that purpose, I have developed the New- Matsumoto Method.
Methods: The New Matsumoto Method is used. Results: The efficacy of the following drugs and therapies can be examined by the above-mentioned methods. 1) The prescribed drugs with side effects 2) The drugs that doctors do not prescribe but is supposed to be effective □@ 3) a) The relationship between the upper layer of blood cells governing natural healing power and supplements, Chinese medicine, massage, acupuncture, moxa cautery, Qigong, exercise, balneothrapy, etc. b) Each therapy should be tested separately, and the upper and lower layer of blood cells (ULRBC and LLRBC) should be examined before and after each therapy. If the conditions of ULRBC and LLRBC are normalized or relieved, the therapy can be considered as effective; otherwise, it should not be considered as effective. When a therapy appears to be effective despite that no effects are detected in the test, it might be caused by mental factors: □gillness comes from the mind□h.

9.3

MYSTERIOUS CHAINS OBSERVED DURING INCUBATION OF BLOOD CELLS - FIRST REPORT

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Introduction: In the subjects with diabetes, hepatitis C, cirrhosis, and Parkinson's disease, Mysterious Chains (MC) are observed during incubation of the Upper Layer Blood Cells (ULBC) separated using MH Method. This article is the first report on those MCs. Method: 1. Obtain ULBC with MH Method. 2. 0.5 ml of ULBC is added to 3 ml of RPMI-1640 in a flask (CORNING) using a 2.5ml-glass-syringe with a 23-gauge needle. 3. 2 is cultured in an incubator under the condition of 5% CO2□Eat 37C, and observed with an inverted phase-contrast microscope. Result: (1) Thick and long MCs were emerged from white blood cells. (2) Medium-sized, thinner and long MCs were emerged from Black Spots (Rice Grains = blood platelets). (3) Small and short MCs were emerged from red blood cells. *The number of MC rapidly decreased when Reverted Cells were emerged in ULBC. Conclusion: 1. In the diseases where the cells consisting of tissues were degenerated and necrotized, resulting in scar tissues, the cases where MCs were found were predominant. 2. It is highly possible that MC is associated with progression of diseases 3. The drugs to inhibit emergence of MC should be developed without delay. 4. The incubated Leucocytes and 20mg/day of MINO can inhibit emergence of MC. 5. Other drugs might have effectiveness to inhibit emergence of MC. It is very important to select the most effective drugs using the New Matsumoto method.

9.4

RELATIONSHIP BETWEEN LIVER DISEASES AND MYSTERIOUS CHAIN - FIRST REPORT

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Introduction: When the Upper Layer of Red Blood Cells (ULRBC) collected from the patients with liver diseases using Matsumoto-Hagiya Method (M-H Method) is cultured in an incubator under the condition of 5% CO2 at 37C, MC can be observed in some cases. MC and its changes after drugs are added are reported in this article. Method: 1. MH Method is used. 2. New Matsumoto Method (N-M Method) is used. 3. The drugs of glycyron, glutatione, liver hydrolysate, ursodeoxycholic, L-cycteine, Tiopronin, minocycline hydrochloride and incubated Leucocytes (iL) are used. Result: 1. MC has the following two types: thick and long one derived from leucocytes and thin and long/short one derived from Black Spots. 2. Using N-M Method, the most suitable and effective drugs vary case by case. 3. Using MH Method, MCs are found in a part of those with hepatitis B, most of those with hepatitis C and all cases with cirrhosis. Conclusion: 1. MC might be closely associated with progress from hepatitis to cirrhosis. 2. The drugs with little side effects, which can extend the lives of blood cells, should be chosen to use for hepatitis and cirrhosis through the test of N-M Method. 3. The drugs which can inhibit emergence of MC should be used for liver diseases through the test of N-M Method.

9.5

RELATIONSHIP BETWEEN THE DRUGS FOR DIABETES AND MYSTERIOUS CHAIN

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Introduction: When the Upper Layer of Red Blood Cells (ULRBC) collected from the patients with diabetes using Matsumoto-Hagiya Method (M-H Method) is cultured in an incubator under the condition of 5% carbon dioxide at 37C, MC can be observed in some cases. Also the number and shape of MC can be changed by adding of the drugs for diabetes. MC and its changes after drugs are added are reported in this article. Method: 1. MH Method is used. 2. New Matsumoto Method (N-M Method) is used. 3. Seven sorts of drugs, glibenclamid, glimepiride, nateglinide, acarbose, voglibose, pioglitazone hydrochloride and metformin hydrochloride, are used. Result 1. Both cases of MC (+) and (-) exist among the patients with diabetes. 2. MC may emerge in some cases of MC (-) through adding of certain sorts of anti-diabetic drugs. 3. MC may increase more in some cases of MC (+) through adding of certain sorts of anti-diabetic drugs. 4. Some anti-diabetic drugs can inhibit emergence of MC. 5. MCs always emerge from the leucocytes in all cases with diabetic renal failure. Conclusion: It is highly possible that anti-diabetic drugs increase MC, resulting in renal failure. It is suspected that the disease become severe by administration of the drugs earlier than no administration in some cases, suggesting possibility of iatrogenic disease.

9.6

RELATIONSHIP BETWEEN DEMENTIA/PARKINSON'S DISEASE AND MYSTERIOUS CHAIN

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Introduction: When the Upper Layer of Red Blood Cells (ULRBC) collected from the patients with dementia or Parkinson□fs disease using Matsumoto-Hagiya Method (MH Method) is cultured in an incubator under the condition of 5% CO2 at 37C, MC can be observed in some cases. Also the number and shape of MC can be changed by addition of the drugs generally considered as effective for those diseases. Method: 1. MH Method is used. 2. New Matsumoto(N-M) Method is used. 3. The drugs of amantadine hydrochloride, trihexyphenidyl hydrochloride, droxidopa, pramipexole hydrochloride hydrate, levodopa , donepezil hydrochloride, 20mg/day of minocyclin hydrochloride, incubated Leucocytes (iL) and L-cysteine are used. Result 1. Using MH Method: Small and short MCs or large and long MCs are emerged from erythrocytes in Parkinson□fs disease; meanwhile, large ones are emerged from leucocytes in dementia. 2. Using N-M Method: In cases with Parkinson□fs disease, 20mg/day of minocyclin hydrochloride and iL often show the strongest effect to inhibit emergence of MC. Levodopa often shows side effects, followed by trihexyphenidyl hydrochloride and droxidopa. Amantadine hydrochloride shows relatively little side effects. 3.In cases with dementia, 20mg/day of minocyclin hydrochloride and iL show effectiveness for lots of them. Aricept can inhibit about 60% of MC emergence at the most, suggesting little effectiveness. L-cysteine meanwhile, attains good results in some cases. It can not be expected that other drugs show effectiveness.

9.7

IMPAIRMENTS IN FACTORS OF MUSCLE AEROBIC METABOLISM RELATE TO LOW INHERITED EXERCISE CAPACITY

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Epidemiological studies reveal a strong link between low aerobic capacity and metabolic diseases. Rats artificially bred for low aerobic exercise capacity score high on metabolic syndrome risk factors. Large-scale artificial selection was used to produce rat strains, which differ by their treadmill running capacity: low-capacity runners (LCR) and high-capacity runners (HCR) (Koch & Britton: Physiol Genomics 2001). In this study we used rats (n=24) from the 18th generation. These two populations differed in their maximal running capacity by ~600 %. Capillarization was greater in HCR in slow soleus muscle ($p<0.01$) and in fast EDL muscle ($p<0.05$). Electron microscopy showed that subsarcolemmal mitochondrial area was 96% larger ($p<0.01$) in HCR in soleus, the largest stocks localizing close to capillaries. HCR had greater percentage of EDL myosin heavy chain (MHC) of type 2A/X ($p<0.01$) and LCR more type 2B ($p<0.05$). In addition to lower aerobic capacity, LCR had higher blood glucose ($p<0.01$) and body weight ($p<0.001$), which all are considered as risk factors of metabolic syndrome. Microarray results showed 126 upregulated and 113 downregulated genes in HCR. Functional clustering revealed that genes upregulated in HCR gastrocnemius were related to mitochondria and lipid metabolism. In conclusion, these differences between HCR and LCR rats may represent early factors in the pathogenesis of complex metabolic diseases.

9.8

CESSATION OF DAILY PHYSICAL ACTIVITY LEADS TO TISSUE SPECIFIC CHANGES IN PALMITATE OXIDATION IN MALE RATS

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Regular exercise has been shown to increase fatty acid oxidation and mitochondrial content in skeletal muscle and liver. This study sought to determine whether tissue specific decreases in ex vivo fatty acid oxidation contribute to the increase in adipose tissue with the cessation of voluntary running. 3-week old ad libitum, low-fat fed, male rats had access to voluntary running wheels for 6 weeks, after which the wheels were locked for 5 (WL5) or 173 (WL173) hours. A third group of rats (SED) never had access to voluntary running wheels. Ex vivo fatty acid oxidation was measured in red gastrocnemius (RG), liver, and isolated epididymal adipocytes and in isolated mitochondria from RG and liver. Mitochondrial enzymatic activities did not differ among groups in any of the tissues examined. However, in the RG, daily physical activity increased palmitate oxidation by 91% at WL5 compared to SED ($p<0.05$), and was approaching SED levels at WL173. While, liver whole homogenate palmitate oxidation was significantly elevated only at WL173 by 46% and 65% over WL5 and SED respectively ($p<0.05$). Whereas, isolated adipocytes increased fatty acid oxidation by 81% at WL5 and remained 71% higher at WL173 compared to SED ($p<0.05$). In conclusion, fatty acid oxidation in the RG dropped with reduced physical activity, while oxidation levels increased in the liver at WL173, and remained high at both WL5 and WL173 in adipocytes. Funded by Life Science Fellowship/The College of Vet Med.

9.9

REDUCED DAILY STEPS DECREASES INSULIN SENSITIVITY AND INCREASES INTRA-ABDOMINAL FAT MASS IN RATS AND HUMANS

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When 4-wk-old, male rats ended 3 wks of voluntary wheel running for 53 hrs, their enhanced insulin sensitivity and Akt Ser^{473} phosphorylation per unit of Akt were reversed (J. Physiology 562:829, 2005.); further, the cessation of daily running for 53 hrs also increased weights of omental and epipdidymal fat pads (J. Physiology 565:911, 2005.). To determine if these events translate to humans, the Pedersen lab had eight 27-yr-old men (body mass index (BMI) = 22.9± 1.4kg·m^{-2}) decrease their pedometer-recorded daily steps from a mean value of 6,203 to 1,394 with determinations made at pre and at 1, 2, and 3 weeks into reduced stepping. In a second study, ten 24-yr-old men (BMI=22.1± 0.8kg·m^{-2}) reduced daily steps from a mean value of 10,501 to 1,344 with measurements made pre and 2-weeks post. In study 1, area under the curve for plasma insulin during an oral glucose tolerance test increased after 1, 2 and 3 weeks of reduced stepping compared to baseline, demonstrating reduced insulin sensitivity (JAMA 299:1261, 2008). In study 2, hyperinsulinemic-euglycemic clamp revealed reduced peripheral insulin sensitivity and decreased insulin stimulated Akt Ser^{473}in skeletal muscle, but no change in hepatic glucose production after 2 weeks of reduced stepping (In review). Taken together, the identified metabolic abnormalities seem to represent a unique link between reduced stepping in rats and young healthy men and the development of risk factors contributing to chronic disorders.

9.10

DETRIMENTAL EFFECTS OF INACTIVITY ON INSULIN ACTION: ROLE OF ENERGY SURPLUS

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A reduction in standing and ambulation (physical inactivity) reduces insulin action. Unless energy intake is reduced to match expenditure, a concurrent energy surplus may, at least partly, be responsible for the lower insulin action. The purpose of this study was to evaluate the effect of inactivity with and without energy surplus on insulin action. Seven young (27.5 ± 4.2 yrs), lean (20.0 ± 5.0% fat), fit (VO_{2peak}= 50.6 ± 1.8 ml/kg/min) men (n=5) and women (n=2) completed each of 3, 24-hour conditions: 1) high energy expenditure (e.g. standing, ambulating) in energy balance= LOW-SIT BAL; 2) low energy expenditure (sitting) with no change to energy intake (i.e. surplus)= HIGH-SIT SUR; 3) sitting with energy intake reduced to match low expenditure= HIGH-SIT BAL. Insulin action was measured during a glucose infusion the following morning,12 hours after a standardized meal. Steady-state plasma insulin (SSPI) was higher in HIGH-SIT SUR (49.3 ± 3.5 uU/mL) compared to HIGH-SIT BAL (41.2 ± 4.1 uU/mL) and LOW-SIT BAL (36.4 ± 3.1 uU/mL). Insulin action, estimated from steady-state plasma glucose ·

SSPI, was 11% greater in LOW-SIT BAL compared to HIGH-SIT BAL and 29% higher compared to HIGH-SIT SUR. These preliminary results suggest the detrimental effect of inactivity on insulin action is magnified if energy intake is not reduced to match low energy expenditure. Analysis of glucose kinetics will determine effects on hepatic glucose output and glucose disposal. Supported by an ACSM FRG.

9.11

PHYSICAL ACTIVITY VS. PHYSICAL FITNESS: ASSOCIATIONS WITH METABOLIC HEALTH IN PATIENTS AFTER GASTRIC BYPASS SURGERY, OBESE AND NON-OBESE CONTROLS

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Debate exists as to whether physical fitness (PF) is more beneficial than physical activity (PA) for metabolic health. We hypothesized that PF and not PA would be related with metabolic health in a group of 9 patients after gastric bypass surgery (GBS), 8 obese (Ob), and 7 non-obese (N-Ob) controls (age= 39±6, 28±7, 28±10 yr; BMI= 30±6, 39±4, 24±2 kg/m^2, respectively). PA was determined with accelerometry, PF with VO_2max, body fat with DXA, and insulin resistance with HOMA. Blood lipids and leptin were assessed. ANOVA was used to detect differences between active (n=13) vs. inactive (n=9), and fit (n=10) vs. unfit (n=12); and regressions to test associations between moderate-vigorous PA (MVPA), VO_2max, and metabolic variables. Active vs. inactive subjects had lower %fat (39±4 vs. 53±5), abdominal fat (303±60 vs. 522±72 cm^2), and leptin (0.5±0.1 vs. 0.8±0.1 ng•ml^{-1}•kg$^{-1\,fat}$). Fit vs. unfit subjects had lower %fat (33±3 vs. 53±3), abdominal fat (264±60 vs. 499±55 cm^2), and leptin (0.4±0.1 vs. 0.8±0.1 ng•ml^{-1}•kg$^{-1\,fat}$). Only fit vs. unfit had lower cholesterol (157±8 vs. 183±7 mg/dl), LDL (83±7 vs. 104±7 mg/dl), and insulin resistance (0.9±0.5 vs. 2.3±0.4). VO_2max and MVPA were correlated with %fat (r=-.72 and -.62), abdominal fat (r=-.48 and -.55), and leptin (r=-.58 and -.61). We conclude that PA and PF provide similar benefits in most of the metabolic variables studied. Lower lipids were an additional benefit only related to PF. Funded by NIH CTSA UL1-RR24150 and KL2-RR024151.

9.12

INFLUENCE OF EXERCISE AND PERIVASCULAR FAT ON CORONARY ARTERY VASOMOTOR FUNCTION IN A FAMILIAL HYPERCHOLESTEROLEMIC PORCINE MODEL OF ATHEROSCLEROSIS

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Our lab has shown that left circumflex coronary artery (LCX) perivascular adipose tissue (PAT) blunts endothelin-1 (ET-1) stimulated contractions in normal pigs on low and high fat diets. Other studies report that PAT exerts anti-contractile effects on agonist-induced arterial contraction via release of a relaxing factor. The purpose of this study was to test the hypotheses that PAT blunts LCX contraction in FH pigs and that exercise training (EX) increases this anti-contractile effect. Male FH pigs were divided into EX (n=8) and sedentary (SED) (n=8) groups. LCX reactivity was evaluated in vitro, with intact or removed PAT (+/-PAT), to angiotensin II (AngII), bradykinin (BK), ET-1, and sodium nitroprusside (SNP). LCX relaxation induced by BK and SNP was not altered by EX or -PAT; although SED +PAT tended to have greater maximal (max) BK relaxation than SED -PAT. AngII-induced LCX contraction was nearly 2-fold higher in EX +PAT than SED +PAT, this trend reversed following PAT removal (p>0.05). Max AngII contraction also tended to be greater in LCX of EX +PAT than -PAT. ET-1-induced max contraction of LCX tended to be greater in SED -PAT than in SED +PAT, whereas PAT had no effect on ET-1 induced contraction in EX LCX. We conclude that the anti-contractile effects of PAT on LCX contraction depends on the constrictor agent used in FH pig LCX. Also, results indicate that EX had only a moderate influence on the anti-contractile effects of PAT. (NIH HL-52490).

9.13

DAILY PHYSICAL ACTIVITY PREVENTS AGING AND OBESITY INDUCED SKELETAL MUSCLE INSULIN RESISTANCE IN THE OLETF RAT

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We sought to determine if daily voluntary wheel running (VWR) would sustain skeletal muscle glucose transport across the lifespan of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, rats which are hyperphagic, obese, and develop type 2 diabetes at ~18-22 weeks of age. At four weeks of age, OLETF rats began VWR (OLETF-EX) while additional OLETFs served as obese sedentary controls (OLETF-SED). Long-Evans Tokushima Otsuka (LETO) rats served as lean sedentary controls (LETO-SED). Rats from each group were sacrificed at 13, 20 and 40 weeks of age. Wheels were locked 2 days before sacrifice. Glucose transport under basal and insulin-stimulated (100 nM) conditions was measured in extensor digitorum longus muscle preparations. Daily exercise (~5-8 km/d) suppressed weight gain and body fat % to the level of the LETO-SED and ~70% of OLETF-SED animals at all ages. No differences in glucose transport were observed at 13 or 20 weeks; however, at 40 weeks of age, both basal and insulin stimulated glucose transport were 30-40% lower in the OLETF-SED and LETO-SED than the OLETF-EX. These results show that daily physical activity maintains basal and insulin-stimulated glucose transport in hyperphagic, obese rats across the lifespan and suggests physical inactivity is obligatory for the development of obesity and aging induced skeletal muscle insulin resistance. Funding provided by the University of Missouri, Department of Internal Medicine.

9.14

IMPAIRED MAXIMAL FORCE AND REDUCED FATIGUE RATES CHARACTERIZE THE SKELETAL MUSCLE OF 90% PARTIAL PANCREATECTOMIZED DIABETIC RATS

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Patients with long-term type 1 diabetes (T1D) can present with muscle pain, atrophy and weakness (i.e. myopathy). The effects of T1D on muscle fatigue are similar to some studies reporting increased fatigue while others report fatigue resistance. The objective of this study was to measure maximal force (F_{max}) and fatigue using in situ stimulation in isolated gastrocnemius plantaris soleus (GPS) muscle of partial pancreatectomized (Px) rats. Male, Sprague Dawley rats (100-120g) were randomly assigned to either Px or sham surgery groups. Changes in body mass (BM) and fed blood glucose levels were monitored for 8 wks. Px were hyperglycemic by 7 days post surgery (20.6±1.5mM), increasing to 31.8±0.67mM by wk 8, while the shams remained euglycemic (6.7±0.6mM, p<0.01). Px had a lower body mass than shams (Px: 349.1±20.8g vs Sham: 484.4±10.1g; p<0.01). Increasing stimulation frequencies (1 to 70Hz) were used to generate a force frequency curve (FFC) before and after a fatigue protocol that induced intermittent contractions of 50% F_{max} for 2 minutes. GPS mass was less in Px vs shams (1.8±0.1 vs 3.3±0.1g/gBM, respectively; p<0.01). F_{max} was ~50% lower in Px vs shams (12.1±1.3N vs 22.6±1.8N, respectively; p<0.01), but when corrected per gram of mass, F_{max} was similar between groups. During fatigue, Px GPS had a slower rate of decline in force compared to shams (52.8±3.4% vs 69.7±7.2% respectively; p<0.05). Px had an increase in time to peak tension pre- vs post-fatigue as compared to shams (p<0.05). Thus, sustained hyperglycemia/hypoinsulinemia induced by Px in growing rats causes a reduction in muscle mass that results in decreased absolute F_{max} in the lower limb muscles, but surprisingly, increased fatigue resistance. This research was funded by NSERC.

9.15

HIGH-FREQUENCY MUSCLE STIMULATION HAS AN ANABOLIC EFFECT ON BONE AND MAINTAINS PLANTARFLEXOR STRENGTH DURING HINDLIMB UNLOADING

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Long-duration spaceflight results in significant loss of bone and muscle mass and strength. This study's objective was to test whether combining a reduced volume of simulated resistance training with an anti-resorptive pharmacological agent could mitigate hindlimb unloading-(HU) induced bone loss while maintaining muscle strength. Sprague-Dawley rats (6-mo-old) were randomly assigned to cage control (CC, n=12), anesthesia control HU (AN+HU, n=12), alendronate plus HU (ALEN+HU, n=12), muscle stimulation plus HU (STIM+HU, n=12), or a combination of ALEN and STIM (STIM+ALENHU, n=12). STIM was performed every 3 days during 28-d HU (75% peak isometric strength (Po); 4 x 5 reps; 1000ms isometric + 1000ms eccentric). After 28 d, STIM+HU rats had (by in vivo computed tomography) significantly higher total bone mineral content (BMC), total bone mineral density (vBMD), total bone area, and cancellous vBMD at the proximal tibia (p<0.001) than did AN+HU animals. Tibial mid-shaft cortical BMC, area, and cross-sectional moment of inertia increased more in STIM+HU vs. AN+HU and ALEN+HU (p<0.001). Though plantar flexor muscle mass was significantly lower in STIM+HU vs. CC rats, Po was maintained with STIM vs. 10% decrease in AN+HU rats (p<0.05). Alendronate in combination with STIM did not have an additional positive effect on bone. These results demonstrate anabolic effects of low-volume STIM training during HU on unloaded bone and effective maintenance of isometric strength.

9.16

CHRONIC ALCOHOL INGESTION INDUCES SEVERAL FACTORS ASSOCIATED WITH SKELETAL MUSCLE PROTEIN DEGRADATION IN HIV-1 TRANSGENIC RATS

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Long-term alcohol abuse can produce extensive biochemical and structural changes to skeletal muscle that may lead to severe wasting and dysfunction. Likewise, HIV-1 infection is often associated with neuromuscular complications. Yet, the catabolic mechanisms that regulate these myopathies remain largely unknown, particularly when the diseases co-exist. Thus, we used well-characterized rat models of chronic alcohol abuse and HIV-1 to identify these mechanisms and their resultant effect on plantaris muscle morphology. Plantaris muscle cross-sectional area was reduced in rats fed alcohol for 12 wk, in HIV-1 transgenic rats, and alcohol-fed, HIV-1 transgenic rats compared to controls. Next, we analyzed the gene expressions of signaling components related to four catabolic mechanisms, including: MURF-1, myostatin and activin IIB, TGFβ and SMAD3, and TNFα. No changes in any gene were apparent in plantaris muscles form HIV-1 transgenic rats. In contrast, plantaris muscles from alcohol-fed rats had increased expressions of all genes. Interestingly, each catabolic mechanism analyzed in this study - including components of the ubiquitin proteasome system, the myostatin system, and inducible cytokines - was at its highest gene expression levels when the diseases co-existed suggesting extensive activation of these mechanisms associated with protein degradation.

9.17

EFFECTS OF INACTIVITY AND ENERGY STATUS ON APPETITE REGULATION IN MEN AND WOMEN

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Obesity and metabolic disease are associated with time spent in activities requiring low energy expenditure (e.g. sitting). Whether too much sitting alters the perception of hunger and satiety, possibly contributing to increased energy intake and obesity, has not been evaluated. The purpose of this study was to evaluate whether sitting affects hunger and satiety independent of changes in energy status. Six young (27.4 ± 4.6 yrs), lean (20.2 ± 5.4% fat), fit (VO_{2peak}= 50.5 ± 1.9 ml/kg/min) men (n=4) and women (n=2) completed each of 3, 24-hour conditions: 1) high energy expenditure (e.g. standing, walking slowly) with energy balance (intake matched to expenditure)= LOW-SIT BAL; 2) low energy expenditure with no change in intake (energy surplus)= HIGH-SIT SUR; 3) low energy expenditure with energy intake reduced to matched expenditure= HIGH-SIT BAL. Appetite questionnaires, based on a visual analog scale, were given in the morning of the second day, approximately 12 hours after consumption of a standardized meal. In HIGH-SIT BAL and HIGH SIT SUR subjects felt hungrier (+12%, +17%), had a greater desire to eat (+14%, +18%) and reported they could consume more food (+10%, +8%) compared to LOW-SIT BAL. Similarly, in HIGH-SIT BAL (-16%) and HIGH-SIT SUR (-12%) subjects reported feeling less satiated compared to LOW-SIT BAL. These results suggest inactivity may increase perception of hunger and decrease perception of satiety independent of energy status. Supported by an ACSM FRG.

9.18

A COMMUNITY-BASED PROGRAM TO ENHANCE FUNCTION AND WELL-BEING IN INDIVIDUALS WITH CHRONIC PAIN

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Physical function and well-being were examined in individuals with chronic pain who enrolled in a community-based education and exercise program (Y-PEP). The 6-week Self-Management Program developed by Sandra Lefort was adapted to enhance the physical activity component and extend it to a 10-week program by a committee of health care and YMCA professionals. Six men and 14 women (age=55±14 yrs) volunteered to participate in the study and completed, (a) a demographic information form, (b) the Human Activity Profile (Maximal Activity Score, MAS; Adjusted Activity Score, AAS), (c) the Brief Pain Inventory (BPI), (d) Patient Health Questionnaire – Depression (DEP), and (e) the Pain Catastrophising Scale (PCS) at baseline and at end-program. The MAS and AAS scores increased 7% and 12% respectively at end-program ($p<0.05$). The PCS-total score at baseline in males was 68% greater than in females, and decreased 9% at end-study ($p<0.05$). Correlations between the changes in outcome measures at baseline and end-study indicated that greater improvements in AAS were associated with lower ratings of the extent to which pain interfered with daily function (r=-0.45), which were associated with greater improvements in depression (r=0.50), which in turn were associated with greater reductions in PCS (total, helplessness) (r=0.52; r=0.47). Participation in this novel program significantly improved physical function and activity and psychosocial well-being in individuals with chronic pain.

9.19

LOSS OF MYOSIN FROM SINGLE MUSCLE FIBERS IN HEART FAILURE PATIENTS REDUCES FORCE PRODUCTION WITHOUT ALTERING MYOFILAMENT ULTRASTRUCTURE

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Skeletal muscle weakness is common in heart failure (HF) patients. We examined the effect of HF on myofibrillar protein content, ultrastructure and function in 7 patients with chronic HF and 9 sedentary controls to test the hypothesis that functional deficits are related to loss of myosin protein content. Single muscle fibers from HF patients showed a reduction in MHC protein content of 19% ($P<0.01$) when all fiber types were considered together. Examination of individual fiber types showed a 15% reduction in MHC content in Type I fibers ($P=0.06$), a 19% reduction in Type IIA fibers ($P<0.04$) and a 28% reduction in Type IIA/X hybrid fibers ($P<0.02$). Average MHC protein content in patients and controls (n=10 total) was negatively related to the expression of two E3 ubiquitin ligases: atrogin (r=-0.733; $P<0.02$) and MuRF-1 (r=-0.661; $P<0.04$). Despite differences in MHC content, no differences in thick to thin filament ratio or A band length were found. In a subset of HF patients and controls (n=4/group), we found a 12% reduction in single fiber force production per unit cross-sectional area in Type I fibers in HF patients compared to controls ($P<0.05$). Our results show that heart failure is accompanied by loss of MHC protein from single muscle fibers, a reduction that could be due to increased MHC proteolysis. Although no gross alteration of myofilament ultrastructure was noted, MHC depletion was associated with reduced single fiber force production. Thus, muscle weakness in HF patients may be explained by the loss of myosin protein from individual muscle fibers. Support: NIH HL-077418.

9.20

COMPARISON OF OUTCOME IN DIFFERENT METHODS USING OR NON-USING E-WELLNESS SYSTEM

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The purpose of this study was to develop an efficient IT system that contributes to life-style related disease as population approach. The subjects were drawn from people carried out the medical extermination at Mitsuke city in Nigata Prefecture and were 90 people (men: n = 46, average age 65.2, women: n=44, average age 61.7). The subjects were classified into three groups 1) Group had exercise classes twice a week and utilized e-wellness system provides each participant with individual exercise programs based on Evidence-Based Medicine. 2) Group was made an individual calls and consultations by public health nurses, and 3) Group was supported telephone and e-mails and given a group seminar. Life-style related exterminations and body composition was measured before and after the health promotion intervention. After six months this intervention, each three group was found the significant results in lifestyle-related disease extermination. 1) Group was decreased in waist (from 93.8cm to 92.1cm), weight (from 68.0kg to 67.3kg), and Body Mass Index (BMI) (from 26.7 to 26.3). The waist result from 2) Group also found from 92.7cm to 91.5cm. However, 3) Group was no significant differences. Although each three group can be applied the improvement in lifestyle-related disease, 1) Group was found higher result of their body composition than in other 2 groups 2) and 3). It was shown that e-wellness system was a reasonable approach method for life-style related disease prevention.

9.21 Withdrawn.

9.22

ETHNIC/RACIAL DIFFERENCES IN THE EFFECTS OF ACUTE EXERCISE ON INSULIN SENSITIVITY

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Non-Hispanic blacks (blacks) are more insulin resistant than non-Hispanic whites (whites). Ethnic/racial disparities in the response to exercise may contribute to the differences in insulin resistance. Because the beneficial effects of exercise are transient, single exercise bouts have strong implications for opposing insulin resistance. The objective of this study is to compare metabolic responses to a single bout of exercise in 15 blacks and 15 age/gender/BMI-matched whites. Insulin sensitivity, glucose storage, and fasting fat oxidation were assessed by glucose clamp and indirect calorimetry in sedentary black and white participants. Outcome measures were evaluated at baseline and 12 hr. after participants walked on a treadmill at 75%$_{\text{max HR}}$ for 75 min. Preliminary results (blacks n=5, whites n=9) suggest that insulin sensitivity increased after exercise in blacks (pre: 6.2 $\pm$ 2.5 vs. post: 8.3 $\pm$ 2.0 mg/kg/min) but not whites (pre: 6.8 $\pm$ 2.5 vs. post: 6.6 $\pm$ 2.0 mg/kg/min). Non-oxidative glucose disposal (storage) increased more after exercise in blacks than in whites (+37.4% vs. +3.9%). Exercise also raised fasting fat oxidation in blacks (+11.0%) more than in whites (+3.7%). The preliminary data suggest there may be ethnic/racial differences in the insulin sensitivity response to acute exercise. Whether these differences are explained by greater baseline insulin resistance in blacks requires further investigation. Supported by American Diabetes Assoc. 7-04-JF-10.

9.23

PARVALBUMIN, SERCA1, AND SERCA2 EXPRESSION IN SKELETAL MUSCLE IS ACTIVITY-DEPENDENT FOLLOWING SPINAL CORD TRANSECTION AND SPASTICITY

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PURPOSE: to use Western blotting to assess the effect of spinal cord injury and spasticity on skeletal muscle content of parvalbumin (PV) and fast and slow sarco/endoplasmic reticulum Ca^{2+} ATPase isoforms (SERCA1 and 2). HYPOTHESIS: PV, SERCA1, and SERCA2 contents are reduced with injury and spasticity. METHODS: In adult rats, sacral spinal cord transection (ST, n=6) led to chronic tail muscle spasticity, and sacral spinal cord isolation (SI, n=6) led to chronic tail muscle inactivity. ST and SI rats were compared to normal controls (n=6; 1-way ANOVA). In adult cats, hemisection and unilateral deafferentation (HSDA, n=5) led to chronic unilateral hindlimb paralysis, but crossed reflexes generated some activity in the paralyzed medial gastrocnemius muscle. The HSDA cats were compared to normal controls (n=5; T test). Significant differences accepted at $P<0.05$. RESULTS: In ST rats PV content was significantly reduced compared to normal. In SI rats there were large reductions in PV content compared to both normal and ST and in SERCA1 content compared to normal. There were no changes in SERCA2 content due to ST or SI. In HSDA cats PV, SERCA1, and SERCA2 contents were all significantly reduced compared to normal. CONCLUSION: Overall, PV, SERCA1, and SERCA2 contents are reduced with injury and spasticity, consistent with the longer and larger muscle and motor unit twitches and increased fatigability previously observed in these models. SUPPORT: CIHR, AHFMR, NSERC, CFI, NCE.

10.0: OXYGEN TRANSPORT

10.1

PROBLEMS OF THE BLOOD USED FOR BLOOD TRANSFUSION AND BLOOD PRODUCTS

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The blood which has undergone tests currently conducted before production of the blood for transfusion and various blood preparations still might have lots of risk. More trouble will occur if the current production method is continuously used. A new method to check blood and the results to be improved by introduction of it are reported and proposed in this article. Method: 1. Matsumoto Method 2. Matsumoto-Hagiya Method (MH Method) Results: 1. Matsumoto Method *f*À-type leucocytes, Orange Cells, Fish-shaped erythrocytes, degenerated erythrocytes, Rice Grains, Grouping, Huge leucocytes, yellow bright Particles, Ennyu Circle, Hagiya Flower and blood cell aggregation are found in many samples of blood. 2. M-H Method RC (Reverted Cells), degenerated leucocytes/erythrocytes, Orange Cells, Fish-shaped erythrocytes, small, medium and large Rice Grains, Fibrin Meshes, Black Spots, Huge leucocytes, small, medium and large Mysterious Chains, Moving Micro Livings, Firefly Cells, Black Firefly Cells, Ghost Cells, etc. are found in some samples of blood. All of the findings mentioned above may show the presence of harmful diseases, suggesting it is unsuitable for use. Discussion and Conclusion: The blood at risk of many diseases is currently defined as healthy/normal and used for transfusion and blood products. In addition to the current standards of examination for blood collection, Matsumoto Method and Matsumoto-Hagiya Method should be introduced to improve the safety of blood transfusion and blood products.

10.2

ADVERSE EFFECT BY ANTICOAGULANT AND GVH

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Method: 1. In the test groups, anticoagulant is added to the Upper Layers of Red Blood Cells (ULRBC) obtained by Matsumoto-Hagiya Method (M-H Method) and New Matsumoto-Hagiya Method (New M-H Method), respectively; only ULRBC are used as the control groups. 2. The same amount of Pseudomonas aeruginosa is added to the blood solutions prepared in 1. Then all of them are cultured in an incubator under the condition of 5% carbon dioxide at 37C, and observed with an inverted phase-contrast microscope while recorded in photos. Result: 1. ULRBC obtained by M-H Method: Little activities of ULRBC and proliferation of Pseudomonas aeruginosa in countless number were observed in the test group with anticoagulant; in the control group without anticoagulant, however, proliferation of the bacterium were not found within 24 hours. Also ULRBC showed vigorous activities peculiar to RBC such as spinning, torsion and movement to left and right as if they are attacking Pseudomonas aeruginosa in the latter. 2. ULRBC obtained by New M-H Method: In anticoagulant group, ULRBC showed poor metamorphosis and little movements peculiar to RBC after the bacterium was added. Conclusion: According to the above test results, it can be concluded that anticoagulants reduce activities of red blood cells, making them almost dead like fossil. The existing interpretation of GVH might be wrong; the symptom resulting from pan-erythropathy and pan-leucopathy caused by large amount of coagulant taken into the body during blood transfusion of 10,000 ml or more was incorrectly defined as GVH. It is more scientific to believe that GVH does not actually exist.

10.3

A NEW APPROACH OF TRANSFUSION THERAPY OF PRESERVED SELF-BLOOD

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Purpose: Use of preserved self-blood for operation, where massive bleeding is expected, has been getting popular recently. The study to examine whether the therapy is safe and good for patients was conducted and reported in this article. Method: 1. The blood cells are collected from patients and incubated using Matsumoto Method for observation. 2. The blood cells (1) with coagulant are treated using Matsumoto-Hagiya (M-H) Method and New M-H Method. After Pseudomonas sp. is put into the Upper and Lower Layers of RBC, they are cultured in an incubator under the condition of 5% carbon dioxide at 37C. 3. The blood cells (1) without coagulant are prepared in the same manner (2) as the control groups. 4. 2 and 3 are

diachronically observed with an inverted phase-contrast microscope. Result: 1. Much more sick cells such as ƒÀ-type WBC, deformed RBC, Fish-shaped RBC, Orange Cell, Rice Grain and so on were found in the blood collected from patients before operation than healthy subjects. 2. Enhanced proliferation of Pseudomonas sp. were found in Upper and Lower Layers of RBC with both M-H and New M-H Methods. Discussion: The blood cells of patients before operation include lots of sick cells in bad condition. Coagulants also tend to weaken the resistance to bacterial infection. The activity of blood cells, moreover, is lost by preservation for long time. I, therefore, stand against transfusion therapy of preserved self-blood.

10.4

LONG-TERM ACCLIMATIZATION TO MODERATE ALTITUDE: A 4-YEAR CROSS-SECTIONAL ANALYSIS

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Acclimatization to moderate altitude (MA) is thought to be minimal and occur rapidly; however, previous research at the US Air Force Academy (USAFA, 2210m) suggested that complete acclimatization required more than 46 weeks. In an attempt to elucidate the additional acclimatization time, we cross-sectionally analyzed 102 freshmen through senior USAFA cadet subjects previously residing at either sea level (SL) or MA before attending this unique, well-controlled MA institution. Significant altitude-related hematological differences were observed among only freshmen, with MA subjects having a significantly higher hemoglobin concentration ([Hb]; +2.5%), serum ferritin (+59%), and significantly lower soluble transferrin receptor (-11.4%) levels. However, both freshmen and sophomore subjects from SL were significantly less economical (6.5% and 1.7%, respectively), had a lower relative VO_{2peak} (5.6% and 1.9%), and ran 1.5 miles slower (4.6% and 3.6%) than their MA peers. There were no significant altitude-related differences in any of these parameters among juniors and seniors. While hematological differences between former SL and MA subjects dissipate after 1 year of chronic exposure to 2210m, altitude-related differences in performance persist for more than 16.5 months, but are ameliorated after 22 months. These results suggest that adaptations which affect performance require more than hematological acclimatization alone, and may implicate changes within skeletal muscle.

10.5

ENLARGED O_2 DEFICIT WITH CO_2-INHALATION DURING HEAVY EXERCISE

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O_2 uptake kinetics may be delayed during experimental acidosis. The purpose of the present study was to use CO_2-inhalation to evoke respiratory acidosis and then examine whether this increased O_2 deficit in the initial exercise phase. Nine physically active (VO_2max 54±4 ml·min^{-1}·kg^{-1}; x±SD) young males performed 'light' (LI; ~45% VO_2max; 122±15 W) and 'heavy' (HE; ~75% VO_2max; 253±29 W) cycle exercise for 6 min while inhaling (in random order) normal air (Atm) or a 4.2 % CO_2 mixture (21% O_2, balance N_2; $HiCO_2$). After 10 min pre-breathing at 40 W, gas exchange was measured with Douglas bags at baseline (40 W), and at 0-2, 2-3, and 5-6 min of LI and, after a 6 min break, HE exercise. O_2 deficit (liters) was calculated as $3 \cdot VO_{2\ min\ 5\text{-}6} - 2 \cdot VO_{2\ min\ 0\text{-}2} - 1 \cdot VO_{2\ min\ 2\text{-}3}$. Blood PCO_2 increased from 42±3 mmHg in Atm to 50±2 mmHg ($P<0.001$) in $HiCO_2$; blood pH decreased from 7.43±0.03 to 7.37±0.02 ($P<0.001$). Changes persisted during exercise. Baseline VO_2 averaged 1.20 l·min^{-1} with ns differences between experimental conditions. Exercise VO_2 was higher ($P<0.001$) in $HiCO_2$ than in Atm, both in LI (0.12±0.11 l·min^{-1}) and in HE (0.14±0.15 l·min^{-1}). O_2 deficit in HE was higher for $HiCO_2$ than Atm (2.23±0.54 vs. 1.89±0.47 l; $P<0.05$). Corresponding values in LI averaged 0.62±0.22 and 0.55±0.21 l (ns). Conclusion: Inspiration of CO_2-enriched air (respiratory acidosis) increased O_2 deficit in heavy exercise, but had no effect in light exercise. Supported by the Danish Ministry of Cultural Affairs.

10.6

EFFECTS OF HYPOXIA ON $\dot{V}O_2$MAX AND LACTATE ACCUMULATION RATE IN EXERCISING GOATS

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We hypothesized that reduction in maximum aerobic power (VO_2max) resulting from breathing hypoxic gas would induce stoichiometric increases in net anaerobic power. As a result, increased running speed above that required to elicit VO_2max should result in equivalent rates of plasma lactate accumulation for equivalent increases in running speed above VO_2max independent of inspired O_2 concentration. Furthermore, the slope of the plasma lactate accumulation rate vs. speed relationship above VO_2max should represent net anaerobic power equivalence with the O_2 consumption vs. speed (aerobic power) relationship below VO_2max. To test this hypothesis, we ran goats on a treadmill at speeds below and above those that elicited VO_2max and measured rates of O_2 consumption and plasma lactate accumulation while goats breathed gases of varying O_2 concentration. Hypoxia reduced VO_2max and caused plasma lactate concentration to begin increasing at lower speeds. The best fit for energetic stoichiometry between the slopes of the aerobic (VO_2) and net anaerobic (plasma lactate accumulation rate) power curves was 1 ml O_2 (STPD) s^{-1} kg^{-1} being energetically equivalent to a plasma lactate accumulation rate of 10-11 mM min^{-1}, similar to the value reported for horses. (Supported by the U.S. Army Medical Research and Materiel Command (Contract No. W81XWH-06-C-0051) through L-3/Jaycor and approved by the UC Davis Animal Care and Use Committee in conformance with NRC and APS guidelines.)

10.7

BETA-ALANINE SUPPLEMENTATION REDUCES ACIDOSIS DURING HIGH-INTESITY CYCLING, BUT HAS NO EFFECT ON VENTILATION OR OXYGEN UPTAKE

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Introduction : Carnosine is thought to contribute to homeostasis during muscle contractions as a pH buffer. The chronic ingestion of beta-alanine, the rate-limiting precursor of the dipeptide carnosine (beta-alanyl-L-histidine) has been shown to elevate skeletal muscle carnosine content. The present study aimed to investigate whether oral supplementation of beta-alanine could reduce acidosis during high-intensity cycling and thereby affect ventilation and oxygen uptake. Methods: 14 male physical education students participated in this placebo-controlled, double-blind study. Subjects were supplemented orally for 4 weeks with 4.8g/day placebo (maltodextrine) or beta-alanine. Before and after supplementation subjects performed a 6-min cycling exercise at an intensity of 50% between ventilatory threshold and maximal oxygen uptake. Capillary blood samples were taken for blood gas analysis and oxygen uptake kinetics were calculated with a bi-exponential model on the breath-by-breath data of three repetitions. Results: Acidosis at 6 min of high intensity cycling was significantly reduced by beta-alanine but not placebo supplementation ($p=0.03$). There were no differences in capillary lactate and bicarbonate concentrations nor in ventilation and oxygen uptake kinetics between both groups. Conclusion: Beta-alanine supplementation reduces acidosis during high-intensity cycling, without sparing bicarbonate. The reduction in acidosis has however no effect on the fast or slow component of oxygen uptake kinetics.

11.0: BLOOD FLOW REGULATION

11.1

SKELETAL MUSCLE BLOOD FLOW RESPONSE TO RHYTHMIC EXERCISE DURING HYPOPERFUSION IN HUMANS

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We tested: 1) whether the pressor response to exercise with muscle hypoperfusion improves blood flow (BF) to active muscles; and 2) whether the rise in sympathetic outflow evoked by concurrent exercise and hypoperfusion prevents restoration of BF to active muscles. Healthy subjects (n=10) performed forearm exercise (10% and 20% of max) during intra-arterial balloon inflation. Each trial included; baseline, exercise prior to inflation (control), exercise with inflation, and exercise after deflation (3 min each). Forearm blood flow (FBF; ultrasound), local (brachial artery), and systemic arterial pressure (MAP; Finometer) were measured. Exercise (10 % and 20%) was repeated during phentolamine (Phent) infusion (α-antagonist). Forearm vascular conductance (FVC; ml/min/100mmHg) was calculated from BF (ml/min) and local MAP (mmHg). FVC acutely fell with balloon inflation during all trials ($P<0.001$). FVC (Δ from nadir) recovery during steady state exercise with inflation was 61±6 and 106±17 (10% and 20% respectively; $P<0.01$) and 107±16 and 139±14 during Phent infusion (10% and 20% respectively; $P<0.03$). FVC recovery was greater at 10% with Phent compared to without ($P=0.016$) and similar at 20% ($P=0.17$). Systemic MAP, heart rate, and estimated cardiac output were not augmented during balloon inflation, indicating that FBF is restored during exercise with hypoperfusion via local dilator mechanisms that are partially restricted by sympathetic outflow at lower intensities. Supported by NIH HL 46493.

11.2

MYOCARDIAL BLOOD FLOW AND ADENOSINE A2A RECEPTOR DENSITY IN ENDURANCE ATHLETES AND UNTRAINED MEN

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Previous human studies have shown divergent results concerning the effects of exercise training on myocardial blood flow (MBF) at rest or during adenosine-induced hyperemia in humans. We studied whether these responses are related to alterations in adenosine A2A receptor (A2AR) density in the left-ventricular (LV) myocardium, size and work output of the athlete's heart, or to fitness level. MBF at baseline and during intravenous adenosine infusion, and A2AR density at baseline were measured using positron emission tomography by novel A2AR tracer in 10 healthy male endurance athletes (ET) and 10 healthy untrained (UT) men. Structural LV parameters were measured with echocardiography. LV mass index was 71 % higher in ET than UT (193 ± 18 g/m2 vs 114 ± 13 g/m2, respectively). MBF per gram of tissue was significantly lower in the ET than UT at baseline, but this was only partly explained by reduced LV work load since MBF corrected for LV work was higher in ET than UT, as well as total MBF. The MBF during adenosine-induced hyperemia was reduced in ET as compared to UT, and the fitter the athlete was, the lower was adenosine-induced MBF. A2AR density was not different between the groups and was not coupled to resting or adenosine-mediated MBF. The novel findings of the present study show that the adaptations in the heart of highly trained endurance athletes lead to relative myocardial 'overperfusion' at rest. On the other hand hyperaemic perfusion is reduced, but is not explained by A2AR density.

11.3

DO GENDER DIFFERENCES EXIST IN FUNCTIONAL SYMPATHOLYSIS?

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We hypothesized that sympathetic activation in exercising skeletal muscle evokes less vasoconstriction in females compared to males. We measured forearm blood flow (Doppler Ultrasound of the brachial artery), blood pressure (brachial artery), and heart rate (ECG) during rest and steady-state dynamic forearm exercise (20 contract/min) while α-adrenergic agonists [$\alpha_1$phenelphrine(PE) or α_2, clonidine(CL)] were infused through a brachial artery catheter. 15% and 30% maximal voluntary contraction (MVC) exercise trials increased forearm vascular conductance (FVC) ~2 and ~3-fold, respectively. Data are presented mean±SE. Infusion of PE decreased FVC 60%±11 and 6%±14 in males (n=3-4) and 51%±19 and 6%±12 in females, at rest and 15% MVC, respectively. At 30% MVC, FVC increased 12%±4 in males and 12%±14 in females. Infusion of CL decreased FVC 51%±21, 23%±23, and 12%±14 in males and 41%±7 15%±7, and 4%±30 in females at rest, 15% MVC, and 30% MVC respectively. These preliminary data implicate that during exercise, α_1-adrenergic vasoconstriction is similar between males and females, and that females respond less to α_2-adrenergic vasoconstriction when compared to males. Funded by the UW-Virginia Horne Henry Foundation.

11.4

CEREBROVASCULAR REACTIVITY FOLLOWING MILD TRAUMATIC BRAIN INJURY IN VARSITY HOCKEY PLAYERS

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We examined the effects of mild traumatic brain injury (mTBI) on cerebrovascular reactivity (CVR) in varsity hockey players. 15 subjects were divided into healthy (n = 12) and mTBI (n = 3) groups. The mTBI subjects had either previously (< 4 months) or were currently suffering from mTBI. Using blood flow velocity (MCA_V) (transcranial Doppler) and P_{ETCO_2}, voluntary breath holding (BH) and hyperventilation (HV) (5 x 20s; 40s rest) were used to evaluate CVR, which was defined as % change in MCA_V per mmHg change in P_{ETCO_2}. Resting MCA_V was 54 ± 7 cm/s (healthy) and 57 ± 10 cm/s (mTBI). Resting P_{ETCO_2} was 39 ± 2 mmHg (healthy) and 36 ± 3 mmHg (mTBI). MCA_V change following BH was not different between groups (4 ± 7 vs. 6 ± 6 cm/s, p = 0.291), but was significantly different during HV (-19 ± 8 vs. -13 ± 7 cm/s, p = 0.013). P_{ETCO_2} was not significantly different between groups (BH = 6 ± 4 vs. 7 ± 3 mmHg, p = 0.444; HV = -13 ± 5 vs. -11 ± 3 mmHg; p = 0.086), resulting in no change in CVR following BH and HV between groups (BH =1.6 ± 5.3 vs. 1.5 ± 2.5, p = 0.937; HV = 2.5 ± 0.9 vs. 2.0 ± 1.0, p = 0.166). These results showed that the MCA can be successfully isonated in mTBI, and our protocol provided adequate hypocapnia and hypercapnia. Although there was a trend toward significance between groups in P_{ETCO_2}, the lack of statistical significance was likely related to the small n (3) in the mTBI group. Funding: Canadian Institutes of Health Research, Saskatchewan Health Research Foundation.

11.5

EFFECTS OF ARM ELEVATION ON BOTH HANDS' VASOREGULATION MEASURED BY PHOTOPLETHYSMOGRAPHY

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Our goal is to investigate the vasoregulation of both hands' blood flow during arm elevation (AE) with total light absorbance (TLA) and pulsating component (PC) of photoplethysmogram (PPG). This study was approved by the institutional review board (H-0602-055-168). PPG probes were inserted into both second fingers. Signals from both PPG probes were processed by a 12-bit analog/digital converter at a sampling rate of 100 Hz. The amplitude of PC of PPG of both fingers was adjusted to the same before start of AE procedure. It consisted of right and left hand, in supine and sitting position, and without tourniquet and with tourniquet. The data were compared in eight settings. Single pulse shape of PPG also analyzed based on absolute and relative position of dicrotic notch in one PPG wave, pulse amplitude, maximum time derivative of PPG, and PPG amplitude variability by Fourier transformation. PC of PPG was increased in male and was decreased in female during AE. TLA of PPG in supine position had greater value than those in sitting position. The amount of TLA increase was the highest in sitting position with tourniquet and the lowest in supine position without tourniquet. There were sometimes rebound increases of TLA in the contralateral finger after lowering the elevated arm. There were more dicrotic notches in supine position without tourniquet. There seems to be many dynamic vasoregulations during AE. Granted by College of Medicine, Seoul National University (800-20060097).

11.6

PHYSICAL TRAINING EXPANDS COLLATERAL FUNCTION INDEPENDENT OF SYMPATHETIC ACTIVATION IN RATS WITH FEMORAL ARTERY OCCLUSION

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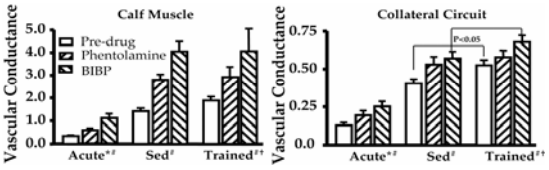
To study the effects of ischemia and physical training on α-adrenergic and Neuropeptide Y (NPY) control of collateral blood flow (BF_{coll}), adult male rats received left femoral artery (FA) occlusion for 6 hr (Acute, n=8), or FA bilaterally occluded for 21 d while limited to cage activity (Sed, n=10) or run on treadmill twice per day for 21 d (Tr, n=10). BF_{coll} was determined during running with microspheres at pre-drug, Phentolamine (Phent., α1, α2-adrenergic inhibitor), and BIBP (NPY Y1 receptor inhibitor) infusion. Blood pressures (BP, ~132 mmHg) were reduced ~24% and ~36% by Phent and BIBP respectively. BF_{coll} to calf m. at pre-drug [13±1.6, 48±2.1 and 75.6±4.4 ml/min/100 g in Acute, Sed and Tr groups respectively ($p<0.01$)], with Phent and BIPP increased with sympathetic inhibition (cf., calf m. figure). However, Phent + BIBP did not eliminate the training increase in collateral conductance. Thus, the training-induced BF_{coll} increase depends upon structural enlargement of the collateral circuit vessels.



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11.7

VASCULAR RESPONSE TO ACIDOSIS DURING DYNAMIC HANDGRIP EXERCISE

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Metabolic acidosis may alter blood flow at rest, although its effect on exercising muscle blood flow (MBF) is unclear. The purpose of this study was to determine if a prior metabolic acidosis alters MBF during moderate and heavy handgrip exercise. Seven males performed hand-grip exercise corresponding to 5% (moderate) and 10% (heavy) of maximal forearm strength during control (CON) and acidosis (acetazolamide 500 mg/d 3 d; AC) conditions. Brachial artery diameters and velocities (MBV) were measured continuously during exercise using Doppler ultrasound. No difference in MBF or arterial diameters were detected between CON and AC conditions at rest or during moderate intensity exercise. No significant difference was observed for MBF between CON (421 ± 177 ml/min) and AC (375 ± 71 ml/min) during heavy intensity exercise. However, heavy intensity exercise resulted in an increase in arterial diameter compared to rest for CON (rest 4.87 ± 0.55 mm vs. exercise 5.27 ± 0.60 mm; $p<0.05$) but, no difference in arterial diameter was observed for AC (rest 5.14 ± 0.75 mm vs. exercise 5.19 ± 0.54 mm; $p>0.05$). When expressed as a percent change from rest to heavy intensity exercise, the increase in diameter was greater ($p<0.05$) during CON (8.2 ± 4.1%) compared to AC (1.3 ± 4.2%). These findings suggest that prior metabolic acidosis may alter vascular tone at rest but that the tight coupling between MBF and metabolic requirements persists during exercise.

11.8

MOTOR UNIT DISTRIBUTION AFFECTS HOW RAPID ONSET OF VASODILATION SPREADS IN RESISTANCE NETWORKS

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Brief tetanic contraction of skeletal muscle initiates rapid onset (< 1s) of vasodilation (ROV) of arterioles that ascends into feed arteries (FA). Whereas muscles supplied by multiple FA contain anastomotic arterioles between respective resistance networks, signal transmission between these networks is poorly defined. Superior and inferior regions of the gluteus maximus muscle (GM) are supplied and controlled by respective gluteal FA and motor nerves. We tested the hypothesis that contracting one region of GM causes ROV that spreads into the adjacent (quiescent) region along arteriolar anastomoses. In anesthetized male C57BL/6 mice (3 mo, 25 g), the left GM was exposed for intravital microscopy and irrigated with physiological saline (36 °C, pH 7.4). Stimulating the inferior nerve (100Hz, 500 ms) produced brief tetanic contraction of inferior GM and initiated ROV in arterioles (diameter: rest, 24±1 μm, response, 38±5 μm) of the active muscle region that ascended into supplying FA (rest, 43±7 μm, response, 50±2 μm) but not along arteriolar anastomoses into the quiescent muscle region (rest, 16±1 μm) that dilated (to 46±3 μm) with 100 μM sodium nitroprusside. We conclude that regional motor unit activation produces ROV that spreads into vessels supplying active but not inactive muscle fibers. Thus, vasomotor responses initiated by motor unit recruitment are coordinated to direct blood flow to active regions of individual skeletal muscles. (Support: NIH HL086483).

11.9

RESPONSE OF PROSTAGLANDINS AND NUTRITIVE BLOOD FLOW TO 8 WEEKS OF EXERCISE TRAINING IN AGED HUMAN SKELETAL MUSCLE

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The purpose of this study was to determine if prostaglandins regulate alterations in muscle nutritive blood flow response to long-term exercise training in aged individuals. Local thigh muscle nutritive flow and 6-keto-prostaglandin F1α (PGF1α) were monitored using microdialysis. Dialysate samples were collected continuously during acute exercise before and after 8 weeks of exercise training from 13 healthy older participants (7 aged men (AM), and 6 aged women (AW)). The exercise training regimen consisted of 8 weeks of training for 1hr/day at 65-70% VO_2peak. PGF1α content was higher during exercise after, compared to before, training in both AM and AW (AM:33.2 ± 1.5 vs. 37.3 ± 0.8 pg/ml; AW: 30.2 ± 0.5 vs. 37.5 ± 0.6 pg/ml; $P<0.05$). However, PGF1α content did not differ between the groups. Nutritive blood flow during exercise was not changed in response to exercise training in either group. In conclusion, our data demonstrate that PGF1α response to acute exercise increases with long-term training in AM and AW, and suggest changes in exercise-induced PGF1α with training may not result in training-induced alterations in muscle nutritive blood flow response to acute exercise. NIH AG-19209 (Hickner); MD Choi supported by EAS.

11.10

LIMB BLOOD FLOW AND MICROVASCULAR EXCHANGE RESPONSE TO SEVEN DAYS OF EXERCISE TRAINING IN YOUNG AND AGED MEN

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Limb blood flow and local microvascular exchange have been reported to be lower in aged than young males; however, the effects of short-term exercise training on concerted changes in limb blood flow and microvascular exchange in these groups have not been determined. Purpose: To determine the effects of seven days of cycle ergometry training on limb blood flow and microvascular exchange. Methods: Leg limb blood flow was measured with plethysmography at rest and local muscle microvascular exchange was measured in the vastus lateralis at rest and during dynamic cycling exercise with microdialysis before and after 7 days of exercise training in healthy young males (25.5 ± 1.5 yr, YM) and healthy aged males (64.3± 2.3 yr, AM). The exercise training consisted of 7 consecutive days of cycle ergometry training for 1hr/day at 65-70% VO_2peak. Results: Two-way repeated measures ANOVA on resting limb blood flow revealed a main effect for time, in that resting limb blood flow was increased with training. Microvascular exchange at rest and at 65% VO_2peak was increased (lower ethanol outflow/inflow ratio) with training in YM but not in AM. Conclusion: Our data indicate that seven days of exercise training increases limb blood flow in young and aged males, but may increase muscle microvascular exchange in young males to a greater extent than in aged males. NIH AG-19209 (Hickner); MD Choi supported by EAS.

12.0: MUSCLE AS AN ENDOCRINE ORGAN: INTERTISSUE INFLUENCES

12.2

MUSCLE CYTOKINES: IL-6 AND OTHER IL-6-LIKE FAMILY MEMBERS

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The concentration of plasma interleukin-6 (IL-6) increases during physical exercise, but until recently the cellular origin of this increase was unknown. Recent work has identified skeletal muscle as the major source of exercise-induced IL-6 and the term "myokine" was thereby coined to refer to factors released from muscle. Myokines may represent the link from working muscle to other organs such as the adipose tissue and the liver, and may also serve an autocrine/paracrine function. Indeed, IL-6 exerts many diverse metabolic functions such as activation of skeletal muscle glucose transport and fatty acid oxidation, increasing hepatic glucose output and stimulation of adipose tissue lipolysis. The understanding of IL-6 as an

endocrine regulator of metabolism has prompted the study of IL-6 related family members in the context of energy metabolism and anti-obesity therapies. Ciliary neurotrophic factor (CNTF) is a 22 kDa cytokine that shares signaling homology with IL-6. Although best known as a neuro-protective factor we show that CNTF signals through the CNTF-IL6R-gp130β receptor complex to increase fatty acid oxidation and reduce insulin resistance in skeletal muscle by activating AMP-activated protein kinase. We also show that CNTF re-programs adipose tissue to promote mitochondrial biogenesis, enhancing oxidative capacity and reducing lipogenic capacity, thereby resulting in loss of adipose mass. Thus, the discovery that contracting muscle is a cytokine-producing organ has created a new paradigm: skeletal muscle as an endocrine organ. Since these pioneering studies, several other myokines have been identified and include IL-8, IL-15 and brain-derived neurotrophic factor (BDNF).The discovery of new myokines and their receptors could serve as targets in the treatment of metabolic disorders and other diseases.

12.4

INTERLEUKIN-6-AMPK INTERACTION IN SKELETAL MUSCLE

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Previous studies have established that AMPK is activated in multiple tissues in response to exercise. One possible mediator of this effect is the sympathetic nervous system. Another is IL-6, which is synthesized and released by skeletal muscle during exercise. In keeping with such a role for IL-6, it has been shown to activate AMPK in muscle and adipose tissue. In addition, the increases in AMPK in these tissues caused by exercise are substantially diminished in IL-6 KO mice. Despite this, the mechanism by which IL-6 activates AMPK is not clear. We report here that IL-6-induced AMPK activation in incubated rat extensor digitorum longus muscle is associated with a transient decrease in energy state (3 fold increase in AMP:ATP ratio) and that both changes are inhibited by propranolol, suggesting IL-6 increases β-adrenergic signaling. In keeping with this possibility, IL-6 concurrently increased the concentration of cAMP in the EDL, an effect inhibited by both propranolol and the adenyl cyclase inhibitor, 2'5' dideoxadenosine. IL-6 also increased glycogen breakdown and lipolysis in this muscle and caused a sustained increase in the abundance of UCP3 and PGC1α. These results suggest that IL-6, at concentrations potentially exposed to the muscle cell during exercise, increases the concentration of cAMP, and secondarily, the AMP:ATP ratio, AMPK activity and the abundance of proteins that enhance mitochondrial function. They also suggest that by virtue of these effects on substrate availability and catabolism, IL-6 helps the muscle cell to maintain its energy state during physical activity. Kelly M and Ruderman NB et al. IL-6 regulation of AMPK: Potential Role in the systemic response to exercise and prevention of the metabolic syndrome. Diabetes. 2006 Dec;55 Suppl 2:S48-54.

12.5

SKELETAL MUSCLE AS AN ENDOCRINE ORGAN: INTERTISSUE INFLUENCES

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Metabolic flexibility. The ability of skeletal muscle to respond to a variety of conditions, termed metabolic flexibility, while not entirely a new concept, may have important implications for the pathophysiology of obesity and type 2 diabetes mellitus (T2DM). Normal healthy muscle increases its reliance on glucose in response to insulin after a meal. The relative inability to respond to insulin, i.e. insulin resistance, is a hallmark characteristic of T2DM. In addition, both obesity and T2DM have been associated with an impaired capacity for fatty acid oxidation. Diet-induced weight loss and exercise can each improve insulin sensitivity in obesity and T2DM. However, the distinct effects of weight loss and exercise on fatty acid metabolism in the setting of obesity and T2DM have not been clearly elucidated. Clinical investigations into the effects of these lifestyle modifications provide important evidence concerning whether these components of metabolic inflexibility are acquired or genetic. Moreover, examination of underlying mechanisms of metabolic flexibility within skeletal muscle may provide further insight into the role of muscle in pathophysiology of obesity and T2DM as well as likely therapeutic targets for these and related conditions.

13.0: STEM CELLS AND NUCLEAR DOMAINS IN SKELETAL AND CARDIAC MUSCLE

13.2

SKELETAL MUSCLE STEM CELLS: WHERE THEY COME FROM AND WHAT THEY DO

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We aim at characterizing the properties of canonical and noncanonical sources of myogenic cells needed to support maintenance and regeneration of adult skeletal muscles. Specifically, we study satellite cells, the main source for new myoblasts, and microvasculature-associated cells, a potential source for myofiber nuclei. Resident satellite cells were shown to provide differentiated progeny and to self-renew and are thus considered stem cells. How the satellite cell pool is replenished, and whether all satellite cells can self-renew is yet unknown. Using mice that express GFP driven by regulatory elements of the nestin gene, we identified GFP expression in all satellite cells of all muscle groups examined. GFP expression declined in proliferating satellite cells, but was reacquired by Pax7+, nonproliferating, mononuclear progeny in cultures containing dense myotube networks. FACS-sorted reappearing GFP+ cells gave rise to myoblasts that proliferated, differentiated and produced new GFP+ cells. These data imply that the dynamics of nestin-GFP expression reflects the dynamics of satellite cell self-renewal. We now investigate the role of parent myofibers in maintaining the satellite cell pool using nestin-GFP mice. We also explore the effect of exercise on the abundance and performance of satellite cells in aging. Additionally, we have recently pointed to vascular smooth muscle/pericytes as a noncanonical source of myofiber nuclei, which undergo myogenic reprogramming within host myofibers. Exploring this phenomenon is of interest both in muscle hypertrophy and atrophy where satellite cell contribution is unresolved and as an autologous source for cell-based therapy in cases of severe muscle wasting. (NIH and USA-IL BSF). **References:** Day K, Shefer G, Richardson JB, Enikolopov G, Yablonka-Reuveni Z. (2007) Nestin-GFP reporter expression defines the quiescent state of skeletal muscle satellite cells. Dev. Biol. 304: 246-259. Kirillova I, Gussoni E, Goldhamer D, Yablonka-Reuveni z. (2007) Myogenic reprogramming of retina-derived cells following their spontaneous fusion with myotubes. Dev Biol. 311: 449-463. Yablonka-Reuveni z. Day K, Vine A, Shefer G. (2008) Defining the transcriptional signature of skeletal muscle stem cells. J Anim Sci. 86 (14 suppl): E207-E216.

13.3

EXTRACELLULAR REGULATION OF SATELLITE CELL ACTIVATION

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The resident myogenic stem cells in skeletal muscle, satellite cells, remain in a non-proliferative quiescent state in uninjured adult muscle. In the quiescent state they remain refractory to many factors that modulate proliferation and differentiation of activated satellite cells. Experiments conducted in vivo and in vitro identified hepatocyte growth factor (HGF) and nitric oxide (NO) as agents that trigger the activation of quiescent satellite cells and the dramatic transcriptional changes that are encompassed in the "activation process". Satellite cells rapidly hypertrophy as expression of a variety of proteins is initiated leading to up-regulation of metabolic pathways, entry into the cell cycle, cell migration, differentiation and fusion. The pre-transcriptional events that trigger these intracellular cascades are initiated by changes in the extracellular environment of the muscle fiber and satellite cell. Muscle injury resulting from mechanical perturbation is the most common physiological activator of satellite cells. HGF resides in skeletal muscle in association with heparan sulfate proteoglycans and as such does not bind to the c-met receptor on satellite cells until it is released in response to injury. Gaps remain in our understanding of the pathway from mechanical insult to HGF release from its tethering in the ECM, but steps in the pathway are thought to include calcium ion influx into the damaged cell, Ca-calmodulin activation of NO synthase, activation of matrix metalloproteinases and cleavage of a HGF-proteoglycan complex that subsequently binds the c-met signaling receptor. (Muscular Dystrophy Association 3685; USDA-NRI Grant number 2005-35206-1525).

13.5

DELIVERY OF PROIGF-1: EFFECT ON MYOCYTES AND STEM CELLS FOLLOWING MYOCARDIAL INFARCTION

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Insulin like-growth factor-I (IGF-1) is synthesized as a pro-hormone from different isoforms that arise via alternative splicing. These isoforms differ in their E-domain regions and their expression dynamics in response to tissue injury. There is increased expression of the minor isoform (IGF-IEb), also known as mechano-growth factor (MGF), during the acute phase following a myocardial infarction (MI). Therefore, we were interested in determining whether the unique E-domain of MGF has distinct biological function. Systemic delivery of a stabilized synthetic peptide corresponding to the E-domain of MGF administered during an MI demonstrated anti-apoptotic actions on cardiac myocytes, prevention of cardiac hypertrophy and a significant improvement in contractile function. Immunohistochemical analysis revealed numerous small troponin I (TnI) positive cells that co-express both Nkx2.5 and islet-1 in the viable myocardium of 2-week E-domain treated mice. Analysis of the resident stem cell population within the hearts of E-domain treated mice at earlier time points, indicated an increase in the number of c-Kit+ and Sca-1+ cells suggesting that these cells may contribute to the appearance of the small TnI positive cells in the E-domain treated hearts. These data support that administration of the E-domain derived from the pro-hormone form produced during injury maybe used to facilitate the actions of IGF-I produced by the tissue to improve cardiac function and mobilize resident stem cell populations. REFENCES: Mills P, Lafrenière JF, Benabdallah BF, El Fahime el M, Tremblay JP. A new pro-migratory activity on human myogenic precursor cells for a synthetic peptide within the E domain of the mechano growth factor. Exp Cell Res. 313:527-37, 2007. The MGF E-domain peptide enhances migration myogenic precursor cells derived from skeletal muscle.

14.0: SOMATIC AND SYMPATHETIC NEURAL CONTROL DURING EXERCISE

14.2

CONTROL OF MOTOR UNIT ACTIVITY DURING VOLUNTARY CONTRACTIONS

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The force exerted during a contraction depends on the number of motor units recruited and the average rates at which they discharge action potentials. The functional consequences of motor unit activity depend on how the activity is distributed across the motor unit pool and how this changes with time, as demonstrated by the changes in steadiness with advancing age and the adjustments in motor unit activity during fatiguing contractions. First, the force exerted during a steady contraction is never constant but varies about an average value. The variability in force is strongly related to the discharge variability of the active motor units. Because the variability in motor unit discharge during brief isometric contractions is similar for young and old adults, the reduced steadiness that can be observed in old adults during longer contractions is caused by a difference in synaptic input received by the motor neurons. Second, the capacity to sustain a submaximal force involves a progressive increase in the net excitatory drive to the motor neuron pool, but this does not attenuate the decrease in discharge rate of motor units that were active from the onset of the contraction. Consequently, the contribution of each motor unit to the muscle force depends on the difference between its recruitment threshold and the magnitude of the required force, and the amount of synaptic input required to recruit previously inactive units. These studies demonstrate that task characteristics influence the synaptic input delivered to the motor neurons and thereby modulate motor unit activity. Supported by NIA award AG009000.

14.3

NEW INSIGHTS INTO ARTERIAL BAROREFLEX CONTROL OF SYMPATHETIC NERVE ACTIVITY DURING DYNAMIC EXERCISE IN HUMANS

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Activation of the sympathetic nervous system plays a critical role in mediating the cardiovascular adjustments necessary for performing and sustaining exercise. The vital role of sympathetic nerve activity (SNA) for vascular regulation and arterial blood pressure (BP) control during exercise is highlighted by the dramatic fall in BP with physical activity in patients whom lack a functional sympathetic nervous system. However, despite its clear importance, there is little direct information regarding the regulation of sympathetic outflow during dynamic exercise in humans. Recent studies in our laboratory and by others have demonstrated a progressive and dynamic resetting in the arterial baroreflex (ABR) control of muscle SNA (MSNA) from low to moderate to high intensity dynamic exercise. Interestingly, along with this time and exercise

intensity dependent resetting of the ABR, baroreflex-MSNA sensitivity appears well maintained during low and moderate intensity exercise with increased sensitivity during higher exercise intensities. These changes in ABR control of MSNA appear to manifest from central (i.e., central command) and peripheral (i.e., exercise pressor reflex) neural influences that allow for the continued regulation of SNA and vascular conductance from rest to high intensity dynamic exercise and thus, ultimately preserve the control of BP during exercise.

14.4

SKELETAL MUSCLE REFLEXES AND THE CARDIOVASCULAR RESPONSES TO EXERCISE

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The skeletal muscle exercise pressor reflex (EPR) plays an integral role in regulating the cardiovascular response to physical activity. The reflex is activated during contraction by stimulation of skeletal muscle receptors responsive to either mechanical distortion or the metabolic by-products of muscular work. Stimulation of these receptors generates somatosensory signals that are transmitted to the central nervous system via thinly myelinated Group III (predominately mechanically-sensitive) and unmyelinated Group IV (predominately metabolically-sensitive) skeletal muscle afferent fibers. Activation of these fibers during exercise induces increases in heart rate and blood pressure primarily by elevating sympathetic nerve activity. Recently, it has been suggested that the EPR contributes importantly to the abnormally exaggerated cardiovascular response to exercise in heart failure and hypertensive patients. In heart failure, EPR overactivity appears to be predominately driven by the mechanically-sensitive component of the reflex, whereas, the sensitivity of the metabolically-sensitive component may be reduced. In contrast, evidence suggests exaggerations EPR function in hypertension are mediated by the overactivity of both the mechanically and metabolically-sensitive components of the reflex. Continued research to determine the pathophysiology of EPR dysfunction in both heart failure and hypertension may lead to the development of novel therapeutic strategies targeted at improving cardiovascular hemodynamics during exercise in these patient populations. Supported by HL088422.

14.5

INTERACTION OF AGE AND SEX IN SYMPATHETIC CONTROL OF MUSCLE BLOOD FLOW

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The sympathetic nervous system plays a major role in the regulation of blood flow and its distribution during exercise, but little is known about the impact of aging on vascular responses to sympathetic stimulation in active muscles. Dinenno et al (2005) reported age-related declines in metabolic inhibition of sympathetic stimulation in exercising forearms of men. Similarly, Koch et al (2003) reported an age-associated increase in responsiveness to a cold pressor test (CPT) during cycling exercise at 60% VO_{2peak}. By contrast, our most recent data suggests there is less vasoconstriction in older vs. younger men (O: 5±10%, Y: 14±10%, P=0.045) in response to sympathetic stimulation by ischemic handgrip (IHG) during 20 watt single-leg knee extension exercise. Interstitial epinephrine (quadriceps microdialysis in 5 younger, 4 older men) tended to decrease when IHG was superimposed on leg exercise in younger men, but increase in older men (P=0.07). Pascualy et al. (1999) found that the increase in norepinephrine but not epinephrine was greater in older men than younger men in response to CPT. Collectively, these data suggest that the balance between α and β_2-mediated responses at the smooth muscle could mediate vascular responsiveness to sympathetic stimulation. Also, the mode of exercise may influence interpretation of the influence of age on effective metabolic inhibition of sympathoexcitation in men. (NIH R01 AG-018246, T32 AG-00048,M01 RR-10732).

15.0: COMPARATIVE EXERCISE PHYSIOLOGY: LINKING ANIMAL LOCOMOTION TO HUMAN PERFORMANCE

15.2

METABOLIC STRATEGIES FOR SUSTAINED ENDURANCE EXERCISE: LESSONS FROM THE IDITAROD

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Racing sled dogs are the premier ultraendurance competitors, with events of up to 1100 miles completed in 9 days or less. Sled dogs have enormous aerobic capacity, with untrained dogs averaging 175 ml/kg/min VO2max. VO2max in fully-conditioned dogs is unknown, but may approach 300 ml/kg/min. Despite their high aerobic capacity, muscle fiber type distribution is typical of untrained humans (40% Type I, 60% Type II fibers). Sled dogs (25 kg) have been shown to burn up to 12,000 kcal/day on multiple sequential days during exercise, and do so by consuming diets delivering DE of up to 70% fat. This diet will reliably produce ketosis during initial stages of exercise, but preliminary data suggests that this is a desirable trait intended to efficiently support exercise. The most striking feature of sled dogs is their ability to rapidly adapt to sustained strenuous exercise in 24 – 48 hr. Conditioned sled dogs will display most of the metabolic alterations seen in human endurance athletes during the first day of exercise, including intramuscular substrate depletion, lipolytic hormone profiles, markers of cellular injury, and oxidative stress. However, with subsequent consecutive days of exercise at the same intensity, these changes are reversed so that within 4 days, the metabolic profile of the dogs has returned to resting baseline despite the continued performance of sustained strenuous exercise. The mechanism of this rapid adaptation is unknown at this time, but may involve regulation of sarcolemmal transporters and changes in mitochondrial efficiency. Funded through DARPA NBCH1030016, DARPA-FY07-0018.

15.3

SPECIALIZATIONS OF MUSCLE SERVING HIGH PERFORMANCE MOTOR FUNCTIONS IN HORSES

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Horses are elite athletes, trained to achieve speed and performance but highlighted because of recent high-profile breakdowns in races. Evaluation of motor function for such extreme animal athletes can offer insight into failure mechanisms and limiting factors for other forms including human athletes. Attention most often focuses on appendicular anatomy and biomechanics, however, adaptation of horses to athletic events also is related to cardiovascular and respiratory specializations that facilitate sustained high speed locomotion. Recent comparative work has identified common themes in tendon strain and breakdown, muscle-tendon elastic storage mechanisms, and properties of the airway related to maximal physiologic performance. Clinical research focused on maintaining patent airways or sound appendicular conformation also extends to areas such as human sleep disorders or biomechanics and exercise-related injury. We review translational aspects of equine programs towards human applications and note the unique perspectives gained from the study of equine disease and training protocols. REFERENCES: Butcher, MT, Hermanson, JW, Ducharme, NG, & Bertram, JEA (2007) Superficial digital flexor tendon lesions in racehorses: a connective tissue symptom of a muscle fatigue problem. Equine Vet J 39,540-545. Pfau, T, Witte, TH, Wilson, AM (2006) Centre of mass movement and mechanical energy fluctuations during gallop locomotion in the Thoroughbred racehorse. J Exp Biol 209, 3742-57.

15.4

COMPARATIVE EXERCISE PHYSIOLOGY AND NEUROBIOLOGY OF MICE BRED FOR HIGH LOCOMOTOR ACTIVITY: LESSONS FOR HUMAN PERFORMANCE

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The evolution of behavior may entail changes in both motivation and ability. For example, an evolutionary transition from sit-and-wait to active foraging might require an increase in the "desire" to engage in locomotor activity, or perhaps the "reward" received from activity, and an enhanced ability for sustained, aerobically supported exercise. As one test of this broad hypothesis about behavioral evolution, which has implications for human athletic performance, my laboratory has performed long-term selective breeding for high voluntary wheel running from a base population of outbred Hsd:ICR laboratory house mice. After 50 generations, comparisons with four non-selected control lines indicate that the four replicate selected lines exhibit differences in the neurobiological underpinnings of wheel running as well as morphological and physiological differences that appear to represent adaptations to enhance endurance performance, such as elevated maximal oxygen consumption and larger femoral heads. Preliminary studies indicate a reduced susceptibility to the adverse effects of a high-fat diet. Comparisons of the four selected lines provide evidence of "multiple solutions" to the adaptive problem of how to evolve a highly active animal. In addition, we have observed some evolutionary changes that may be maladaptive in general but tolerable in the context of the selection regime. Our results demonstrate that replicated selection experiments are a powerful way to elucidate the genetics and evolution of complex traits. (NSF IOB-0543429). Middleton, K. M., S. A. Kelly, and T. Garland, Jr. 2008. Selective breeding as a tool to probe skeletal response to high voluntary locomotor activity in mice. Integr Comp Biol In press. Rhodes, J. S., S. C. Gammie, and T. Garland, Jr. 2005. Neurobiology of mice selected for high voluntary wheel-running activity. Integr Comp Biol 45:438-455.

15.5

AERIAL REFUELING IN NECTARIVOROUS FLYING VERTEBRATES: MECHANISMS AND CONVERGENT EVOLUTION

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Hovering flight and nectarivorous diet have resulted in the convergence of physiological and biochemical traits in hummingbirds and nectar bats as they evolved to become small and to derive most of their dietary calories by hovering to feed on floral nectar. When hovering, these animals sustain some of the highest known mass-specific rates of aerobic metabolism among vertebrates. After their overnight or daytime fast, hummingbirds (Selasphorus rufus) and nectar bats (Glossophaga soricina) initially forage using fatty acid oxidation (RQ ≈ 0.7) as their energy source. Repeated feeding on sucrose solutions results in rapid increases in RQ values until RQ ≈ 1.0, indicating carbohydrate oxidation. High V_{max} values for hexokinase and high biochemical capacities for glucose oxidation in the flight muscles of both hummingbirds and nectar bats lead to the hypothesis that dietary sugar directly fuels energy metabolism. Recent work combining flow-through respirometry with the use of stable carbon isotope techniques reveals that recently-ingested sugar fuels about 95% of flight muscle metabolism in hummingbirds and about 80% in nectar bats. In contrast, humans are able to support only 25-30%, at most, of exercise metabolism with recently-ingested sugar.

16.0: EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE

16.1

EXTRACELLULAR MATRIX AND BIOMECHANICAL RESPONSE OF RAT TENDON TO MECHANICAL LOAD EXERCISE AND NANDROLONE DECANOATE

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Anabolic-androgenic steroids (AAS) impairs tissue remodeling by down regulating matrix metallopeptidase (MMP) activity in tendons. The MMP activity is influence by angiotensin I-converting enzyme (ACE). This study evaluated the biomechanical properties of the superficial flexor tendon (SFT) in AAS-treated rats associated with jumping. MMP-2 and ACE activities were determined to evaluate the tendon remodeling. Forty Wistar rats were used: Sedentary (S); trained (T); AAS-treated (5mg/Kg, twice a week) sedentary rats (AAS); and AAS-treated and trained (AAT). Trained groups carried out jumps in water at 32°C: 4 series of 10 jumps each, a 30-second interval between the series, for 7 weeks, with 50-80% overload of the animal weight. The SFT was submitted to a gradual increase in load. Analysis of MMP-2 activity was done in proximal, intermediate and distal region of SFT extracts by zymography. ACE activity was

determined by a substrate fluorescent detection in tendon samples. In the biomechanical test of SFT, which exercise was associated with AAS, the maximum displacement and maximum load were lower indicating an impaired ability of AAST group to support load. Training increased MMP-2 in all regions of SFT but this effect was abolished by AAS. Training, AAS or the association of both resulted in lower ACE activity. Training increases tissue turnover, which is inhibited by AAS and impairs the biomechanical properties of the SFT. Support: FAPESP, CNPq.

16.2

MUSCLE CONTRACTILE AND COLLAGEN PROTEINS EXERT DIFFERENT SENSITIVITY TO CONTRACTIONS AND NUTRIENTS

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Objective. We investigated the effect of exercise intensity on myofibrillar (myo) and muscle collagen (col) protein fractional synthesis rate (FSR) in the fed and fasted state. Methods. We applied a primed, continuous infusion of 1-^{13}C-leucine. After a resting period knee-extension resistance exercises were completed, one leg with a light (LE) and the other leg with a heavy (HE) exercise loading. Muscle biopsies were obtained bilaterally from vastus lateralis, so that FSR could be calculated as a resting, an early (½-3 hr), and a late (3-5½ hr) post exercise period. Results. At rest during fasting, myo- and colFSR was 0.077±0.007 and 0.086±0.014 %/h (P=.52), respectively. LE improved myoFSR transiently and immediately whereas HE revealed a delayed improvement (interaction: P=.03). The colFSR was elevated evenly by different loading (time-effect: P=.002) with no temporal difference (P=.77). Feeding elevated myoFSR ~2 fold (P=.001) at rest and myoFSR remained unchanged following LE and HE (P>.32). Oppositely, resting colFSR was not influenced by feeding (0.060±0.018 %/h, P=0.29) and exercise elevated (P=.02) colFSR evenly irrespective of loading (P=.68). Conclusion. MyoFSR is influenced by the exerted force produced during exercise and manipulated by the availability of nutrients. Whereas, the colFSR does not seem to sense the force production, but may respond just to the intramuscular shear during movement, and is not manipulated by nutrients.

16.3

MATRIX METALLOPROTEINASE-EXPRESSION IN HUMAN SKELETAL MUSCLE IN RESPONSE TO EXERCISE

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The current study explored the effect of exercise training on the expression and activity of Matrix metalloproteinases (MMPs) in human skeletal muscle, and if the skeletal muscle fibres contribute to exercise induced MMP-expression. Eleven subjects performed one-legged exercise four times per week for five weeks. The subjects exercised one leg for 45 min with restricted blood flow, followed by exercise with the other leg at the same absolute workload with unrestricted blood flow. mRNA and proteins were analyzed in biopsies from the vastus lateralis muscle obtained at rest before the training period, after 10 days and after five weeks of training as well as 2 hours after the first exercise bout. MMP-2, MMP-14 and tissue inhibitor of MMP (TIMP-1) increased robustly in the muscle tissue after 10 days of training regardless of exercise condition. MMP-2 mRNA was detectable in laser-dissected myofibers and myofiber MMP-2 expression increased with exercise training. In contrast, MMP-9 increased immediately after the first exercise bout and MMP-9 mRNA remained elevated throughout the training program. MMP-2 transcripts was 100-fold more prevalent than MMP-9 in this material. Still, the activity of MMP-9 after a single bout of exercise was comparable to that noted from MMP-2 after 10 days of exercise. Altogether, the present findings support MMPs to be involved in skeletal muscle remodelling in non-pathological conditions such as voluntary exercise in humans.

16.4

IMPACT OF GENDER AND CHRONIC RESISTANCE TRAINING ON HUMAN PATELLAR TENDON DRY MASS, COLLAGEN CONTENT, AND COLLAGEN CROSS-LINKING

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Collagen content and cross-linking are believed to be the major determinants of tendon structural integrity and function. These qualities of tendon are also affected by gender and chronic resistance training. Patellar tendon biopsies were taken from 3 groups: untrained men (M, n=8, 25±1y, 1RM: 53±3kg), untrained women (W, n=8, 23±2y, 1RM: 29±2kg), and resistance-trained (10±1y trained) men (RTM, n=8, 24±2y, 1RM: 71±6kg). Biopsies were analyzed for dry mass, collagen content, and collagen cross-linking (hydroxylysylpyridinoline, HP). The dry mass component of tendon was significantly lower in women than men (M: 376±8, W: 343±5µg dry mass/mg tendon wet wt, p<0.01), and was not influenced by chronic resistance training (RTM: 364±20µg dry mass/mg tendon wet wt, p>0.05). The lower tendon dry mass in women reduced (p=0.08) collagen content per tendon wet weight (M: 339±14, W: 306±11µg collagen/mg tendon wet wt). Collagen content of tendon dry mass was not influenced by gender (p>0.05) or resistance training (p>0.05) (M: 903±38, W: 892±29, RTM: 881±43µg collagen/mg tendon dry mass). Similarly, the cross-linking of collagen was not impacted by gender (p>0.05) or training (p>0.05) (M: 401±47, W: 418±35, RTM: 424±38mmol HP/mol collagen). Collagen and collagen cross-linking of the patellar tendon dry mass are remarkably consistent, whereas the absolute amount of collagen in the tendon may help explain gender-related differences in tendon function. NIH R01 AG20532.

16.5

ACETAMINOPHEN BUT NOT IBUPROFEN CONSUMPTION DURING 12-WEEKS OF KNEE EXTENSOR RESISTANCE TRAINING ALTERS *IN VIVO* PATELLAR TENDON PROPERTIES IN OLDER HUMANS

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Millions of individuals consume ibuprofen (IBU) or acetaminophen (ACET) daily. Several in vitro and animal studies suggest, however, that IBU and ACET can alter tendon metabolism and may influence adaptations to resistance training. We randomly assigned individuals to a placebo (n=11, 67±2 y), IBU (n=11, 64±2 y; 1200 mg•d^{-1}), or ACET group (n=10, 65±1 y; 4000 mg•d^{-1}) in a double-blind manner. Before and after 12-weeks of knee extensor resistance training, in vivo patellar tendon mechanical properties and MRI-determined cross-sectional area (CSA) and signal intensity were measured. Tendon CSA increased with training at the mid (7.2%) and distal (7.8%) tendon (p<0.05) in the ACET group only. Similar regional changes in signal intensity were also observed in the group that consumed ACET. When normalized to pre-training force levels, stiffness and stress were not altered in any group. However, tendon strain, increased (26%, p<0.05) and modulus decreased (-22%, p<0.05) with training in the ACET group. The increased strain in the ACET group, supported by the large decrease in modulus and change in signal intensity, strongly suggests that the material properties of the patellar tendon were altered. These changes in the tendon could influence physical function and have important implications for the use of ACET during exercise training. NIH R01 AG020532, APS Postdoctoral Initiative Award.

17.0: GENDER DIFFERENCES

17.1

RESTORATION OF MUSCLE STRENGTH FOLLOWING 3-WEEKS OF CAST IMMOBILIZATION IN SUPPRESSED IN WOMEN COMPARED TO MEN

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The purpose of this pilot study was to investigate sex-related differences in the loss and recovery of muscle strength following immobilization. Five healthy men and five healthy women underwent 3-wks of forearm immobilization, and four men and five women acted as controls. Wrist flexion muscle strength was assessed at baseline and weekly during the immobilization protocol and one-week after cast removal. Central activation was assessed before and after immobilization and after 1-wk of recovery to determine what percentage of the muscle could be activated voluntarily. Men and women lost strength at a similar rate during immobilization. However, after 1-week of recovery strength had returned to within 1% of baseline in the men, but remained ~ 30% below baseline in the women (p=0.03). Both sexes displayed reduced central activation after immobilization (p=0.02) but their respective decreases were similar (p=0.82). These findings suggest sex-dependent adaptations to and recovery from limb immobilization, with strength recovering slower in women. As such, sex-specific rehabilitation protocols may be warranted with women requiring additional or more intensive rehabilitation programs following periods of disuse. Future work is needed to determine the extent and mechanisms of these differences.

17.2

THE ANABOLIC RESPONSE TO EXERCISE TRAINING IS GREATER IN OLDER MEN THAN OLDER WOMEN

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We have recently shown that elderly men have a greater muscle anabolic response to feeding than elderly women (PLoS One 3:1875-83, 2008). The purpose of this study was to determine whether there are sex differences in the anabolic response of muscle to exercise training in the elderly. Rates of muscle protein synthesis (MPS) were measured during postabsorptive conditions and feeding using stable isotope-labeled tracer techniques in 5 men and 4 women, who were matched on age (65-80 y) and body-mass index, before and after a 3-month training program including strength, endurance, flexibility, and balance exercises. In men, exercise training increased the rate of MPS by ~50% (fasted: 0.044 ±0.008 vs 0.074 ± 0.018 %/h, fed: 0.078 ±0.010 vs 0.108 ± 0.008 %/h; effect of exercise: P=0.083); however, the anabolic response to feeding (i.e., the increase in the MPS rate from basal values which was significant at P<0.01) was not different before and after training (0.033 ± 0.009 vs 0.034 ± 0.017, respectively; P=0.98). In women, exercise training increased the rate of MPS by only ~15% (fasted: 0.062 ± 0.005 vs 0.073 ± 0.021 %/h; fed: 0.064 ± 0.016 vs 0.083 ± 0.010 %/h, respectively; effect of exercise: P=0.43) and the feeding induced-increase in MPS remained insignificant after exercise (0.002 ± 0.017 vs 0.010 ± 0.022 %/h, respectively; P=0.82). Our preliminary findings indicate that elderly men have a greater muscle anabolic response to exercise training compared with elderly women. This research was supported by grants from the US NIH.

17.3

SPRINT EXERCISE AND MUSCLE GROWTH IN A GENDER PERSPECTIVE

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Background: 4 wks of sprint training induced an increase in muscle cross-sectional area in women, but not in men. An explanation for the disparity may be that women have a greater activation of factors that contribute to muscle growth after sprint exercise. mTOR- pathway is characterized by a cascade of phosphorylations leading to increased protein translation stimulating skeletal muscle growth. Transcriptional regulation of IGF-1 and myostatin may also contribute to control of muscle growth. It was hypothesized that sprint exercise induces different activation profiles in men and women. Methods: 18 young physically active men and women performed 3 bouts of sprint exercise with 20 min rest in between. Muscle biopsies were taken in thigh muscle at rest and 2.5 hours after 3rd bout. Western blot and real time-PCR were applied. Results: phosphorylation of AKT (p<0.05), mTOR (p<0.05), p70S6 kinase (p<0.01) and S6 (p<0.001) increased in women only. p70S6 kinase increased in both genders (p<0.05), but less in men (gender*time; p<0.05). At mRNA level, myostatin decreased in women (p<0.05) but not in men (gender*time; p<0.1). Higher IGF-1 expression in women both pre and post exercise (gender; p<0.01) was observed. Conclusion: Down regulation of myostatin, generally higher IGF-1 expression and increased activation of AKT, mTOR, p70 and S6 in women may partly explain the increase in muscle fibre area by sprint training in women. Grant: Swedish National Centre for Research in Sports.

17.4

PEAK EXPIRATORY FLOW IN YOUNG ATHLETES

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Peak Expiratory Flow (PEF) has been used to test ventilatory capacity. Objective: To measure the resting PEF among young volleyball and basketball players in order to know the average values for this group of athletes and comparing with post exercise PEF measure. Methods: We studied 57 male volleyball players (15,7±1,4yrs, 73,7±12,3kg and 1,82± 0,7m); 60 female volleyball players (16±2,3yrs, 62,4±6,5kg and 1,69±0,6 m); 49 male basketball players (15,1±1,2 yrs, 74,8±12,9kg and 1,84±0,8m); 7 players had previous history of asthma (2 male e 5 female, all volleyball players), all were asymptomatic. PEF was measured with portable Peak Flow Meter (Boehringer Ingelheim, 50 a 700 L/minute), using technical recommendations. All athletes underwent to a ramp treadmill protocol. Statistical analyses were descriptive and independent t-test. Results: The medium PEF pre and post exercise values in the study group were: volleyball, male pre 447,4±70,4L/min x post 459,4±67,5L/min, female pre 382,3±52,8 L/min x post 381,3±55,7L/min; basketball, pre 486,4±73,4L/min x post 488,8±72,4 L/min. No statistically difference was observed between pre and post exercise. Only the asthmatic group had reduced PEF post exercise. Conclusions: There is no difference of PEF between pre and post exercise among healthy volleyball and basketball players. PEF are easy to measure and should be used for assessment of athletes' health status.

17.5

SEX DIFFERENCES IN EXERCISE TRAINING RESPONSES TO ACUTE HYPERGLYCEMIA AND ISOMETRIC HANDGRIP

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Previous work has demonstrated gender differences in sympathetic responses to isometric exercise, with women exhibiting lower sympathoexcitation. Acute hyperglycemia, a sympathetic stressor, has been associated with altered cardiovascular responses. Yet, the sympathoexcitatory responses to endurance training of obese men and women are unknown. Purpose: To determine the effect of aerobic exercise training on hemodynamic responses to isometric handgrip exercise during a fasted and hyperglycemic state in middle aged, obese (BMI = 36.5 kg/m^2) men and women. Methods: Hemodynamic measures at rest and during hand grip exercise were determined (blood pressure (BP), total peripheral resistance, systemic arterial compliance (SAC), cardiac output) before and after 4-mo of endurance exercise training (4d/wk). Handgrip exercise was performed for 3 min at 30% of maximal voluntary contraction in a fasted and acute hyperglycemic state. Results: Men (n=23) and women (n=34) had similar increases in VO_{2peak} with training. No sex by training interactions were observed in the fasted state, whereas men had greater increases versus women in the change from rest to handgrip exercise SBP (44 vs. 35 mmHg) and DBP (21 vs. 18 mmHg) and greater decreases in SAC (-0.38 vs. -0.32 mL/mmHg), ($p<0.05$) following endurance training, whereas women exhibited no changes. Conclusions: These data suggest endurance exercise training elicits differential cardiovascular responses to sympathoexcitation in men and women.

17.6

GENDER DIFFERENCES IN MUSCLE EFFICIENCY DURING SHORT-TERM EXERCISE

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Women have a higher contribution of fatty acid oxidation during exercise and greater resistance to muscular fatigue compared to men. Previous research also suggests that estrogen elicits glycogen-sparing effects. We sought to determine the influence of gender on muscle efficiency during short-term exercise. To determine this, we examined efficiency during 10-min light and 10-min heavy exercise using cycle ergometry in 33 women and 31 men (age=28±6 v 29±5 yrs, for women and men, respectively), (Ht=167±7 v 180±7 cm, $p<0.05$; Wt=64±10 v 82±10 kg, $p<0.05$; BMI=23±3 v 25±3, $p<0.05$; VO2peak=31±6 v 39±7 ml/kg/min, $p<0.05$, for women and men, respectively). We measured power output and VO2 between genders during light exercise (watts=65±17 v 98±21, $p<0.05$) (VO2=16.6±3 v 18.9±3ml/kg/min, $p<0.05$) and heavy exercise (Watts=129±36 v 195±43, $p<0.05$) (VO2=26.9±6 v 33.8±6ml/kg/min, $p<0.05$, for women and men). Both groups maintained similar percentages of their VO2peak for light exercise (VO2/VO2peak=54±8% v 53±8%) and for heavy exercise (VO2/VO2peak=88±15% v 92±14% for women and men respectively). Muscular efficiency was calculated by dividing the work performed by energy expended (light ex eff= 15.9±2 v 16±2,) (heavy ex eff=17.2±2 v 16.6±1.6, $p<0.05$ for women and men). Change in efficiency was then calculated (Δeff=18.3±4 v 17.4±3). These results suggest that muscle efficiency is slightly higher in women than in men, possibly due to differences in substrate utilization during exercise.

17.7

SEX BASED DIFFERENCES IN RESTING SKELETAL MUSCLE SUGGEST MEN AND WOMEN ARE TRANSCRIPTIONALLY "PRIMED" FOR KNOWN PHYSIOLOGICAL DIFFERENCES IN METABOLISM

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Women oxidize more fat as compared to men during endurance exercise and several groups have shown that the mRNA content of selected genes involved in fat oxidation are higher in women. We used a targeted approach to determine their potential role in explaining the observed sex differences in exercise substrate selection. Vastus lateralis biopsies were obtained from healthy men(N=12) and women(N=12). Global mRNA content was evaluated with gene arrays (Affymetrix, HG_U95A chip) and targeted mRNA content by RT-PCR, with protein content determined with Western blotting. Gene array analysis revealed 66 differentially expressed genes, including; metabolism, mitochondrial function, transport, protein biosynthesis, cell proliferation, signal transduction pathways, transcription and translation. We confirmed that the following were higher in women using RT-PCR: acyl-coenzyme A acyltransferase 2 (ACAA2), trifunctional protein â subunit (HADHB), catalase, lipoprotein lipase (LPL), and uncoupling protein-2 (UCP-2). At the protein level, we confirmed the trifunctional protein á subunit, yet did not find a sex difference in the protein content of HADHB, ACAA2, or catalase. In conclusion, the differences in the basal mRNA content of resting skeletal muscle suggest a transcriptional "priming" directionally supportive of known physiological differences in metabolism. Furthermore, trifunctional protein differences may be an important factor explaining some of the sex differences in metabolism.

17.8

GENDER DIFFERENCES IN MAXIMAL MOTOR UNIT FIRING RATES

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The purpose of this study was to examine differences in maximal motor unit firing rates (MUFRs) in the tibialis anterior muscle. Gender differences in the response of the maximal firing rates to isometric strength training were also examined. A total of 28 (14 male and 14 female) subjects participated in the study. On 2 occasions, separated by 2 weeks, subjects performed three isometric maximal voluntary isometric contractions (MVCs) of the dorsiflexors while motor unit activity was monitored with a needle electrode placed in the tibialis anterior. During the two weeks between sessions, half of the subjects participated in isometric strength training of the dorsiflexors 3 days/week. At baseline males had higher MVC force than females ($p<.01$), but there was no difference in maximal MUFR ($p=.16$). There was a significant increase in MVC force ($p=.02$) and maximal MUFR ($p=.03$) in response to training, but no interaction with gender for either MVC ($p=.27$) or MUFR ($p=.99$). Males demonstrated a 23% increase in MVC and a 15% increase in maximal MUFR in response to training, while females demonstrated a 21% increase in MVC and a 13% increase in maximal MUFR. The results of this study demonstrate that differences in maximal MUFR cannot explain gender differences in MVC force. Also, males and females show similar adaptations in force and MUFR in response to isometric strength training. This study was supported by a grant from the American College of Sports Medicine.

18.0: NEURAL CONTROL

18.1

MOTONEURON EXCITABILITY MODULATION DURING PASSIVE MUSCLE STRETCHING; COMPARING BETWEEN TWO ELECTROMYOGRAM METHODS

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Objectives: This study aimed to distinguish physiological attributions from experimental attributions (e.g. signal cancellation) that associated with depressions of H-reflex parameters regarding passive muscle stretching in previous studies, and to better understanding of stretching speeds – alpha motoneuron (αMN) excitability relationship. **Methods**: we used two surface EMG recording methods, monopolar (belly-to-tendon) and bipolar (belly-to-belly), to measure soleus muscle's H-wave and M-wave parameters (the peak-to-peak maximal amplitude and the slope of stimulus-response curve) during resting (relaxed muscle) and during maximal stretched muscle with passive stretching speeds of 2°, 5° and 10° sec^{-1}. **Results**: In bipolar recording method, αMN was inhibited in all passive stretching speeds of 2°, 5° and 10° sec^{-1}. However, in monopolar recording method, passive stretching speed of 2° sec^{-1} inhibited αMN, while passive stretching speed of 5° sec^{-1} excited αMN. 54~60% of maximal H-wave amplitude was lost in bipolar method when compared with monopolar method. **Conclusions**: Assessing the effect of passive stretching exercise on αMN excitability through detecting changes in H-Reflex parameters (maximal H-wave and H-wave curve slope) depended on: (a) speed of muscle stretching and (b) surface EMG recording method. For the later, monopolar recording method was preferred, one as it overcame signal cancellation (main potential problem in bipolar recording method).

18.2

EFFECT OF GENDER ON THE HEART RATE VARIABILITY RESPONSE TO SUBMAXIMAL EXERCISE IN DOGS WITH HEALED MYOCARDIAL INFARCTION

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Differences in cardiac autonomic regulation may contribute to the varying cardiovascular risk noted between males and females. These differences may become more obvious when the autonomic nervous system is activated during a physiological stress such as exercise or as the result of myocardial infarction. Therefore, a retrospective analysis of the heart rate and heart rate variability (0.24-1.04 Hz frequency component) responses to submaximal exercise was made in dogs with healed myocardial infarctions (female n=162, male n=83). Exercise elicited significant (ANOVA, $P<0.01$) and similar increases in heart rate in both female (pre-ex 128.6 ± 2.4; ex 210.5 ± 3.3 beats/min) and male (pre-ex 120.5 ± 3.6; ex 209.9 ± 4.4 beats/min) animals. Thus, there were no gender differences. Correspondingly, heart rate variability decreased significantly ($P<0.01$) and to a similar extent in both female (pre-ex 6.7 ± 0.2; ex 1.4 ± 0.2 ln ms^2) and male (pre-ex 6.6 ± 0.2; ex 1.8 ± 0.2 ln ms^2) animals. Once again, gender differences were not noted between the groups. In a similar manner, the heart rate and heart rate variability responses to exercise onset, as well as the heart rate recovery following the termination of exercise, did not differ between male and female dogs. Thus, these data demonstrate that submaximal exercise elicited similar cardiac autonomic responses in male and female dogs with healed myocardial infarctions. (supported by NIH grants, HL-68609 & HL-086700).

18.3

OXIDATIVE STRESS IN SKELETAL MUSCLE SENSITIZES MECHANORECEPTORS IN HEART FAILURE

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The enhanced skeletal muscle mechanoreflex (mediated via group III fibers) contributes to the exaggerated exercise pressor reflex in chronic heart failure (CHF). However, the mechanism responsible for sensitization of mechanoreceptors is not clear. Here, we proposed that oxidative stress sensitizes mechanoreceptors in skeletal muscle of animals with CHF. We recorded discharge from group III fibers in response to passive stretch (500 grams, 60 s) before and after hindlimb arterial infusion of the superoxide dismutase (SOD) inhibitor diethylthiocarbamate (DETC) or the SOD mimetic tempol in decerebrated rats. The data showed that the expression of SOD protein in triceps surae muscle was significantly decreased in CHF rats compared with

sham rats. Pretreatment with DETC significantly increased group III fiber discharge in response to stretch in sham rats (6.09 ± 0.80 vs. 3.03 ± 0.41 Hz, P<0.05, n=6), but not in CHF rats (5.30 ± 1.04 vs. 5.03 ± 1.36 Hz, P>0.05, n=6). Tempol attenuated the response of group III fibers to stretch in both sham (2.15 ± 0.35 vs. 2.98 ± 0.37 Hz, P<0.05, n=6) and CHF rats (3.04 ± 0.49 vs. 5.35 ± 0.83 Hz, P<0.05, n=6). The data indicate that oxidative stress sensitizes mechanoreceptors in CHF. Supported by NIH PO1 HL 62222.

18.4

EFFICACY OF HIGH-PASS FILTERING OF SURFACE ELECTROMYOGRAM FOR ASSESSING FORCE FLUCTUATIONS DURING STEADY CONTRACTION

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The purpose of the study was to examine the efficacy of high-pass filtering of surface electromyogram (EMG) for assessing force fluctuations during steady isometric contraction. Eleven healthy young adults (20-35 yrs) produced isometric dorsiflexion force at 20% of maximal force for 10 s. Surface EMG from the tibialis anterior muscle was processed in three ways: full-wave rectification (R-EMG), full-wave rectification followed by a low-pass filtering at 2 Hz (RL-EMG), and high-pass filtering at 300 Hz followed by full-wave rectification and then low-pass filtering at 2 Hz (HRL-EMG). There was no clear peak in cross-correlation function (CCF) between force and R-EMG in any subjects. A clear peak appeared in one subject for force and RL-EMG (0.37 for CCF peak) and in four subjects for force and HRL-EMG (0.53-0.69). These four subjects had greater standard deviation of force (0.40-0.50 % MVC) compared with other subjects (0.15-0.38 % MVC) who did not show a clear peak. There was a clear peak in CCF between first derivative of force (dF/dt) and all processed EMGs. In addition, CCF between dF/dt and HRL-EMG (0.13-0.40) was significantly greater ($P < 0.05$) compared with CCF between dF/dt and R-EMG (0.12-0.22). The results suggest that high-pass filtering of EMG helps in enhancing the elucidation of common characteristics between surface EMG and force fluctuations during steady contraction. Supported by Grant-in-Aid for Scientific Research in Japan (20700476).

18.5

GADOLINIUM-SENSITVE MECHANOGATED CHANNELS CONTRIBUTE TO THE STIMULATION OF GROUP III BUT NOT GROUP IV AFFERENTS DURING DYNAMIC EXERCISE

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The exercise pressor reflex, which arises from the contraction-induced stimulation of group III and IV afferents, is evoked by metabolic stimuli signaling a mismatch between blood/oxygen demand and supply in the working muscles. Nevertheless, mechanical stimuli also play a role in evoking the exercise pressor reflex. To determine this role, we examined the effect of gadolinium, which blocks mechanogated channels, on the responses of group III and IV afferents to low level dynamic exercise, evoked by stimulation of the mesencephalic locomotor region in decerebrate cats. Gadolinium (Gd3+) (10 mM; 1 ml) injected into the femoral artery significantly reduced the responses of group III afferents to dynamic exercise by 77% (n=7; p=0.046) but had no effect on the responses of group IV afferents (n=5) to exercise. Using microdialysis, we measured the interstitial ATP release (n=5) during low-level dynamic exercise before and after Gd3+ (10 mM; 1 ml) injected into the femoral artery. Gd3+ had no effect on the increases in interstitial ATP (65% before Gd3+ and 87% after Gd3+) evoked by dynamic exercise, suggesting that gadolinium inhibited the responses of group III afferents to exercise by blocking mechanogated channels and not by preventing ATP release. We conclude that gadolinium-sensitive mechanogated channels contribute to the stimulation of group III but not group IV afferents during dynamic exercise. Supported by NIH HLB Grant 30710.

18.6

ACID SENSING ION AND EPITHELIAL SODIUM CHANNELS DO NOT CONTRIBUTE TO THE MECHANORECEPTOR COMPONENT OF THE EXERCISE PRESSOR REFLEX

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Amiloride, injected into the popliteal artery, has been reported to attenuate the reflex pressor response to static contraction of the triceps surae muscles. Both mechanical and metabolic stimuli arising in contracting muscle evoke this effect, which has been named the exercise pressor reflex. Amiloride blocks both acid sensing ion channels (ASICs) as well as epithelial sodium channels (ENaC). We wanted to determine if ASICs/ENaCs on muscle mechanoreceptors play a role in evoking the exercise pressor reflex. We assessed this by measuring renal sympathetic nerve activity (RSNA) during the first 2-5 s of contraction. During this period of time, the sudden tension developed by contraction onset briskly discharges mechanoreceptors, whereas it has little effect on the discharge of metaboreceptors. Thus, we examined the effect of amiloride (0.5 µg/kg) injected into the popliteal artery on the pressor and renal sympathetic responses to static contraction of the triceps surae muscles in decerebrated cats. Amiloride attenuated the pressor response to contraction (Δ 32±5 before vs Δ 16±3 mmHg after; $P < 0.05$; n=15). Before amiloride, RSNA rose within 2 secs after contraction onset and stayed elevated throughout ($P < 0.05$ vs baseline). After amiloride, RSNA was still elevated at 2 and 5 secs but by 10 secs was attenuated ($P < 0.05$ vs before). Our findings lead us to conclude that ASICs and ENaCs play little role in evoking the mechanical component of the exercise pressor reflex. NIH grant AR 051503.

18.7

INFLUENCE OF BRAIN DOPAMINE ON THERMORREGULATION AND RUNNING PERFORMANCE IN RATS

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To assess the role of central dopaminergic systems on heat balance and running performance, 2.0 µL of dopamine solution [5 x 10^{-3} M] (DA, n=6) or 2.0 µL of SCH-23390 hydrochloride solution (D1-antagonist) [5 x 10^{-3}M] (SCH, n = 6) or 2.0 µL of eticlopride hydrochloride solution (D2-antagonist) [5 x 10^{-3}M] (Eti, n=6) or 2 µL of 0.15 M NaCl (SAL, n=6) was injected into lateral cerebral ventricle of male Wistar rats immediately before animals started exercise in a progressive protocol. The rats started running at 10 m.min^{-1}, 5% inclination, and treadmill speed was increased by 1 m.min^{-1} every 3 min until fatigue. Oxygen consumption (VO_2) and body temperature (Tb) were recorded during exercise. Body heating rate (BHR), heat storage (HS), workload (W) were calculated. DA treatment induced a 45% increase in W ($p<0.05$) showing a VO_2max 29% higher with a higher increase in Tb (0.75ºC) compared to saline treatment. DA treatment also induced a higher heat storage tolerance ($p<0.05$) despite an increased heat dissipation rate (~ 33% higher $p<0.05$). In contrast, SCH and Eti treatments markedly reduced running performance by 83% and 59% respectively ($p<0.05$) showing marked decrease in VO_2max (-79%, SCH; -45%, Eti, $p<0.05$) and a persistent post-exercise hyperthermia. Our data demonstrate that increased DA activity in central nervous system has an ergogenic effect and improves heat storage tolerance by activating central D1 and D2-dopaminergic receptors. Support by CNPq, FAPEMIG.

18.8

EFFECTS OF A SINGLE BOUT OF AEROBIC EXERCISE IN THE SYMPATHETIC NERVE ACTIVITY OF PRE-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS

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Introduction: The aerobic exercise has been studied in several populations and it seems to be effective reducing blood pressure and sympathetic nerve activity (SNA) but its effects in chronic kidney disease patients (CKD) are not fully understood. Purpose: The aim of this study was to evaluate the hemodynamic and neural responses after a single bout of aerobic exercise in CKD pre-dialysis subjects. Methods: 4 patients (54±3 years old) participated of two experimental sessions in a random order: exercise session (ES): 45 minutes of cycle ergometer at 50% do VO2 peak and a control session (CS) 45 minutes of rest (sited position). After the sessions, SNA (microneurography), mean blood pressures (MBP) (Dixtal), heart rate (HR) (ECG) and forearm blood flow (FBF) (occlusion plethysmography) were registered during 5 minutes. For data analysis, a t-student test was used with Newman-Keuls test. Values of $p<0,05$ were considered to be statistically significant. Results: The SNA in the ES was reduced compared to CS (26±6 vs 30±7 bursts/min, p=0,03). There was no statistically difference between ES and CS in FBF (3±1 vs. 2±1 ml.min-1.100ml-1, p=0,3); MBP (117±12 vs. 113±16 mmHg, p=0,5) and HR (71±10 vs. 63±11 bpm, p=0,1). Conclusions: A single bout of aerobic exercise reduced SNA in CKD patients. These are preliminary results, although it is expected that the aerobic exercise may reduce blood pressure and increase FBF of this subjects as observed in other populations. Funding source: FAPESP 07/51945-4.

18.9

BOTH CENTRAL COMMAND AND EXERCISE PRESSOR REFLEX ACTIVATE CARDIAC SYMPATHETIC NERVE ACTIVITY IN DECEREBRATE CATS

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Both static and dynamic exercise are known to increase cardiac pumping function as well as arterial blood pressure. Feedforward control by central command and feedback control by the exercise pressor reflex are thought to be neural mechanisms underlying these effects during exercise. To date, it remains unknown how each mechanism activates cardiac sympathetic nerve activity (CSNA) during exercise, especially at its onset. Thus, we examined the response of CSNA to stimulation of the mesencephalic locomotor region (MLR, i.e., central command) and to static muscle contraction of the triceps surae muscles or stretch of the calcaneal tendon in decerebrate cats. We found that MLR stimulation immediately increased CSNA, which was followed by a gradual increase in HR, mean arterial pressure, and ventral root activity in a stimulus intensity dependent manner. The latency of the increase in CSNA from the onset of MLR stimulation ranged from 97 to 178 ms. Both static contraction and tendon stretch also rapidly increased CSNA. Their latency from the development of tension in response to ventral root stimulation ranged from 98 to 155 ms. These findings suggest that both central command and muscle mechanoreflex play a pivotal role in controlling cardiac pumping functions via activation of cardiac sympathetic outflow at the onset of exercise.

18.10

EXERCISE NORMALIZES ENHANCED NEURONAL EXCITABILITY OF HYPOTHALAMIC PREAUTONOMIC NEURONS OF HYPERTENSIVE RATS

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Exercise training (ET) has been associated with a variety of beneficial cardiovascular adjustments in hypertensive individuals, including reduced sympathoexcitation, a common finding during hypertension. However, the precise mechanisms by which ET improves the central control of cardiovascular function in hypertensive individuals is still incompletely understood. In the present study, we obtained electrophysiological recordings from preautonomic neurons in the hypothalamic paraventricular nucleus (PVN) that innervate the nucleus of the solitarii tract (NTS). Recordings were preformed in hypothalamic slices obtained from normotensive (NT) and renovascular hypertensive (HT) rats, that underwent either a sedentary (SD) or a moderate exercise training (ET) protocol. Neuronal excitability was measured by generating input-output plots (i.e., number of evoked actions potentials as a function of depolarizing steps of increasing magnitudes). Our results indicate increased PVN-NTS neuronal excitability and action potential firing in HT-SD when compared to NT-SD rats (~40% increased maximal firing discharge, $P< 0.001$). This difference was normalized in HT-ET rats (HT-ET vs. HT-SD, $P< 0.001$; NT-SD vs. HT-ET $P> 0.3$). Our results demonstrate that ET efficiently reverted increased neuronal excitability of preautonomic PVN neurons of hypertensive rats, likely constituting an underlying mechanism by which ET improves cardiovascular control in this disease.

18.11

HEIGHTENED SYMPATHETIC NERVE ACTIVITY INCREASES FLUCTUATIONS IN MOTOR OUTPUT

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An autonomic innervation is supplied to intrafusal muscle fibers in cat hindlimb muscles (Barker and Saito 1981). The purpose of the study was to test if heightened muscle sympathetic nerve activity increases fluctuations in motor output of a hand muscle in humans. Muscle sympathetic

nerve activity was increased by applying lower body negative pressure (LBNP) while subjects performed low force isometric and anisometric contractions involving abduction of the index finger (5% of maximal force). The coefficient of variation of force during the isometric contraction was 4.1 ± 2.0% at baseline and increased significantly ($P < 0.05$) with the application of LBNP (5.2 ±2.6% at -10 mmHg, 5.1 ± 2.8% at -25 mmHg, and 6.1 ± 1.9% at -40 mmHg). The standard deviation of acceleration during the eccentric contraction increased significantly ($P < 0.05$) from 0.273 ± 0.120m/s^2 at baseline to 0.288 ± 0.111 m/s^2 at -10 mmHg, 0.300 ± 0.094 m/s^2 at -25 mmHg, and 0.385 ± 0.110 m/s^2 at -40 mmHg. There was no change in the standard deviation of acceleration during the concentric contraction. Discharge rate variability of motor units in the first dorsal interosseus muscle (n = 6) tended to increase from 18.5 ± 7.2% at baseline with an increase in LBNP, reaching 28.0 ± 14.8% at -40 mmHg during isometric contraction. The results indicate that heightened sympathetic nerve activity increases fluctuations in motor output during low force contractions probably due to increased muscle spindle sensitivity. [NIH (NINDS) NS052480].

18.12

THE EFFECT OF CONTRACTION MODE AND INTENSITY ON AGONIST/ANTAGONIST CO-ACTIVATION

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The objective of the present investigation was to examine the effect of contraction mode, intensity, and gender on agonist/antagonist muscle co-activation during isokinetic actions. Thirty healthy young adults performed isokinetic (45 deg/s) concentric and eccentric maximal-effort elbow flexor contractions (MVC), followed by nine sub-maximal contractions (10-90% MVC, 10% increments, random order) during two separate experimental sessions. Agonist/antagonist co-activation was quantified as the elbow extensor surface EMG during all flexor contractions, normalized to its' respective maximal level. The results demonstrated significant contraction intensity ($p<0.001$), gender ($p<0.001$) and contraction mode ($p<0.001$) main effects, indicating that co-activation: (1) increased significantly from 10-90% MVC (5.40% to 12.01%), (2) was significantly greater in women than men (12.06% vs 3.68%), and (3) was significantly greater during concentric than eccentric contractions (9.82% vs 5.92%). A significant gender by contraction intensity interaction demonstrated that women displayed greater increases in co-activation, as compared to the men, across 10-90% MVC. The major findings of the present investigation demonstrated that during constant velocity elbow flexor contractions of incremental intensities, extensor co-activation significantly increased more for women than men, and is related to the magnitude of the resulting absolute net flexor torque.

18.13

SPONTANEOUS PHYSICAL ACTIVITY TRIGGERS NEUROPLASTICITY EVENTS IN RAT SPINAL CORD

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Objectives: Physical activity can stimulates neuroplasticity events in spinal cord by changes in morphology, biochemistry and functionality. The aim of this work was identify neuroplasticity mediated by neurotrophic factors, neuromodulators and by growth associated protein 43 (GAP-43). Methods and Results: Male Wistar rats were kept according to Brazilian Committee of Animal Experimentation. The animals of trained group were submitted to physical activity in a running wheel (12 cm of ratio, Columbus, USA) for 5 weeks, 7 days/week in their active phase. In the rest phase they were maintained in cages without running wheel. The rats of sedentary group were maintained in cages without running wheel. The spinal cords were processed for in situ hybridization. The mRNA of GAP-43 of cervical anterior horn was more expressed in trained group. In posterior horn of lumbar intumescence, the mRNA of substance P was 150% higher in the trained group than in sedentary one. However, the analysis of mRNA signal of brain derived neurotrophic factor revealed a diminution in anterior horn of cervical and lumbar levels and in cervical lateral funiculus after exercise. Derived neurotrophic factor mRNA expression reduced in the trained group in lumbar lateral funiculus. Conclusion: The spontaneous physical activity promotes modifications in spinal cord tissue, triggering neuroplastic events. This approach can be used to promote central nervous system health, e.g. promoting protection and increasing the functionality. Supported: FAPESP, CNPq.

19.0: MUSCLE FUNCTION & ADAPTATION I

19.1

HYPERTROPHIC SIGNALING IN ISOLATED MATURE MUSCLE FIBERS INDUCED BY IGF-1 BUT NOT BY HIGH LINEAR STRAIN

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We investigated the separate and combined effects of high linear strain and insulin-like growth factor-1 (IGF-1) on muscle fiber cross-sectional area (CSA) and serial sarcomere number. Mature, single muscle fibers of Xenopus laevis were cultured at a sarcomere lenght of 2.3 µm ("slack") or at 12% over slack ("high strain") for 10 to 24 days in serum-free medium with or without human IGF-1 (n=5-7). Tetanic force and CSA of fibers cultured at slack without IGF-1 remained unchanged. Fibers cultured at high strain without IGF-1 reduced tetanic force by 1.4±0.2% per day, whereas fiber CSA was constant. In contrast, tetanic force of fibers cultured at slack with IGF-1 increased by 1.0±0.1% per day, whereas CSA increased by 33.4±3.8% after 16.6±0.6 days. CSA of high strained fibers increased with IGF-1 to 28.8±3.7% after 16.6±1.4 days. The IGF-1 induced increase in tetanic force at high stain (0.6±0.2% per day) was lower than at slack. For all conditions, number of sarcomeres in series and myonuclei were unchanged. IGF-1 increased actin mRNA, whereas high strain reduced it. IGF-1 mRNA was doubled by IGF-1, but not affected by high strain. p-Akt levels were independent of high strain and IGF-1. We conclude that high strain imposed on an isolated muscle fiber does not stimulate hypertrophy or increase the serial sarcomere number, whereas IGF-1 may stimulate hypertrophic signaling via increasing IGF-1 mRNA and induce hypertrophy by increasing actin mRNA.

19.2

THE ACUTE EFFECTS OF HEAVY RESISTANCE EXERCISE ON THE LOCAL INFLAMMATORY RESPONSE IN PHYSICALLY-ACTIVE, POST-MENOPAUSAL WOMEN IN THE ABSENCE OF HORMONE REPLACEMENT THERAPY

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This study examined the effects of a single bout of heavy resistance exercise on local markers of inflammation in physically-active, post-menopausal women not undergoing HRT. 24 women (54.54±3.89 yr, 159.67±5.22 cm, 72.43±15.58 kg) performed an exercise regimen consisting of 3 sets of 10 repetitions (80% 1RM) on the angled leg press, squat, and knee extension exercises. Blood samples and vastus lateralis biopsies were obtained prior to, and 3h post-exercise. Blood was also obtained 24 and 48h post-exercise. Whole blood was analyzed with a standard hematology analyzer and mRNA expression with RT-PCR. Blood and muscle data were analyzed using multivariate analysis of variance (MANOVA); muscle soreness data was analyzed using analysis of variance (ANOVA). Muscle soreness was significantly greater than baseline at 24 and 48h post-exercise, with no differences noted at 3h post while circulating neutrophils were significantly elevated at 3h post compared to all other time points. Significant time effects ($p<0.05$) were noted for skeletal muscle mRNA expression of TNF-α, IL-1β, IL-6, IL8, SOCS2, COX2, SAA1, SAA2, cfos, and Jun-B. Strong trends for significance were seen for IL12 (0.062) and IKKB ($p= 0.06$). No significant changes were observed for mRNA expression of IL2, IL5, IL10, NFkB, AP1, or IL-4 (undetectable) mRNA. These results indicate that a single bout of heavy resistance exercise up-regulates pro-inflammatory gene transcription in post-menopausal women not undergoing HRT.

19.3

AGE-RELATED ADAPTATION IN SKELETAL MUSCLE CHARACTERIZED BY PERFORMANCE AND MOLECULAR MECHANISMS

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We have shown that aging increases injury susceptibility and, more recently, impairs skeletal muscle's ability to adapt to chronic exposures of stretch-shortening contractions (SSCs). In the present study, performance and molecular pathways associated with the adaptive response in young and old rats were compared. Following 4.5 weeks of repetitive SSC exposure, performance increased in young rats and decreased in old rats. Our data also revealed several pools of genes, including early transcription regulators, cell cycle regulators, muscle regulatory factors (MRFs) and stress-responsive factors that were differentially expressed with age. Specifically, old rats exhibited an increased expression in sets of genes associated with the stress-related response in comparison with young rats, while concurrently displaying a decreased expression in sets of genes associated with muscle growth and adaptation (increased muscle performance and hypertrophy) when compared with young counterparts. In conclusion, understanding the sets of genes specifically associated with chronic mechanical loading leading to either a positive (adaptation) or negative (mal-adaptation) response has immediate relevance for the development of new strategies that optimize muscle performance and muscle quality in aging skeletal muscle.

19.4

TISSUE OXYGENATION OF LIMB AND RESPIRATORY MUSCLES DURING PROGRESSIVE INSPIRATORY LOADING

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PURPOSE: To assess the changes of muscle oxygenation in sternocleidomastoid (SCM) and the parasternal (PS) and external intercostal (EIC) muscles during incremental inspiratory threshold loading in healthy subjects using non invasive near-infrared spectroscopy (NIRS). METHODS: Ten healthy males (28±4yr) performed maximal inspiratory pressure (MIP) manoeuvres and then an inspiratory muscle threshold loading test, during which NIRS and EMG monitoring was performed via surface probes or electrodes on the SCM, 2nd PS intercostal, 8th EIC, and the vastus lateralis (VL). Muscle tissue oxygenation, deoxygenation and blood flow were estimated from the oxygenated (O_2Hb), deoxygenated (HHb) and total hemoglobin (tHb) signals, respectively using NIRS. Subjects started at a load of 100 gm and 50 gm were added at 2-minute intervals until task failure. Respiratory rate was 10 breaths/min with a duty cycle of 33%. RESULTS: ΔtHb increased in PS and SCM during progressive threshold loading and task failure whereas the quiescent VL showed a greater negative ΔtHb during loading and task failure. CONCLUSION: During incremental loading in healthy man, ΔtHb increases and O_2Hb is maintained in the inspiratory muscles. Our results are consistent with the hypothesis that blood flow "steal" from quiescent limb muscles is a mechanism to maintain muscle tissue oxygenation of the inspiratory muscles during loading.

19.5

EFFECT OF EXERCISE ON PROTEIN METABOLISM IN THE MUSCLE OF UREMIC MICE

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In patients and animals with chronic kidney disease (CKD) there is loss of muscle mass due to increased protein degradation. Exercise may play a preventative role in CKD. To test the effect of exercise on muscle protein metabolism, two exercise regimens were used: resistance training was achieved by overloading (OL) the plantaris muscle of mice by removing gastrocnemius and soleus muscles, and treadmill running was used for endurance training. Uremia resulted from 5/6 nephrectomy of the mice. Animal protocols were IACUC approved. Plantaris muscle weight was significantly increased in OL groups (uremic vs. uremic+OL; $P<0.01$), but not in treadmill groups. Protein synthesis was increased in OL group, but not in treadmill group. The rate of protein degradation is attenuated in plantaris of OL+uremic mice compared to control uremic mice, but not in treadmill+uremic group. Protein degradation in EDL muscle is reduced in treadmill+uremic vs. uremic mice. To identify signaling pathways regulated by exercise, we measured IRS-1/Akt protein. Tyrosine phosphorylated IRS-1 is 2.1-fold increased and Akt phosphorylation is 2.5-fold increased in OL muscle vs. control muscle ($P<0.01$). Overall, resistance exercise enlarges muscle size due to increased protein synthesis and decreased protein degradation. The mechanism of exercise response includes up-regulation of the IRS-1/Akt signaling pathway. We conclude that resistance exercise may contribute to the prevention of muscle wasting in uremia.

19.6

CHANGES IN BASAL AND INFLAMMATION-INDUCED HSP25 AND αβ-CRYSTALLIN IN MOUSE SKELETAL MUSCLE FOLLOWING EXERCISE TRAINING

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The small heat shock proteins (Hsp), Hsp25 and αβ-crystallin (αβC) may protect tissues during inflammatory insults; however no studies have investigated whether exercise training increases basal or inflammation-induced expression of these Hsps in skeletal muscle. Muscle is a primary source of IL-6 during both exercise and inflammation and may modulate Hsp expression. These studies tested the hypothesis that 2 weeks of wheel running (Ex) increases basal and inflammation-induced Hsp25 and αβC protein and that these changes are associated with IL-6 levels in mouse skeletal muscle. We compared Hsp25, αβC, and IL-6 protein levels after systemic inflammation induced by lipopolysaccharide (LPS) in the skeletal muscles of sedentary (Sed) or Ex mice. Hsp25 and αβC were quantified with Western blot and IL-6 with Elisa 4 h after LPS or saline. In Sed mice, LPS significantly increased Hsp25 (1.5±0.1 fold), but not αβC (1.1±0.1) relative to saline. In Ex mice, LPS-induced Hsp25 or αβC were not different from saline. Wheel running significantly increased basal Hsp25 and αβC 2.2±0.1 and 3.0±0.4 fold, respectively. IL-6 protein was significantly elevated by LPS in both Sed and Ex groups, with a significantly greater response in Ex mice. The major results provide evidence that wheel running is associated with greater basal, but not inflammation-induced Hsp25 and αβC expression, despite a greater IL-6 response to LPS following exercise training. This work was supported by NIH AR049855.

19.7

ADAPTATION OF THE RAT'S SOLEUS TO COMBINED AEROBIC EXERCISE TRAINING AND HEAT ACCLIMATION -GENOMIC PHYSIOLOGICAL ASPECTS

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In this investigation we studied the physiological and genomic aspects of adaptation in the soleus following acclimation to combined heat and exercise training. Rats were divided into controls (C), ACC at 34°C, EX-acclimated to aerobic exercise (treadmill at 24°C), EXAC- heat and aerobic training. The acclimation periods were 2 or 30 days. Isometric force generation was measured using isolated muscle preparations stimulated at 1-100 Hz, and global genomic responses of homeostatic genes were detected using a cDNA Atlas array (Clontech, Rat no.1.2). Only muscles excised from EXAC rats subjected to 1 mo acclimation demonstrated markedly elevated force generation ($p<0.05$), with a significant decrease in relaxation velocity. All treatment groups demonstrated reprogramming of gene expression with stressor-specific dynamic profiles. Improved force generation in the EXAC soleus coincided with significant up-regulaion in the expression level of genes encoding sarcoplasmic Ca^{2+} transporting proteins (SERCA 2, ITPR), glycolysis rate limiting enzyme (PFK), mitochondrial lipid metabolism (CPTII) and stress proteins favoring antiapoptotic activity. Our data suggest that specific cross talk between genes assigned to: transport, metabolism and stress differed in abundance and/or expression level contributed to the physiological advantage demonstrated by EXAC. We hypothesize that longer acclimation is required to generate improved muscular performance in the ACC and the EX groups.

19.8

LONG TERM RELIABILITY OF MUSCLE FUNCTION AND SIZE IN THE KNEE EXTENSORS

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In vivo muscle function and size are routinely measured before and after physiological interventions and therefore, establishing the long term reliability of these measurements is important. This study determined the reliability of strength measures, muscle contractile properties (evoked forces and rates of force development), muscle morphology (cross-sectional area [CSA] via MRI) and performance (steadiness and endurance) in the knee extensors (KE). Nine subjects (5M;4F) underwent 2 testing sessions separated by 30 days. Reliability was moderate-to-high with coefficient of variations (CV) of 2-17% and intraclass correlation coefficients (ICC) of 0.80-0.99. Of the 14 variables assessed, 3 (one-repetition maximum [1-RM], evoked rate of force development, and force exerted at the completion of the endurance test) were heteroscedastic and displayed different variances among subjects. Muscle CSA and KE isometric force demonstrated the highest reliability (ICCs=0.99), followed by 1-RM (ICC=0.98) and evoked rate of force development and relaxation (ICC=0.94 and 0.96, respectively). The variables with the lowest, yet still acceptable correlations include: force exerted at the completion of the endurance test (ICC=0.80) and twitch and doublet force (ICC=0.82 and 0.83, respectively). In vivo measurements of muscle function and morphology on the KE are reliable over a 30 day time period. This long term reliability is important to the interpretation of intervention studies.

19.9

CALCIUM TRANSIENTS CONTRIBUTE TO THE CONTRACTION-INDUCED ELEVATION OF HEAT SHOCK PROTEIN 72 MRNA IN ISOLATED SINGLE SKELETAL MUSCLE FIBERS

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The present study tested the hypothesis that the elevation in heat shock protein 72 (HSP72) mRNA in skeletal muscle which occurs in response to a single bout of contractions is due to the repeated transient increase in cytosolic $[Ca^{2+}]$ ($[Ca^{2+}]_c$). Living, intact fast-twitch skeletal muscle fibers from Xenopus laevis were injected with the cytosolic Ca^{2+} indicator fura 2. Individual fibers were incubated for 15 min in either standard Ringer's solution (EX; n=6), or in 10 μM N-benzyl-p-toluene sulfonamide (BTS, n=6), an inhibitor of cross-bridge cycling, prior to 15 min of tetanic contractions at 0.33Hz. Following treatment, individual fibers were allowed to recover for 2 hr before isolation of total cellular mRNA, followed by relative quantification of HSP72 and HSP60 mRNA via qPCR. Initial peak developed tension of BTS fibers significantly ($p<0.05$) decreased to 8±3% of pre-BTS values, whereas peak relative $[Ca^{2+}]_c$ remained unchanged from pre-BTS incubation values. Mean relative peak developed tension and relative peak $[Ca^{2+}]_c$ of EX fibers significantly ($p<0.05$) decreased throughout the contractile protocol (developed tension: 12±6% initial values; $[Ca^{2+}]_c$: 31±7% initial values). However, while peak developed tension remained depressed in BTS fibers, peak $[Ca^{2+}]_c$ was significantly elevated relative to EX fibers throughout the contractile period. When normalized to within-fiber HSP60 content, comparative quantification of HSP72 mRNA content revealed a significant increase ($p<0.05$) in fibers of both the BTS-treated group (12.9±5.7 fold) and EX fibers (16.3±6.5 fold) relative to rest fibers (n=13), with no difference between groups. These data suggest that in these single skeletal muscle fibers, increased $[Ca^{2+}]_c$ contributes to the elevation of HSP72 mRNA content in response to contractions.

19.10

LOW GLUCOSE ENHANCES OXIDATIVE CAPACITY OF RABBIT SKELETAL MUSCLE CELLS IN CULTURE

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Objective: We investigated whether metabolic adaptation, as associated with fast-to-slow transformation of skeletal muscle cells, is induced by a) low intracellular ATP, b) low intracellular glycogen, or c) low extracellular glucose concentration. Methods: We used adult fast-type myotubes from rabbits cultured on microcarriers. These myotubes were treated with a) 5 mM 3-guanidinopropionic acid to reduce intracellular ATP concentration, b) cell culture medium lacking glucose to decrease intracellular glycogen content, or c) 0.2 mM 1,4-dideoxy-1,4-D-arabinitol and 0.5 mM N-Butyldeoxynojirimycin in cell culture medium lacking glucose to inhibit glycogen breakdown during low extracellular glucose supply. Results: We found that neither low ATP nor low glycogen content of the myotubes are decisive triggers of metabolic adaptation. Instead we observed that cell culture medium lacking glucose induces downregulation of GAPDH RT-PCR products and GAPDH enzyme activity to 57 ± 7% and 76 ± 4% of controls, whereas PGC-1α RT-PCR products and citrate synthase enzyme activity increased to 140 ± 15% and 123 ± 9% of controls, respectively. These changes in metabolic markers are observed even when glycogen breakdown is inhibited. Conclusion: Our results indicate that low glucose supply constitutes an effective trigger of metabolic adaptation independent of glycogen content in rabbit skeletal muscle cells. Supported by Deutsche Forschungsgemeinschaft grant Gr 489/20-1.

19.11

RESVERATROL TREATMENT IN A MOUSE MODEL OF ALS

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The underlying causes of denervation of the neuromuscular junction and eventual motor neuron (MN) death in amyotrophic lateral sclerosis (ALS) have not been resolved. The SOD1 G93A mutant mouse is a frequently used animal model of the disease. We hypothesized that resveratrol (RSV; 3,5, 4'-trihydroxystilbene), a polyphenolic molecule that potently enhances mammalian NAD+-dependent SIRT1 deacetylases and has been shown to increase lifespan in yeast, c. elegans, and drosophila melanogaster, would improve motor function and survival in the SOD1 mouse model. Mean survival times were not statistically different ($p=0.23$) between the two groups (control, n=11: 138 ± 6 d vs RSV, n=10: 135±8 d, mean ±SD). Neuromuscular performance on the rotor-rod was not significantly different between RSV-fed and control mice at timepoints corresponding to 50%, 80%, and 90% mean lifespan ($p=0.46$ at all 3 timepoints), nor did RSV treatment attenuate bodyweight loss or symptom onset. Although manipulation of SIRT1 deacetylase activity has been shown to have effects at the protein level in healthy aging organisms, the results of this study lead us to conclude that RSV treatment does not lead to functional improvement or increased longevity in a mouse model of ALS. We speculate that RSV-mediated upregulation of SIRT1 activity is not sufficient to increase motor performance and longevity in this model of ALS. Funding: Childers Lab startup funds.

19.12

SHIFT TOWARDS FASTER GENE EXPRESSION PATTERN IN VASTUS LATERALIS MUSCLE AFTER STRENGTH TRAINING WITH ECCENTRIC OVERLOAD IN ATHLETES

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To investigate the effects of increased eccentric load on muscular adaptation, 25 male strength-trained athletes performed either conventional concentric/eccentric (CON, n=11, 24.5±4.2 yrs, 184±7 cm, 80.5±7.8 kg) or concentric/eccentric knee extension training with eccentric overload (CON/ECC+, n=14, 24.3±3.7 yrs, 185±7cm, 79.8±8.6 kg). The study conformed with the standards set by the Declaration of Helsinki. The mRNA-expression of the myosin heavy chains (MHC) I, IIa, IIx, IIb, lactate dehydrogenase (LDH) A and B, monocarboxylate transporters (MCT) 1 and 4 and androgen receptor (AR) was determined by RT-PCR in vastus lateralis muscle biopsies obtained before and after the 6 wk training period. The fiber type specific expression of MHCs was monitored by in situ hybridisation and myofibrillar ATPase stains. Only after CON/ECC+, MHC IIb, LDH A, MCT 4 and AR mRNA expression was significantly increased and there was a tendency towards increased numbers of biopsies containing type IIA fibres expressing MHC IIxmRNA. In both training groups, LDH B mRNA was significantly elevated; MHC I, IIa, IIx and MCT 1 mRNA levels remained unchanged. The enhanced eccentric load in CON/ECC+ led to an increased expression of mRNAs primarily expressed in fast, glycolytic fibre types and seems to oppose a training-induced transformation from type IIX to type IIA fibres. Supported by the Bundesinstitut für Sportwissenschaft (VF 07/05/66/2004-2005).

19.13

NITRIC OXIDE SYNTHASE INHIBITION IMPAIRS CHRONIC LOW-FREQUENCY STIMULATION-INDUCED SATELLITE CELL ACTIVATION AND PREVENTS SKELETAL MUSCLE ADAPTATION

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The purpose of this time-course study was to determine the necessity of nitric oxide (NO) for CLFS-induced satellite cell activation and fast-to-slow fibre type transition (F-S) in skeletal muscle. Endogenous NO production was blocked by orally administering N^{ω}-nitro-L-arginine methyl ester (L-NAME; 0.75 mg ml^{-1}; ~100 mg kg^{-1} day^{-1}) beginning 2 days before and

throughout 0, 1, 2, 5 or 10 days of CLFS (10 Hz, 12 h d^{-1}) focused on the left tibialis anterior muscle of male Wistar rats (0, 1, 2, 5 or 10d L-Stim; n=6 each group). Groups receiving only CLFS (0, 1, 2, 5 or 10d Stim; n=6 each group) were also studied. Right legs served as internal controls. Continuous infusion of BrdU revealed that CLFS first induced an increase in satellite cell proliferation at 1 day, up to a maximum at 10 days over 0d Stim (mean±SEM: 5.7±0.7 and 20.4±1.0 vs 1.5±0.2 mm^{-2}, respectively, P<0.02) that was delayed in 1d and 2d L-Stim (P<0.05). Myosin heavy chain fibre type and mRNA analyses revealed CLFS-induced F-S began at 5 days (5d Stim) from type IID→IIA and continued at 10 days (10d Stim) from type IIB→I. F-S was almost completely prevented in L-NAME rats, with the exception of a 26% decrease in the proportion of type IID fibres (P<0.04) in 10d L-Stim. We conclude that L-NAME delayed CLFS-induced satellite cell activation and for the most part, prevented F-S. Therefore, these data support a role of CLFS-induced NO-dependent satellite cell activation and skeletal muscle F-S. NSERC and AHFMR.

19.14

CHRONIC HIGH FAT FEEDING ATTENUATES THE SURGICALLY-INDUCED HYPERTROPHY OF SKELETAL MUSCLE

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With the incidence of obesity and obesity related disease such as metabolic syndrome and insulin resistance on the rise, it is critical to understand the effects of diet-induced obesity on insulin sensitive tissues such as skeletal muscle. While a tremendous volume of research exists on the effects of insulin resistance on glucose homeostasis in muscle, there is little data on the effects of obesity on the regulation of skeletal muscle mass. We hypothesized that diet-induced obesity in mice would result in a decreased ability of skeletal muscle to grow in response to an increase in mechanical loading, due to a decrease in the activation of the Akt signaling pathways. C57B/6 mice were fed either a low-fat(LFD) or a high fat diet (HFD) ad lib for 14 weeks before undergoing bilateral functional overload of the plantaris (FO). By 14 days of FO, there was a 10% reduction (P=0.011) in the amount of plantaris growth in response to load in HFD relative to LFD mice. By 30 days the growth deficit increased to 20% in HFD compared to LFD mice (P<0.001). This attenuated growth in HFD mice corresponded to a reduced capacity to activate Akt in response to FO. Activation of Akt was significantly reduced by 93% in HFD vs. LFD mice at both 7 and 30 days of functional overload (P=0.05, P<0.001). This data suggests that diet-induced obesity interferes with the induction of protein synthetic pathways normally activated under loading conditions. Supported by NIH grant HL078615-04.

19.15

DELETION OF MURF1 RESULTS IN IMPROVED FATIGUE RECOVERY IN SKELETAL MUSCLE

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The muscle-specific RING finger protein, MuRF1, is an E3 ubiquitin ligase selectively expressed in skeletal, cardiac and smooth muscle. While MuRF1 has been identified as a key regulator and marker of skeletal muscle atrophy, its target substrates and physiological function in skeletal muscle (both at rest and under atrophy conditions) remain relatively unknown. In this study, the isometric contractile properties of the gastrocnemius (GA) muscle were studied at 9, 12 and 18 months of age in mice with a null allele for MuRF1 and wild type litter-mates (Bodine et al. Science 294: 2001) to investigate the functional significance of MuRF1 in skeletal muscle. The isometric twitch properties of WT and KO mice were similar at all ages. Further, there was no significant difference in the frequency-tension relationship or maximum tension (absolute and normalized) of WT and KO mice at any age. The fatigue index of the GA, determined at 2 and 4 minutes following continuous stimulation at 60 Hz (1 train/sec, 330 ms train duration), was similar in KO and WT mice at all ages. However, recovery of force output, as measured by a 60 Hz contraction, was significantly better in KO than WT mice at 1, 2, 5, 10 and 20 minutes post fatigue test. The difference between KO and WT was apparent at all ages. The reason for the difference in force recovery is unknown; however, preliminary data show an increase in capillary density and arterioles in the KO mice. Supported by an MDA Grant to SCB.

19.16

CARNOSINE LOADING AND UNLOADING IN HUMAN SKELETAL MUSCLE

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The dipeptide carnosine is highly present in human skeletal muscle. The chronic ingestion of β-alanine has been shown to elevate muscle carnosine content. Aim: We aimed to compare the rate of carnosine synthesis in 3 lower leg muscles during β-alanine ingestion. Furthermore, we explored the rate of carnosine elimination from muscle upon cessation of supplementation. Finally, we compared carnosine content with isometric endurance in dorsiflexors. Methods: 20 untrained males participated in a placebo-controlled double-blind study (in agreement with the Declaration of Helsinki) and were supplemented for 5-6 weeks with either 4.8g/day β-alanine or placebo. Muscle carnosine was quantified in soleus, gastrocnemius and tibialis anterior by proton MRS before and after supplementation and 3 weeks into washout. Performance was evaluated by the time to exhaustion of isometric contraction at 45% MVC of the tibialis anterior. Results: β-alanine ingestion significantly increased carnosine content on average by 29%. No difference in absolute increase was observed between muscle types. The time to exhaustion was not affected by the increase in carnosine. After a washout of 3 weeks, only 30% of the increase in carnosine had disappeared. Conclusions: β-alanine ingestion elevates muscle carnosine to the same extent in oxidative and glycolytic muscles. Carnosine-loaded tibialis muscles do not exhibit improved isometric endurance. Muscle carnosine unloading takes 2-3 times longer than loading. Funding source: Grant Found for scientific research (Flanders).

19.17

MECHANICAL OVERLOAD INDUCED SKELETAL MUSCLE PLASTICITY IN THE OBESE ZUCKER RAT

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The purpose of the present study was to investigate the effect of mechanical overload (MOV) on muscle wet-weight (WW), total and myofibrillar protein content, muscle fiber cross-sectional area (CSA), and myosin heavy chain expression in the Obese Zucker rat ($Lepr^{fa}$), an animal model that displays characteristics of type 2 diabetes . Young (2 mo, n = 5) male LZ and young (2 mo, n = 5) male OZ rats underwent unilateral surgical ablation of the gastrocnemius muscle to MOV the fast-twitch plantaris muscle for 8 weeks. MOV increased OZ plantaris WW, total protein content, myofibrillar protein content, muscle CSA, and mean fiber area (MFA) by 41.1, 42.7, 51.8, 40.6, and 41.8% in comparison to the contralateral control plantaris. In contrast, MOV increased LZ plantaris WW, total protein content, myofibrillar protein content, muscle CSA, and MFA by 39.2, 36.7, 46.2, 34, and 41.7% compared to the contralateral control plantaris. MOV increased type IIX MHC expression in the LZ rat plantaris compared to the OZ rat plantaris; however, the difference was not significant (P = .069). Collectively, these results indicate that the OZ rat exhibits a similar skeletal muscle adaptive response when subjected to mechanical overload.

19.18

EFFECTS OF HIND LIMB ISCHEMIC CHALLENGE ON VASCULAR RESPONSES IN LOW AND HIGH CAPACITY ENDURANCE RUNNING RATS

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Background: Endurance exercise training enhances vascular supply and improves capillary density, which can be therapeutic with peripheral arterial occlusive disease (PAOD). The impact of intrinsic predisposition for endurance exercise training is unknown. Two-way forced artificial selection for/against treadmill running capacity produced lines of LCR and HCR rats that can be used to determine the effects of the untrained endurance capacity phenotype in experimental PAOD. Purpose: Determine the influence of intrinsic endurance capacity on vasculogenic responses following peripheral ischemia. Methods: Peripheral artery ischemia was created by unilateral permanent ligation of the femoral artery. Two weeks after occlusion, soleus and plantaris muscle from the ischemic and contralateral control limb were obtained for histologic analysis of capillary density. Results: In non-ischemic tissue, capillary density was lower in LCR vs HCR in both plantaris (41.93 ± 0.66 vs 47.24 ± 0.65, p<0.05) and soleus (49.65 ± 1.30 vs 56.20 ± 1.60, p<0.05). In ischemic plantaris, LCRs increased both total capillaries (48.46 ± 0.85 vs 41.93 ± 0.66, p<0.05) and capillaries per myocyte (5.06 ± 0.10 vs 4.37 ± 0.06, p<0.05), while the HCR only demonstrated an increase in capillaries per myocytes (5.25 ± 0.11 vs 4.69 ± 0.08, p<0.05). Conclusions: The vasculogenic response to femoral artery occlusion was limited to the plantaris muscle, was differentially expressed depending on intrinsic running capacity, but was not abolished in LCRs. Supported in part by NIH RR-17718.

19.19

EFFECTS OF HIND LIMB ISCHEMIC CHALLENGE ON FAT OXIDATION IN LOW AND HIGH CAPACITY ENDURANCE RUNNING RATS

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Background: Endurance exercise training improves fatty acid oxidation (FAO), limits obesity, and improves tolerance to peripheral ischemic disease, but the impact of intrinsic endurance exercise capacity (EEC) is unknown. Forced artificial selection for/against treadmill running capacity produced lines of LCR and HCR rats that can be used to determine the effects of the untrained EEC phenotype in experimental models of disease. Purpose: Determine the influence of intrinsic endurance capacity on distal tissue metabolic responses following peripheral ischemia. Methods: Peripheral artery ischemia was created by unilateral ligation of the femoral artery in LCR and HCR animals. Two weeks after occlusion, red, white, and mixed gastrocnemius (RG, WG, MD) were obtained from the ischemic and contralateral control limb. FAO rates were determined using ^{14}C labeled palmitate. Results: In non-ischemic tissue, RG from LCR had higher FAO (1105.71 ± 57.06 vs 621.19 ± 54.20, p<0.05) while HCR MG exhibited higher FAO than LCR (415.10 ± 31.74 vs 255.82 ± 90.12, p<0.05). With ischemia, FAO in HCR RG increased (919.76 ± 46.52, p<0.05), but decreased in LCR (657.54 ± 57.30, p<0.05). Ischemia decreased FAO in the HCR MG (217.14 ± 20.37, p<0.05) but did not alter FAO in the LCR MG. Conclusions: Intrinsic exercise capacity influences both the type of muscle responding, and the direction of the response within tissue. LCRs demonstrated an overall loss of FAO capacity in response to ischemia, but HCRs compensated a loss in MG FAO with an increase in RG FAO. Supported in part by NIH RR-17718.

19.20

THE ROLE OF IMMUNE CELL INFILTRATION IN ADAPTATIONS TO SKELETAL MUSCLE OF ADULT AND OLD MICE FOLLOWING EXERCISE

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The ability of muscles of old mice to adapt and repair following contractions is reduced. We hypothesise that altered immune cell sequestration may play a major role in this failed adaptation. Adult (4 month) and old (26 month) mice were subjected to a non-damaging isometric contraction protocol. Mice were killed up to 24 hours post-contractions. Muscles were analysed for immune cell infiltration using immunohistochemical techniques and NFkappaB and AP-1 transcription factor (TF) DNA binding activity by mobility shift assay. Serum was analysed for cytokine content. Data demonstrated an aberrant adaptive response in muscles of old compared with adult mice. Increased TF activation was seen immediately following the contractions in muscles of adult mice. This was delayed, to peak at a greater level at 1 hour post-contractions, in old mice. This was associated with a greater increase in IL6 in the serum of old mice. A secondary phase of TF activation occurred at 24 hours in muscles of adult, but not old, mice. In adult mice, 97% of the neutrophils detected were recruited to the blood vessel wall within 1 hour of the contractions. This process was delayed in muscle of old mice. Data demonstrate that the two phases of TF activation in muscles of adult mice following isometric contractions were altered in muscles of old mice and suggest that these two phases may play a role in cytokine production and adaptive responses. The authors thank the University of

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19.21

TRADE-OFF BETWEEN FORCE AND SPEED IN MAMMALIAN MUSCLE FIBERS

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Cotton rats (Sigmodon hispidus), compared to commonly utilized laboratory rats, exhibit a higher level of locomotor activity and have a greater tendency to jump in an attempt to escape confinement, when housed under captive conditions. The goal of this project was to examine contractile properties of fast and slow limb muscle fibers in cotton rats to determine whether the fibers have inherent physiological properties that subserve the apparent rapid and powerful muscle contractions employed during locomotion. Single, skinned fibers were isolated from slow-twitch soleus and fast-twitch lateral gastrocnemius and tibialis anterior muscles. Maximal force generating ability (force/cross-sectional area, Po/CSA) and maximal shortening velocity (Vmax) were determined for each fiber. Mean Po/CSA was 55% and 65% greater in slow soleus fibers than in fast gastrocnemius and tibialis fibers, respectively. Mean (± SEM) Vmax, in fiber lengths/sec, was 1.65 ± 0.07, 6.05 ± 0.11, and 5.83 ± 0.24 in slow soleus, fast gastrocnemius, and fast tibialis fibers, respectively. The difference in Po/CSA between slow and fast fibers in cotton rat muscles is much greater than the difference (16%) between slow and fast fibers in Sprague Dawley rats. The results suggest that there is a greater trade-off between Po/CSA and Vmax in limb muscle fibers in cotton rats than in laboratory rats, such that fast fibers that are associated with faster and more powerful contractions have significantly lower maximal force generating ability. This is consistent with a general trade-off between force and speed in vertebrate muscle fibers, as proposed by Rome et al., 1999 (PNAS 96:5826-5831). Supported by the National Science Foundation.

19.22

INHIBITING CONTRACTION CAUSES TEMPERATURE-DEPENDENT INCREASE IN K_M AND V_{MAX} OF ADP-STIMULATED MITOCHONDRIAL RESPIRATION IN PERMEABILIZED SKELETAL MYOFIBERS

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This study examined the effects of an inhibitor of skeletal muscle contraction on in situ measures of mitochondrial respiration at different temperatures. Deep gastrocnemius muscle fiber bundles from Sprague-Dawley rats were saponin-permeablized for oxygraphy of mitochondrial respiration with and without the skeletal muscle myosin II inhibitor N-benzyl-p-toluene sulphonamide (+/-BTS) at 22, 30 and 37°C. Respiratory fluxes (JO_2) were recorded during titration of ADP atop saturating complex I substrate glutamate+malate, followed by addition of oligomycin (Olg) and finally the uncoupler FCCP. At 22 and 37°C, the K_m and V_{max} of oxidative phosphorylation (OXPHOS) for ADP did not significantly differ between +BTS and -BTS. However, the K_m and V_{max} of OXPHOS for ADP were significantly greater +BTS than –BTS at 30°C (K_m = 54.3 and 5.8 μM ADP; V_{max} = 252.0 and 162.5 pmol $O_2 \cdot sec^{-1} \cdot mg$ dry wt^{-1}, respectively, $p<.05$). While the Olg JO_2 increased with temperature, BTS had no significant effect. FCCP JO_2 was greater +BTS than –BTS at 30° (257.6 and 155.3 pmol $O_2 \cdot sec^{-1} \cdot mg$ dry wt^{-1}, respectively, $p<.01$). Interestingly, -BTS, there was no significant difference in FCCP JO_2 across all three temperatures. These findings suggest the kinetics of ADP-stimulated mitochondrial JO_2 measured in permeabilized fibers is affected by both contraction and temperature. We conclude that maximal mitochondrial JO_2 is realized at 30°C with BTS in saponin-permeabilized myofibers. Support: NIH DK073488.

19.23

THE TIME COURSE OF MUSCLE HYPERTROPHY, STRENGTH, AND MUSCLE ACTIVATION WITH INTENSE ECCENTRIC TRAINING

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Early strength increase with training is normally attributed to neural adaptations but recent evidence suggests that muscle hypertrophy occurs earlier than previously thought (Seynnes et al. J Appl Physiol 2007). Our purpose was to examine the time course of adaptation through 20 days of training and 5 days of detraining. Twenty-two untrained subjects trained one arm every 2nd day for 20 days. Subjects performed isokinetic eccentric biceps training at 90°/s (6 sets of 8 reps). Muscle thickness (MT) (cm) via ultrasound, strength (Nm) and muscle activation (electromyography) were measured before, during and after training (9 time points). MT increased after 8 days of training (3.66±0.11 to 3.90±0.12; $p<0.05$) and remained above baseline until the end of training (3.97±0.12). After 5 days of detraining MT decreased (3.97±0.12 vs. 3.85±0.11; $p<0.05$), but remained higher than baseline ($p<0.05$). MT did not change significantly in the untrained arm at any time point. Strength decreased after 8 days of training (65.6±4.1 to 57.5±3.5; $p<0.05$) and remained suppressed throughout the study. Muscle activation amplitude increased after 14 days of training ($p<0.05$) and remained elevated throughout the study. In conclusion, biceps muscle thickness increases very rapidly with frequent intense eccentric training although this type of training appears to impair strength. These findings provide additional evidence that muscle hypertrophy may occur much faster than has been generally accepted.

19.24

STRESS RESPONSIVE MIR-23A ATTENUATES SKELETAL MUSCLE ATROPHY BY TARGETING MAFBX/ATROGIN-1

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MicroRNAs (miRNAs) are small non-coding RNAs that interact with 3' UTR of specific target mRNAs to down-regulate translation. Recently, miRNA have been shown to play an important role in skeletal muscle development. On the other hand, their roles in muscle adaptation and plasticity remain to be determined. We searched miRNAs that regulate the expression of Atrogin-1, which is a key molecule of muscle atrophy. Luciferase reporter with 3' UTR of Atrogin-1 revealed that miR-23a down-regulated Atrogin-1 expression. Forced expression of miR-23a in myotubes and muscle fibers brought resistance against glucocorticoid-induced muscle atrophy. To investigate the stress responsiveness of miR-23a, we applied several stresses to myocyte and found that heat stress up-regulated miR-23a in myotubes and muscle fibers. Interestingly, heat stress exposed myotubes and muscle fibers showed resistance to the muscle atrophy. Down regulation of heat stress-induced miR-23a with LNA-antioligonucleotids led to loose the resistance. These findings suggest that stress responsive miR-23a inhibits skeletal muscle atrophy through post transcriptional regulation of Atrogin-1.

19.25

HUMAN SINGLE FIBER CONTRACTILE FUNCTION DIFFERS BETWEEN VASTUS LATERALIS AND SOLEUS MUSCLES

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The purpose of this study was to investigate potential differences in single fiber contractile physiology of fibers with the same myosin heavy chain isoform (MHC I and MHC IIa) originating from different muscles. Vastus lateralis (VL) and soleus biopsies were obtained from 27 recreationally active females (31 ± 1 y, 59 ± 1 kg). A total of 942 single fibers (MHC I = 562; MHC IIa = 301) were isolated and examined at 15°C for diameter, peak tension (Po), shortening velocity (Vo), and power. Data was statistically significant ($P<0.05$) unless otherwise noted. The soleus had larger fibers (MHC I +18%; MHC IIa +19%), higher Vo (MHC I +13%; MHC IIa +13% ($P=0.058$)], and higher Po (MHC I +18%) compared to fibers from the VL. In contrast, fibers from the VL had higher specific tension (MHC I +18%; MHC IIa +20%), and normalized power [MHC I +25%; MHC IIa +33% ($P=0.079$)] compared to the soleus. No differences in absolute power or MHC IIa Po were detected between muscles. These data highlight muscle specific differences in single fiber contractile function. This should serve as a scientific basis for consideration when making generalizations about single fiber contractile function among different muscles of origin. Further, muscle specific differences in single fiber physiology advances the notion of skeletal muscle diversity. Supported by NIH (AG18409; ST) and NASA (NNJ04HF72G; ST).

19.26

SKELETAL MUSCLE MITOCHONDRIAL MEMBRANE PHOSPHOLIPID FATTY ACID COMPOSITION

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Mitochondria (Mt) are responsible for aerobic ATP production in mammalian cells. Previous work has identified differences between Mt and whole muscle (Wm) phospholipid (PL) fatty acids (FA), however, relative contamination from other membranes was not addressed. The purpose of this study was to improve isolated Mt membrane purity of different skeletal muscle types (soleus, Sol; plantaris, Plan; red gastrocnemius, RG) and compare the PL FA composition to Wm. Lipids from unpurified and purified (60% Percoll) Mt and Wm were extracted, PLs (PC, phophatidyl choline; PE, phosphatidyl ethanolamine; CL, cardiolipin; PI, phosphatidyl inositol; PS, phosphatidyl serine; SM, sphingomyelin) were separated, and FA subclasses (saturated, SFA; monounsaturated, MUFA; polyunsaturated, PUFA) were determined. Western Blot analyses revealed contamination in Mt from sarcolemmal, transverse (t)-tubule, and golgi membranes (12.7, 7.0, and 6.0%, respectively), which Percoll purification improved by 37.2, 49.7, and 34.4%, respectively. Most trends remained similar pre- and post-purification between Mt and Wm, however, differing trends were seen post-purification within muscle types (Sol, higher PE, SFA, and MUFA and lower PI and PUFA; Plan, higher MUFA and lower SM and PUFA; RG, higher PC and PE and lower PS and SM). This data demonstrates the importance of quantifying contamination and utilizing purification techniques when examining subcellular membrane compositions. Supported by NSERC and CIHR.

19.27

THE PIF-POCKET DOMAIN OF PDK1 IS REQUIRED FOR ACTIVATION OF S6K1 AND S6 FOLLOWING AN ACUTE BOUT OF RESISTANCE EXERCISE

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The substrate docking site (PIF-pocket) of the phosphoinositol-dependent protein kinase (PDK1) is required for insulin-stimulated phosphorylation of the ribosomal protein S6 kinase S6K1 on both T389 and T229. Since activation of S6K1 is thought to be involved in muscle hypertrophy following resistance exercise (RE) we hypothesised that the PIF-pocket would be required for S6K1 activation and hypertrophy following RE. Using transgenic mice with a knockin mutation in the PIF-pocket (PIFki) we determined the capacity for muscle hypertrophy in response to 7 days of functional overload (OL) and the activation of S6K1 following insulin treatment or an acute bout of RE. Following 7 days OL, the plantaris of the PIFki mice hypertrophied as normal (wt=26.6±2.6%, PIFki=28.8±2.95%). As previously shown, PIFki blocked insulin-stimulated S6K1 and S6 phosphorylation and the activation of S6K1. $S6^{S240/244}$ and $S6K1^{T389 \text{ and } T229}$ phosphorylation were increased by 1575%, 466% and 380% respectively in WT mice 1 hour after RE. $S6^{S240/244}$ and $S6K1^{T389}$ phosphorylation were lower in the PIFki mice, however $S6K1^{T229}$ increased 359% but with a lower basal phosphorylation. These data suggest that an acute bout of RE requires the PIF-pocket of PDK1 for full activation of S6K1 and S6. Further, either active S6K1 is not required for overload-induced skeletal muscle hypertrophy or new cells are recruited into the growing muscle that do not express the mutant PDK1.

19.28

THE IMPACT OF ACTN3 GENE POLYMORPHISM ON PROGRESSION OF DISEASE IN CHRONIC HEART FAILURE

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A polymorphism (R577X) in the ACTN3 gene results in a lack of a muscle protein á-actinin-3 in individuals with XX-genotype (XX). XX is found ~ 18% of Caucasians but is over-represented in endurance trained athletes. In a knockout mouse loss of á-actinin-3 results in muscle that is more adapted to oxidative metabolism. The aim of the study was to examine the effect of ACTN3-genotype on chronic heart failure. 195 patients and 472 healthy controls were studied. ACTN3-genotype was analysed by allelic discrimination. Expression of ACTN3 mRNA was measured in human cardiac muscle samples obtained during by pass surgery (n=6) and in

skeletal muscle samples from healthy subjects (RR-genotype, n=9) by real-time PCR. The prevalence of XX in healthy controls was in agreement with previous studies on Caucasian population but was higher in the chronic heart failure patients; 28% vs. 18% (p=0.008). XX was however associated with better cardiac function (significantly higher ejection fraction and lower left ventricular mass index in males; ANCOVA; $p<0.05$, but not in females). Analysis of ACTN3 mRNA expression confirmed that ACTN3 is not expressed in human cardiac muscle but is highly expressed in skeletal muscle. Conclusion: Adaptation toward a more oxidative muscle in XX may result in a lower peripheral resistance and thereby a decreased afterload that may protect the overloaded heart in chronic heart failure and thereby slow down progression of the disease and prolong survival.

19.29

INCREASED FIBER SIZE AND INTRAMYOCELLULAR LIPID ACCUMULATION IN SKELETAL MUSCLES OF OSSABAW MINIATURE SWINE WITH METABOLIC SYNDROME

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Ossabaw swine fed excess kcal and atherogenic diets develop metabolic syndrome (MetS) characterized by obesity, dyslipidemia, hypertension, insulin resistance, and glucose intolerance. The purpose of this study was to test the hypothesis that MS could have a detrimental effect on skeletal muscle structure and cause changes in the expression of genes involved in lipid metabolism. Adult male Ossabaw swine were fed high fructose or high fat/cholesterol/fructose diets to induce MetS or dyslipidemic MetS (DMetS), respectively, for 28 weeks and compared to Control (C) chow. MetS swine showed mild MetS, lacking increase in LDL and total cholesterol, both of which were highly up-regulated in DMetS swine. There was 17-30% increase in cross sectional areas of muscle fibers in MetS and DMetS groups compared with C diet for biceps femoris, soleus and plantaris muscles. In plantaris muscles DMetS diet caused 20-40% increase in the number of intramyocellular lipid droplets, while the size of the droplets did not change. This data correlate well with the data on total plasma cholesterol (C=60; DMetS =298 mg/dl) and LDL (C=29; DMetS =232 mg/dl). Lipid droplets were organized into continuous rows along the muscle fiber length. There was ~2-fold increase of CPT-1 and ~5-fold increase of SCD1 mRNA expression in plantaris muscles of DMetS swine. There were no changes in the mRNA expression of GLUT4, CD 36/FAT, FATP 1 and LPL. Support: NIH HL013223 (MS), HL062552 (MS) and IUSM-Northwest (TK).

19.30

NO ASSOCIATION BETWEEN ACTN3-GENOTYPE AND MUSCLE FIBRE TYPE COMPOSITION IN NON-ATHLETES

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Alpha-actinins are structural and regulatory proteins. Alpha-actinin-3 is expressed by the ACTN3-gene and is found solely in type II fibres. A polymorphism (R577X) in the ACTN3 results in a lack of alpha-actinin-3 in individuals with XX-genotype. XX is found in ~18% of Caucasians but is under-represented in elite sprint athletes and over-represented in endurance trained athletes. It has been suggested that alpha-actinin-3 may be involved in the regulation of fibre type composition. The aim of the present study was to examine the association between R577X polymorphism and the fibre type composition in non-athletes. ACTN3-genotype was analysed by allelic discrimination with fluorogenic probes. 63 males and females (XX; n=23, RX; n=17, RR; n=23) were studied. They were moderately trained - training 2-10 hours per week. Fibre type composition was determined in biopsy samples from m. vastus lateralis by myofibrillar ATPase stain. The proportion of type I fibres was (mean±SD) 55.9±12, 57.4±12 and 53.9±16, type IIa 32.2±12, 33.7±10 and 34.7±14, and type IIb 11.7±10, 8.2±5 and 11.1±11 in XX, XR and RR, respectively. In the multiple regression analysis training status and gender but not the ACTN3-genotype had a significant effect on fibre type composition. The present study was thus not able to confirm the earlier reported lower proportion of type IIb fibres in XX than in RR and do not support that the ACTN3 play an important role in the regulation of the fibre type composition.

19.31

INHIBITION OF C2C12 CELL DIFFERENTIATION IN THE PRESENCE OF A SULFATED POLYSACCHARIDE

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A commercially available supplement purports to increase muscle mass by inhibition of the negative regulator myostatin. Our work has shown that the active ingredient, a sulfated polysaccharide (SP), has little effect on C2C12 proliferation. The current aim was to define the effect of SPs on C2C12 differentiation. Cells were maintained under standard culture conditions. At confluence media was changed to DMEM/2% HS with varying doses of SP. After 7 days Western Blots were performed, staining for the contractile proteins MHC and TnT. Immunofluorescence, double labeling MHC or TnT and nuclei, allowed for determination of a fusion index (nuclei in MHC or TnT positive cells/ total number of nuclei). Qualitatively, a dose dependent decrease in the number of multinucleated myotubes and MHC/TnT positive cells was seen with increasing SP. Quantitatively, the fusion index decreased from 0.6 under control conditions to 0.29, 0.21, and 0.19 with increasing SP. When stained for TnT, the measured fusion index similarly decreased (0.76 to 0.35, 0.22, and 0.13). Western Blots confirmed the presence of MHC and TnT in control samples and the lowest SP concentrations. At higher SP concentrations MHC and TnT were markedly reduced, completely absent in cells exposed to 100 ug/ml. This data demonstrates that the SP inhibits differentiation of C2C12 cells. When combined with no effect on proliferation, the purported effect on muscle growth must be questioned.

19.32

PYRUVATE-INDUCED SHIFT TOWARDS LIPID METABOLISM IN C2C12 MYOTUBES

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Substrate influx into mitochondria plays a pivotal role in sustaining oxidative metabolism during muscle contraction. Recent evidence suggests that cellular substrate delivery also influences transcriptional regulation of mitochondrial metabolism and biogenesis. For example, treatment of myoblasts with sodium pyruvate induces mitochondrial biogenesis in a PGC-1α independent manner. The aim of this study was to examine the mechanism of pyruvate action on mitochondrial biogenesis in C2C12 myotubes. Five days following differentiation, C2C12 myotubes were treated for 72h with either Sodium Pyruvate (50mM) or Sodium Chloride (50mM) as an osmotic control. Pyruvate increased the levels of the fatty acid transporter CD36 (61%), β-oxidative enzyme HAD (54%), TCA enzymes PDH (28%) and SDH (21%) and ETC proteins COX4.1 (23%) and ATP-synthase (11%). The glucose transporter GLUT4 (-42%) and the glycolytic enzyme PFK (-57%) were decreased, along with the mitochondrial regulator PGC-1α (-72%). Concomitant with these protein changes, pyruvate increased the expression of COX1 (117%), Cytochrome-C (206%) and the PGC-1α related coactivator (PRC; 207%) mRNA while reducing PGC-1α (-21%) and PGC-1β (-122%) expression. Our data suggests that pyruvate upregulates genes involved in lipid metabolism and mitochondrial biogenesis. Further, the marked increase in PRC expression following pyruvate treatment suggests that PRC plays a role in co-ordinating the response to altered substrate delivery.

19.33

TRAINING INCREASES SKELETAL MUSCLE FATTY ACID TRANSPORT PROTEINS ON THE SARCOLEMMA AND MITOCHONDRIA IN WOMEN

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This study determined if high intensity interval training (HIIT) altered total skeletal muscle as well as sarcolemmal and mitochondrial membrane fatty acid transport protein contents in women. Ten females (22 ± 1 yr, 65 ± 2 kg, VO_2peak: 2.82 ± 0.14 l · min^{-1}) completed six weeks of HIIT consisting of ten, 4 min intervals at ~90% VO_2peak separated by 2 min of rest, three times per week. Resting muscle was sampled before training (PRE) and after two (2WK) and six (6WK) weeks of HIIT. VO_2peak increased 8 and 16% following 2 and 6WK and whole body fat oxidation increased by 66% during a 60 min cycle at ~65% of pre-training VO_2peak following 2WK. Markers of skeletal muscle mitochondrial volume (citrate synthase, β-HAD, malate-aspartate aminotransferase and CPTI activities, and COX4 content) increased by 19-31% following 2WK and 39-64% following 6WK. Training also increased the total muscle $FABP_{pm}$ content by 48% and FAT/CD36 content by 10% following 6WK. Sarcolemmal $FABP_{pm}$ content increased by 14 and 23% following 2 and 6WK, while sarcolemmal FAT/CD36 content was not changed. Mitochondrial $FABP_{pm}$ increased in concert with mitochondrial volume, while mitochondrial FAT/CD36 content increased by 30 and 51% above the increase in mitochondrial volume after 2 and 6WK. This is the first study to demonstrate that exercise training increased human skeletal muscle sarcolemmal and mitochondrial membrane fatty acid transport protein contents. These results suggest that the increased skeletal muscle fatty acid oxidation during exercise following training was related to the increased capacity to transport fatty acids across the muscle and mitochondrial membranes. Supported by NSERC, Canada and CIHR.

19.34

THE EFFECT OF SHORT TERM TRAINING ON VASCULAR ENDOTHELIAL GROWTH FACTOR EXPRESSIONS IN RED AND WHITE GASTROCNEMIUS MUSCLES

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Adult Wistar rats (weighted 229.33 ± 2.76 g) were randomly assigned to control, and exercise groups (n=6/each). The exercise group ran with the speed of 20-25 m/min, duration of 100 min and 10° inclination for three consecutive days following the 10-day adaptation period compose of light exercise protocol on a motorized treadmill. The control group was stayed in the treadmill without running at the same duration with exercise group. The red and white gastrocnemius muscles were collected separately under anesthesia from the exercise group following the exercise and from controls. The mRNA expression of VEGF was evaluated by RT-PCR and agarose gel electrophoresis. The products of the specific primers were two isoforms of VEGF, VEGF164 and 188. All experiments were conducted under the guidelines on the APS "Guiding Principals in the care and Use of Animals" and were in conformation with the Declaration of Helsinki. The Ethics Committee of Ankara University also approved the experimental protocol. Student t tests were used to evaluate the differences between the groups. According to the results, the white gastrocnemius showed increases in both VEGF isoforms with exercise vs. the control group ($p<0.05$/each). Only VEGF164 was higher in the exercise group in the red gastrocnemius ($p<0.05$). In conclusion, short term training causes different effects on VEGF in different types of skeletal muscle fibers. This difference might be related to the oxidative capacity of the white fibers.

19.35

VOLUNTARY WHEEL RUNNING ATTENUATES CANCER CACHEXIA

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Cancer cachexia is characterized by significant decreases in skeletal muscle mass and a slow-to-fast shift in myosin heavy chain (MHC) isoform expression. Physical activity causes increases in both muscle mass and slow MHC isoform expression. As such, physical activity may attenuate cancer cachexia. Resistance activity has been shown to reduce tumor-induced muscle atrophy, but the effects of running activity on cancer cachexia are unknown. To determine the effect of running activity on muscle mass and MHC isoform expression during cancer, mice were injected with Lewis Lung carcinoma cells and were divided randomly into groups with access to running wheels (Exercise = EX) and groups without wheel access (No exercise = NE). The mice in the EX groups ran an average of 4.5 km/day for 21 days. Upon sacrifice, hindlimb muscle mass was measured and MHC isoform content was determined by 1-D SDS-PAGE. In NE mice, cancer was shown to cause a 21% decrease in soleus mass and a 14% decrease in gastrocnemius mass as well as a significant slow-to-fast MHC isoform shift (-9.5% type I MHC, -8.5% type IIa MHC, +19% type IIb MHC) in the soleus muscle. The addition of voluntary wheel running in tumor-bearing animals attenuated these changes in muscle mass and MHC isoform expression, such that there were no significant differences in either muscle mass or MHC content between groups. These results suggest that running activity may be an effective therapeutic strategy for cancer cachexia.

19.36

MYOSTATIN KNOCKOUT MICE RESPOND NORMALLY TO ENDURANCE TRAINING BUT HAVE LOWER EXERCISE CAPACITY

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A recent study reported that triceps of trained $Mstn^{-/-}$ mice, not $Mstn^{+/+}$ mice, weighed less than sedentary $Mstn^{-/-}$ mice. The reason(s) for this difference was not explained but could provide a unique insight into the role of myostatin in maintaining muscle mass. For this reason, the present study sought to explore potential mechanisms of muscle weight between sedentary and trained $Mstn^{-/-}$ mice. Surprisingly, in the present study; contrary to previous observations, muscle weights declined when comparing trained to sedentary for both $Mstn^{-/-}$ and $Mstn^{+/+}$ mice. $Mstn^{-/-}$ and $Mstn^{+/+}$trained muscle exhibited a more oxidative profile. No muscle damage was observed in response to training in either genotype. Similar to previous reports, $Mstn^{-/-}$ muscle contained cytoplasmic lesions; however the frequency was the same in both trained and sedentary $Mstn^{-/-}$ muscle. These results clearly show that $Mstn^{-/-}$ mice respond similarly to $Mstn^{+/+}$ mice to training, however, the reason for reduced muscle weights in trained $Mstn^{-/-}$ and $Mstn^{+/+}$ mice remains unknown. Recent reports show that dogs that are heterozygous for Mstn tend to be classified as better racers. We tested the running capacity of $Mstn^{-/-}$ mice and found them to have lower endurance capacity than $Mstn^{+/+}$ mice. Our data suggest that inhibition of myostatin function may result in increased force at the expense of endurance. This work was supported by the Intramural Research Program of NIDDK, NIH.

19.37

EVIDENCE FOR HIGH FAT DIET INDUCED PEROXISOMAL ACTIVITY IN SKELETAL MUSCLE FROM LOW AND HIGH CAPACITY ENDURANCE RUNNING RATS

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Background: A high fat diet (HFD) induces obesity and skeletal muscle (SKM) insulin resistance (IR). Endurance exercise training (EET) improves fatty acid oxidation (FAO) and protects against obesity/IR yet findings are understood only in the context of mitochondrial (MITO) adaptations. Data from liver and heart demonstrate that peroxisomes (PER) are also capable of FAO although a role for PER in SKM MITO-FAO is relatively unknown. We reported that rats bred for a high (HCR) vs. low (LCR) capacity to run are protected against HFD induced fat gain and IR. A role for PER in conferring this protection is unknown. Purpose: To measure the potential for SKM PER induction of FAO in response to HFD in HCR vs. LCR rats. Methods: LCR and HCR rats were fed either a HFD (50%) or chow diet (CD) for 12 wk. PER (14C-lignocerate) and MITO (14C-palmitate) FAO rates were measured in mixed gastrocnemius (MG) homogenates. PER related protein marker contents were also determined. Results: On CD, MG from HCR had higher MITO FAO, yet similar PER FAO rates vs. LCR rats. When fed a HFD, both strains significantly increased ($P<0.05$) PER and MITO FAO and PMP70 (PER membrane marker) protein content. PEX19 (PER biogenesis marker) was increased ($P<0.05$) in LCR rats only. Conclusions: Similar to MITO changes, SKM PER induction appears to be an adaptive response to HFD. However, it was insufficient to prevent fat gain and IR in LCR rats. Supported by NIH DK061314 and RR-17718.

19.38 Withdrawn.

19.39

HIF-1 SPECIFIC PROLYL HYDROXYLASES IN ELITE ATHLETES

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The hypoxia sensitive transcription factor HIF-1 has been suggested to be involved in skeletal muscle adaptation to endurance-type exercise training. HIF-1 protein levels are regulated by hydroxylation of critical proline residues and subsequent protein degradation of the alpha subunit. Three prolyl hydroxylation domain-containing proteins (PHD1-3) have been identified in mammalian cells, PHD2 appears to be the predominant form that regulates HIF-1alpha protein stability in vivo1. HIF-1 is stabilised in response to an acute bout of exercise in sedentary individuals2 but there is debate regarding the activity of the HIF-1 system in response to long term training. Skeletal muscle biopsies were obtained from the vastus lateralis muscle at rest from 12 males with high oxidative capacity and 9 normally trained male controls. PHD2 mRNA displayed the highest expression levels of the three forms in human skeletal muscle, regardless of training status. Furthermore, PHD2 and 3 mRNA levels were both higher in elite athletes compared to the control individuals and PHD2 protein levels were significantly higher in the elite group. Conclusion: The HIF-1 regulating prolyl hydroxylase PHD2 was significantly higher in elite athletes, which may explain an attenuated HIF-1 activity in response to long term endurance training.

20.0: COMPARATIVE PHYSIOLOGY

20.1

MUSCLE FIBER TYPES IN GHOST CRABS: IMPLICATIONS FOR RUNNING PERFORMANCE

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Ghost crabs are among the most athletic invertebrates, capable of sprinting performances that reach maximal speeds of 1-2 m/s. Previous studies of these animals revealed striking similarities to mammalian runners in terms of aerobic scope, stride frequency, and gait. In the current study, we identified muscle fiber types present in crab leg muscles in relation to their likely roles of powering locomotion. In the broadest terms, the fibers restricted to the proximal and distal regions of the leg extensors and flexors are aerobic with long sarcomeres, while the fibers in the mid-region of the muscles have short sarcomeres and lack aerobic capacity. This pattern is suggestive of a two-geared system, where the proximal and distal fibers serve slow sustained activity, and the mid-region fibers power explosive sprints. We also identified several different myofibrillar protein isoforms in these fibers, including alternate forms of MHC, troponin T, and troponin I. The specific expression of these isoforms is correlated not only with fiber type, but also with animal size, which varies by more than 250-fold. Since stride frequency is correlated with animal size, differential expression of alternate myofibrillar isoforms may provide a mechanism to fine-tune the contractile capabilities of the muscles as the animals grow. These patterns may ultimately help us understand how subtle shifts in myofibrillar gene expression can lead to significant changes in whole animal performance.

20.2

MALIGNANT HYPERTHERMIA IN KANSAS CITY 1965-1985

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Malignant Hyperthermia (MH) is a rare, life-threatening condition most often triggered by exposure to inhaled volatile anesthetic agents or the depolarizing muscle relaxant succinylcholine during surgery. In susceptible individuals, these drugs may induce a myogenic hypermetabolic state with increased skeletal muscle oxidative metabolism, resulting in hypoxia, hypercarbia, acidosis, and hyperthermia. The authors surveyed hospitals in the Kansas City area to obtain information on MH cases between 1965 and 1985. A total of 2,038,200 anesthetics were performed with 38 documented episodes (1:53,636). Twelve anesthetics were administered to known MH susceptible patients with no triggering events (patients were pretreated with dantrium and/or known triggering agents were avoided). Of the 38 MH cases, 87% received succinylcholine which is considered the most potent triggering drug. An inhalation anesthetic agent (halothane, enflorane, isoforane) was used in 84% of the cases. Twenty seven patients had MH on their first exposure to anesthesia (77%). The remaining 7 (23%) had a total of 17 previous anesthetic without triggering. Four of thirtyeight episodes of MH resulted in death. All were in the pre-dantium era (1965-1980). None of the 25 episodes in the post-dantrium era resulted in death. Our data confirms that MH is most often triggered by succinycholine and inhaled volatile anesthetic agents.

20.3

INCIDENCE OF MALIGNANT HYPERTHERMIA IN GREATER KANSAS CITY 1996-2006

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Malignant Hyperthermia has been reported to occur at a rate of 1:50,000 during surgical procedures. 1 Malignant Hyperthermia (MH) occurred at a rate of 1:53,636 general anesthetics in the Greater Kansas City Area during the 1965-1985 time period. There were 38 MH cases in 35 patients.2 During the past ten years (1996-2006) the rate has decreased to 1:597,240 general anesthetics. That decrease is an 11.13 fold decrease which is very significant. There were only 2 cases of MH during the past 10 years. The decreased incidence of Malignant Hyperthermia in the Greater Kansas City Area has occurred after the introduction of Sevoflurane in 1992 as the anesthetic of choice (over 60% usage rate) in most surgical procedures. 119,448 general anesthetics were administered during 2006 in the 17 surgical suites surveyed. Total inhalation general anesthetics: 119, 448 x 10 yrs = 1,194,480. There were two cases of MH during the years 1996-2006. We extrapolated the 2006 number of potent inhalational anesthetics back 10 years which gives a total of 1,194, 448 anesthetics. The incidence of MH is 1:597, 240. 72061 Sevoflurane anesthetics were administered accounting for 60 per cent of the general anesthetics. All other potent inhalation anesthetics totaled 47,387 accounting for the remaining 40 per cent. 19 percent of each group received succinylcholine. A MedLine search of the literature on MH cases with Sevoflurane and found 29 reported cases of MH during sevoflurane anesthesia. In all of these cases succinylcholine was used as the muscle relaxant. All of these MH cases were treated with Dantrolene and the patients survived. Unfortunately, Steven Nook and Stephanie Kulebea did not survive.

20.4

COMPARISON OF MAXIMAL AEROBIC SPEED AND PHYSIOLOGICAL TRANSITION THRESHOLDS ASSESSED IN LABORATORY AND FIELD CONDITIONS IN ENDURANCE RUNNERS

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The aim of this study was to relate physiological variables obtained during an incremental load test (IT) performed in laboratory and field. Ten endurance runners (28.3±6.8years and 10.7±3.1%fat) realized an IT on a treadmill starting at $12km.h^{-1}$ (1% inclination), with increments of $1km.h^{-1}$at each 3min. The transition thresholds (LT) were identified: with $3.5mmol.L^{-1}$(v3,5) and Dmax (vDmax) (CHENG et al., 1992). On the treadmill the maximum oxygen uptake (VO_2max) and the maximum aerobic speed (MAS) were determined according to Billat et al. (1996). The IT on track started at $8km.h^{-1}$ with increments of $1km.h^{-1}$ at each 2min. The VO_2max was predicted (VO_2max_{LB}) by Léger-Boucher equation (1980) and MAS (MAS_{LB}) calculated using Kuipers et al. (1985). The heart rate deflection point velocity (vKara) was identified according to Kara et al. (1996). The $VO_2max=71.4±6.3mL.kg^{-1}.min^{-1}$ was higher than $VO_2max_{LB}=65.54±2.31mL.kg^{-1}.min^{-1}$ (r =-0.51; ns), although similar values of $MAS=18.4±0.7km.h^{-1}$ and $MAS_{LB}=18.6±0.7$ $km.h^{-1}$ were found ($r=0.64$, $p=0.04$). There were no significant differences between the LT, in either absolute (v3,5=14.9±0.7km.h^{-1}, vDmax=15.3±0.6km.h^{-1} and vKara=15.1±1.8km.h^{-1}) or %MAS (v3,5=81.2±5.6%, vDmax=83.0±3.2%, vKara=81.0±8.6%). A significant correlation was found only between the %MAS at v3,5 and vDmax ($r=0.81$). Finally, despite the Léger-Boucher's IT may underestimate the VO_2max of endurance runners it seems to be a valid alternative to estimate LT and MAS.

20.5

CARDIAC FUNCTION DURING EXERCISE AND TEMPERATRUE CHANGE: MATCHING METABOLIC RATES TO SEPARATE INCREASED OXYGEN CONCUMPTION VS PHYSICAL AFFECTS USING A POIKILOTHERMIC MODEL

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The ability of an animal to couple metabolic demand to cardio-respiratory adjustments determines the aerobic scope which the animal can attain. Increased metabolic demands (oxygen uptake) resulting from exercise are met through standard adjustments in cardiac, circulatory, and ventilation functions, along with a number of others. However, at the onset of exercise cardiac and ventilatory parameters have been show to increase before an increase in metabolic demand is observed. Thus the physical act of muscle contractions modulates cardio-respiratory responses prior to increased tissue demands. In the poikilothermic shrimp (Palaemonetes pugio) metabolic demand can be experimentally manipulated using various exercise and temperature regimes allowing one to functionally separate the physical affects of exercise from increased metabolic demand. Animals were exercised at various levels using standard walking and swimming protocols during which time metabolic rate, heart rate, stroke volume and cardiac output was

monitored. Metabolic rates attained during exercise were then matched using various water temperatures where the same parameters and patterns were monitored. Step wise increases in heart rate during increasing exercise have been reported in other crustacean but this pattern was not observed in our experiments. Initiation of walking showed only a minor affect on cardiac parameters when compared to metabolically matched groups. Swimming (tail flexion) was preceded by rapid and significant changes in cardiac parameters. It would appear that as abdominal muscles contract large volumes of blood are mobilized and returned to the heart resulting in increased stroke volume and cardiac output before metabolic demand increases.

20.6

SINGLE MUSCLE FIBER CONTRACTILE FUNCTION OF THE BLACK BEAR

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The purpose of this study was to assess the single muscle fiber contractile properties of the black bear during different loading states (hibernation vs. ambulation) as well as compare MHC I and IIa contractile properties to that previously reported in humans. Following capture and anesthetization, biopsies were obtained from a cross section of bears either during late hibernation (T1) (n=14) or late spring (T2) after reambulation (N=7). Single muscle fibers (MHC I=314, MHC IIa=107) were isolated and studied for diameter, peak tension (Po), shortening velocity (Vo), and power. Data from the two loading states indicate that specific tension (Po/CSA) of MHC I fibers of the bear was significantly ($p<0.05$) decreased (22%) at T2 with no other significant differences in the contractile properties of MHC I or MHC IIa fibers. This stands in contrast to human studies examining the effect of altered loading states. MHC I peak power (PP) and normalized power (NP) and MHC IIa diameter, Vo, PP and NP were all higher in the bear compared to what we have reported in humans. The most noticeable difference occurred in peak power (μN•FL/s) of MHC IIa fibers (133.1 ± 14.4) which was 46% higher than any human normative value we have reported (71.3 ± 17.7). This data highlights the need for future research to confirm the lack of response to altered loading noted here as well as the mechanisms regulating muscle mass and function. Supported by grants from NIH AG18409 & NASA NNJ06HF59G.

20.7

APLASTICITY OF SKELETAL MUSCLE IN VARANUS EXANTHEMATICUS FOLLOWING COMPENSATORY OVERLOAD

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Previous studies suggest that skeletal muscle of Savannah monitor lizards (V. exanthematicus) is limited in its capacity to acclimatize to chronic physiological stress. We utilized a compensatory overload model to determine whether skeletal muscle of V. exanthematicus exhibits plasticity in response to chronic loading. We surgically ablated peroneus longus and brevis from 9 sub-adult V. exanthematicus. Following recovery and eight weeks of normal activity, we euthanized these lizards and excised the gastrocnemius for analysis of myosin heavy chain (MyHC) gene/protein expression, cross-sectional area (CSA), and wet mass. These values were compared against those obtained in gastrocnemius excised from 7 sham lizards. MyHC gene/protein expression, CSA, and wet mass did not differ between the two groups. This finding is in marked contrast to results of mammalian studies demonstrating pronounced hypertrophy and associated changes in MyHC expression patterns following surgical induction of compensatory overload. Absence of a similar phenotypic response in V. exanthematicus suggests a limitation to skeletal muscle plasticity in this species. Supported by NSF grant IOB 0445680 to JWH.

21.0: OXIDANT/ANTIOXIDANT EFFECTS

21.1

OXIDANT/ANTIOXIDANT AND METABOLIC RESPONSE IN MICE DURING A LONG DURATION SWIM

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Justification: There are a few researches about the oxidant/antioxidant response in different tissues during long swimming. Methods: 30 untrained female BalbC mice, adapted to swimming (flotation) previously, were divided into 5 groups: 0, 2, 4, 6, and 8 hours of swimming. TBARS, antioxidant capacity (AOC), and the activities of GPx, SOD and CAT were determined in blood, heart, muscle, liver and kidney. Metabolic and hematological parameters were determined in blood. Results: It was observed S-form of TBARS, CK, LDH and urea response in serum, muscle and heart during swimming. Different response of TBARS concentration was observed in liver and kidney, decrease and increase respectively, reaching the extreme level in 4 hours of swimming. Whereas non-enzymatic AOC diminished at 4 hours in muscle and heart, but increased in liver and kidney. Opposite effects occurred in each of those tissues with respect to antioxidant enzymes. At six and eight hours non-enzymatic AOC increased in muscle and heart and liver. Conclusions: In the 4 first hours of swimming the elimination of waste products, including TBARS, outdid their production and was decreased non-enzymatic AOC in muscle and heart. There were signs of a mobilization of non-enzymatic antioxidants towards the muscle tissue during the last four hours. It can be assumed that the kidney is the principal organ for TBARS eliminating. (1) Pajovic SB, Peji S at all. Physiol Res 2006;55:453; (2) Leeuwenburgh C, Ji LL. J Nutr 1998;128:2420.

21.2

EFFECTS OF ANTIOXIDANT SUPPLEMENTATION AND EXERCISE TRAINING ON SKELETAL MUSCLE ANTIOXIDANT ENZYMES AND MITOCHONDRIAL BIOGENESIS

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We investigated the role of redox regulation on changes in skeletal muscle following endurance exercise training. Male Wistar rats (n=48) were divided into sedentary control (SC), sedentary + antioxidant (SA), exercise (E) and exercise + antioxidant (EA) groups. The antioxidant groups were supplemented with Vitamin E (1000 IU/kg diet) and α-lipoic acid (1.6 g/kg diet) for 14 wk. Exercising animals were treadmill trained (90 min/d, 4 d/wk at 70% VO_2max) during this time. Red gastrocnemius and vastus muscles were excised 48 h after the final training bout. Antioxidant enzymes (xanthine oxidase, XO; manganese superoxide dismutase, Mn-SOD; glutathione peroxidase, GPX) and markers of mitochondrial biogenesis (PGC-1α; citrate synthase) were analyzed. PGC-1α mRNA was similar in SC and E, but was significantly ($p<0.05$) lower in EA (–0.3×) compared with E. There were significant ($p<0.05$) antioxidant × exercise interaction effects for all antioxidant enzymes. XO activity was lower in SA (–0.5×) and EA (–0.4×) compared with SC. Mn-SOD and total SOD activity was higher in SC compared to all other groups. GPX activity was lower in SA (–0.4×) than SC, and higher in EA (1.4×) compared with SA. Citrate synthase and Mn-SOD mRNA expression was similar between the groups. Antioxidants may reduce the beneficial effects of exercise on antioxidant enzyme activity and mitochondrial regulation in skeletal muscle. Funding source: UQ Graduate School Research Travel Grant.

21.3

ANTIOXIDANT SUPPLEMENTATION ENHANCES MUSCLE RECOVERY FROM CONTUSION INJURY IN RATS

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Grape seed extract, GSE, contains free radical scavenging agents, proanthocyanidins, which inhibit oxidative tissue damage. We investigated the effect of Oxiprovin (GSE supplement) on skeletal muscle recovery following contusion injury in rats. Rats were handled according to APS Guiding Principles for the Care and Use of Animals. 40 Wistar rats were divided into 2 groups, orally gavaged with GSE (20 mg/kg/d) or placebo (P, saline 1 ml/kg/d) starting 2 weeks prior to injury. 32 rats (Injured) were anaesthetised and injured non-invasively on one gastrocnemius using 200g dropped from 50cm. Controls (C, n=8) were sham-prepared. Muscle was harvested at 4 hr, 3, 7 and 14 days. Fixed, paraffin-embedded samples were sectioned and stained using 3 satellite cell (SC) markers (CD34, CD56 and Pax-7) and foetal myosin heavy chain (MHCf) (for regenerating fibers). GSE-Injured had significantly more CD56+ SC in the border zone soon after injury (GSE-C: 0.025 ±0.006 vs GSE-Injured 4 hr post: 0.233 ±0.035 SC/myofiber, $p<0.001$). Increases were not seen in P-Injured until day 3 (0.101 ±0.006 SC/myofiber, $p<0.001$). MHCf positive fibres were significantly higher in GSE-Injured by day 3 (vs GSE-C or P-Injured day 3, $p<0.001$), but not until day 7 in P-Injured ($p<0.001$). Chronic GSE supplementation significantly increased satellite cell activation and mobilisation to the injury site early after injury and reduced the time to myofiber regeneration. Funding: Brenn-o-Kem; National Research Foundation.

21.4

OXIDATIVE STRESS AND ANTIOXIDANT MECHANISMS AT THE TRANSITION TO AN AEROBICALLY INTENSIVE LIFESTYLE IN HONEY BEES

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Behavioral development in adult honeybees involves a stereotypical transition from energetically-inexpensive hive work to energetically-expensive foraging behavior at approximately 3 weeks of age. Each day after this transition, a foraging bee (weighing 80 mg) will on average fly 10 km, contract its wing muscles 4,000,000 times, and reduce 60 ml of pure O_2 in its thorax (the body segment housing the flight muscles). Hence, the onset, intensity and duration of foraging behavior should have strong consequences for cellular oxidative stress and antioxidant mechanisms, especially in flight muscle, as well as functional senescence and longevity. In this study we used single-cohort colonies to experimentally manipulate the onset of foraging and compare markers of oxidative damage and antioxidant mechanisms among different tissues (head vs. thorax), age-matched behavioral groups (hive bees vs. foragers) and periods of the day (morning vs. afternoon), with the prediction that such markers are prevalent in high-intensity tissues, behaviors and day-time periods. Foragers upregulated Hsp70, catalase and total antioxidant capacity in their flight muscles over the course of a day, although these changes did not occur or were muted in forager head tissues and hive bee flight muscles and head tissues. The response disappeared with age, which may explain the impairment of flight muscle mitochondria (elevated H_2O_2 and reduced aconitase V_{max}). Supported by NIH FAR055033A and NSF IOS0725030.

21.5

WEEKLY HEAT THERAPY RESTORES GLUCOSE UPTAKE IN INSULIN-RESISTANT SKELETAL MUSCLE: ROLE OF HEAT SHOCK PROTEINS AND STRESS KINASES

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High fat diet (HFD)-induced insulin resistance is associated with glucose intolerance, impaired insulin signal transduction and reduced glucose transport in skeletal muscle. Weekly heat therapy has been shown to protect against HFD-induced insulin resistance. We hypothesize that the beneficial effect of heat therapy on insulin resistance is due primarily to improved glucose uptake and inhibition of multiple stress kinases in skeletal muscle. Male Wistar rats were fed a HFD (60% calories from fat) for 12 weeks, while controls received a chow diet (10% calories from fat). Half the HFD rats received lower-body heat treatment (HT, 41°C for 20 min) and half received a sham treatment (ST, 35ºC for 20 min) once per week. Insulin-stimulated glucose transport and Akt phosphorylation were reduced in soleus and extensor digitorum longus (EDL) muscles with HFD, but restored with HT. Activation of kinases implicated in insulin resistance such as JNK, GSK3-β and IKK-β, were increased with HFD and reduced with HT. Induction of HSP72 and HSP25, proteins previously shown to inhibit stress kinase activation, was significantly higher in EDL muscle compared to soleus. Inactivation of stress kinases was muscle specific, relative to the amount of HSP induction. Our results suggest induction of HSPs with heat therapy results in fast-twitch muscle taking on slow-twitch muscle characteristics as seen by greater HSP expression, improved insulin sensitivity and reduced stress kinase activation.

21.6

HIGH FAT DIET INFLUENCES CNS OXIDATIVE CAPACITY AND DECREASES STRIATAL DOPAMINE TURNOVER: IMPLICATIONS FOR DIABETES AND PARKINSON'S DISEASE

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Type 2 diabetes (T2D) is linked to neurodegenerative disorders, including Parkinson's disease (PD). Individuals with peripheral insulin resistance (IR) exhibit more severe PD symptoms, and many PD patients are glucose intolerant. Thus, lifestyle and diet could serve as predictors of disease progression and severity. IR and dopamine (DA) neuron degeneration are likely mediated by oxidative mechanisms, and oxidative stress is a possible link between these pathologies. Proteins involved in insulin signaling, such as insulin receptor, GLUT4 and insulin receptor substrate 2 (IRS2) exist in the basal ganglia, the brain region affected in PD. Insulin signaling in the CNS influences diverse processes ranging from neuronal survival to cellular metabolism. The purpose of this study was to determine the effect of diet on CNS metabolism. Rats received either a high fat (HF) diet (60% fat) or chow diet (10% fat) for 12 weeks. HF fed animals exhibited signs of IR in the basal ganglia, as inhibitory serine phosphorylation of IRS2 was observed in HF rats. Brain derived neurotrophic factor (BDNF), which promotes neuronal survival and differentiation, was decreased in the cortex of HF rats. In the striatum of HF rats, DA turnover was also decreased. Our results suggest that CNS metabolic deficits could be associated with T2D and PD. Increasing the oxidative capacity of the CNS through diet or exercise could decrease disease progression and severity.

21.7

UNCOUPLING PROTEIN-3 INVERSELY CORRELATES WITH ANAEROBIC THRESHOLD IN FIT, YOUNG MEN

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UCP3 is a mitochondrial protein found principally in skeletal muscle, and thought to reduce ROS production via respiratory uncoupling. We therefore examined the relationships between UCP3 content, O2peak, and the anaerobic threshold (AT). Eleven male subjects were recruited from the Oxford rowing crews. Each subject performed an incremental exercise test to determine peak oxygen uptake. AT was determined using the V-slope method. Percutaneous needle biopsies were taken from the vastus lateralis of each subject, and frozen in liquid N2. UCP3, citrate synthase (CS) and ATP-synthase (ATP-S) content were measured by western blotting. There was no relationship between UCP3 content in whole muscle and O2peak. There was a negative correlation between UCP3 content and AT ($r = -.63$, $P < .05$, see Figure). This relationship was also observed when UCP3 content had been normalised to CS ($r = -.64$, $P < .05$) and ATP-S ($r = -.66$, $P < .05$). Mitochondrial ROS production is highly dependent upon the protonmotive force. As UCP3KO mice display increased muscle ROS-production, it has been suggested that UCP3 may act as an antioxidant by dissipating the protonmotive force. We observed an inverse relationship between UCP3 and AT. Thus, UCP3 might reduce the efficiency of mitochondrial metabolism, forcing muscle cells to employ anaerobic pathways at lower workrates. Alternatively, as UCP3 is lower in trained individuals, the relationship observed may be secondary to intra-group variations in fitness.

22.0: CHO/LIPID METABOLISM

22.1

SUBSTRATE OXIDATION DURING 5H OF TREADMILL WALKING WITH INGESTION OF ^{13}C-LABELLED STARCH

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Subjects engaged in prolonged exercise at low workload are encouraged to ingest carbohydrate (CHO) along with water before and during exercise but there is currently few data on the contribution of ingested CHO to the energy yield in this situation. In this study, 7 healthy young men (26 [4] yo, VO_2max = 55 [6] mL.kg^{-1}.min^{-1}) ingested a pre-exercise meal (~800 kcal; 50% CHO) ~2h before a 5-h treadmill walk (5.1 km.h^{-1}, ~25 %VO_2max) with 5-min breaks every 30 min during which they ingested 30 g of CHO (along with water ad libitum and cheese). The CHO were ingested in the form of starch (pasta) intrinsically labelled with ^{13}C and the contribution of substrate oxidation to the energy yield (%En) was computed using indirect calorimetry corrected for urea excretion combined with measurements of expired $^{13}CO_2$. The %En from protein oxidation was 8-9%. Over the 5-h period, the contribution of fat oxidation decreased from 40 (12) to 23 (16) %En while that of CHO (52 [12] to 69 [17] %En) and exogenous CHO oxidation (29 [5] to 52 [2] %En) increased (peak oxidation rate: 0.64 g.min^{-1}), with a progressive reduction in endogenous CHO oxidation from 23 (9)% to a low of 9 (8) %En at min 210. These results show that, in contrast to what is observed in fasted subjects without CHO ingestion during exercise (Romijn et al., J Appl Physiol 2000 88(5):1707), exogenous CHO supply a very large %En when ingested before and at regular interval during prolonged exercise. Supported by NSERC.

22.2

EVIDENCE FOR THE MITOCHONDRIAL LACTATE OXIDATION COMPLEX IN RAT NEURONS: CRUCIAL COMPONENT FOR A BRAIN LACTATE SHUTTLE

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To evaluate components of the hypothesis of an Intracellular Lactate Shuttle (ILS) in neurons we attempted to determine if monocarboxylate (lactate transporter) isoforms (MCT1 and -2) and lactate dehydrogenase LDH are coexpressed in neuronal mitochondria of rat brains. Immunohistochemical analyses of rat brain cross-sections showed MCT1, MCT2, and LDH to colocalize with the mitochondrial inner membrane marker cytochrome oxidase (COX) in neurons of cortex, hippocampus, and thalamus. Immunoblotting after immunoprecipitation (IP) of mitochondria from brain homogenates supported the histochemical observations by demonstrating that COX coprecipitated MCT1, MCT2, and LDH. As well, using immunohistochemistry and immunocoprecipitation techniques on primary cultures from rat cortex and hippocampus we demonstrated that MCT2 and LDH are coexpressed in mitochondria of cultured neurons. These findings can be interpreted to mean that as in skeletal muscle, neurons contain a mitochondrial lactate oxidation complex (mLOC) that has the potential to facilitate both intracellular and cell-cell lactate shuttles in brain.

22.3

CAN THE ADDITION OF L-ARGININE OR L-GLUTAMINE TO EXERCISE ENERGY-HYDRATION BEVERAGES FACILITATE GLUCOSE AND FLUID DELIVERY?

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Adding L-arginine or L-glutamine to glucose-electrolyte solutions may increase absorption. To assess practical utility, we asked if L-arginine and L-glutamine could enhance glucose and fluid delivery without undue exertion-gastrointestinal distress during exercise. Eight cyclists rode 150 min at 50% of peak power on five occasions while ingesting solutions containing 13C-enriched glucose (266 mM), sodium citrate ([Na+] 60 mM) and either 4.25 mM L-arginine or 45 mM L-glutamine; controls were 2% milk protein, glucose only, or no glucose. L-arginine caused a small increase in exogenous glucose-oxidation rate of 10.9% (90% confidence limits: ±8.5%) and a small decrease in endogenous-fat oxidation of 11.5% (±9.2%), relative to glucose only. Relative to no glucose, reductions of 1-3% in red blood-cell volume, and 2-6 mM plasma sodium concentrations occurred with all other solutions, but there was no clear effect of treatment. Relative to no glucose, plasma glucose concentrations were highest in L-arginine and glucose only, while lactate concentrations decreased 0.20-0.25 mM with L-glutamine and L-arginine. Perceptions of stomach fullness, abdominal cramp, perceived exertion, and muscle tiredness increased (small-moderate effects) in L-glutamine and L-arginine compared with glucose only. While a small increase in glucose delivery is likely with L-arginine, benefits to energy provision maybe offset by a mild increase in gastrointestinal distress and perceived muscle fatigue. Σ

22.4

EVEN IN ATHLETES, EXERCISE DOES NOT INCREASE 24 H FAT OXIDATION

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Fat oxidation during exercise is enhanced by endurance training, but the effects of exercise training on 24 h fat oxidation have not been previously studied. We studied 8 endurance-trained individuals (29 ± 2 yrs, Mean ± SE) under sedentary (CON) and exercise (EX) conditions in a whole-room indirect calorimeter. Subjects participated in regular endurance training including competitive endurance events within the prior year. Aerobic capacity (VO2max) was measured during an incremental cycle ergometer test (F/M, N=5/3, 46.0±1.6/52.6±2.0 ml/kg/min). A diet designed to achieve energy balance was consumed for 3 days prior to each condition and on the calorimeter day (20% fat, 65% carb, 15% protein). On the calorimeter day, meals were served at 0900, 1330, 1730, and a snack was provided at 2015. Physical activity was controlled and did not differ, except on the EX day subjects performed 1 hr of stationary cycling at 55% of VO2max. As expected, 24h energy expenditure was significantly higher on the EX vs. CON day (2690±151 vs. 2295±94 kcal/day, P=0.001). However, 24h RQ did not differ significantly on the EX (0.9234 ± 0.0151) vs. CON day (0.9021 ± 0.0146, P=0.20). Thus, as in our previous studies in sedentary individuals, these results suggest that in endurance trained individuals, exercise does not increase 24 h fat oxidation under fed, energy balance conditions.

22.5

SKELETAL MUSCLE MITOCHONDRIAL OXIDATIVE CAPACITY AND METABOLIC RESPONSES TO A HIGH FAT DIET OR AGING IN RATS BRED FOR HIGH AND LOW AEROBIC CAPACITY

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Reduced aerobic capacity is associated with low mitochondrial oxidative capacity in skeletal muscle (MitoOx) and both are linked to metabolic dysfunction. We previously reported a novel model in which rats were artificially selected over several generations to produce high and low capacity runners (HCR and LCR) with contrasting intrinsic aerobic capacities. Herein we tested if skeletal muscle MitoOx (fat oxidation in isolated skeletal muscle mitochondria) is higher in the HCR than the LCR and determined if these phenotypes provided protection or susceptibility to high fat diet (HFD) or aging-induced insulin resistance and adiposity. On a normal chow diet, the HCR had a 5-fold higher rate of mitochondrial fat oxidation than the LCR. In response to the HFD, only the LCR significantly increased fat oxidation, but rates remained lower than the HFD fed HCR. Aging caused divergent responses but resulted in similar rates of mitochondrial fat oxidation in both groups. HCR rats were protected from both the HFD- and aging-induced doubling of adiposity and insulin resistance witnessed in LCR. The initial higher MitoOx capacities appear to protect (HCR) from HFD-induced metabolic dysfunction; however, this association was lost as both groups displayed similar MitoOx after aging. In conclusion, these results support a link between intrinsic aerobic capacity and MitoOx capacity in muscle and provide evidence that both factors are key determinants of metabolic health.

22.6

EVIDENCE FOR THE INVOLVEMENT OF CAMKKβ IN THE REGULATION OF GLUCOSE UPTAKE IN PERFUSED RAT MUSCLE

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Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) has been implicated in the regulation of fuel metabolism during muscle contraction. The purpose of this study was to determine if CaMKK is involved in the regulation of glucose uptake, lactate release, O_2 uptake, and force production during muscle contraction. Rat hindlimbs were perfused at rest (n=16), with 3mM caffeine (n=15), or during moderate intensity muscle contraction (n=14), and with or without 5μM STO-609, a CaMKK inhibitor. While western blot analysis of muscle homogenates confirmed the presence of both alpha and beta isoforms, CaMKKα activity was immeasurable. CaMKKβ activity was increased ($P<0.05$) 102% by caffeine treatment and 136% by muscle contraction and these increases were prevented by STO-609. Glucose uptake was increased ($P<0.05$) 103% with caffeine treatment and 130% during muscle contraction. STO-609 abolished ($P<0.05$) caffeine- and contraction-induced glucose uptake. Lactate release was increased ($P<0.05$) 50% during caffeine treatment and 134% during muscle contraction and was not affected by STO-609 treatment. O_2 uptake was increased ($P<0.05$) 53% during muscle contraction and was not affected by STO-609 treatment in any group. Initial force production

was not affected by STO-609 during muscle contraction. Tension development decreased by 65% after 10 minutes of stimulation and the rate of decrease was not affected by STO-609. These results provide evidence for the involvement of Ca^{2+}-dependent signaling in the regulation of glucose uptake without changes in O_2 uptake, and force production in contracting skeletal muscle.

22.7

NITRIC OXIDE AND ROS REGULATE SKELETAL MUSCLE GLUCOSE UPTAKE DURING CONTRACTION INDEPENDENT OF AMPK α2

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People with type 2 diabetes have reduced skeletal muscle glucose uptake in response to insulin, but not exercise. The mechanism(s) by which exercise/contraction regulate skeletal muscle glucose uptake (GU) are unclear but may involve nitric oxide (NO) and reactive oxygen species (ROS) signalling via AMP-activated protein kinase (AMPK). This study investigated whether AMPKα2 is required for ROS and NO mediated GU during contraction. 2-Deoxy-D-glucose (2-DG) uptake was examined during contraction of isolated EDL and soleus muscles from mice overexpressing a muscle specific AMPKα2 dominant negative transgene (AMPK DN) or wild type (WT) litter mates. During pre-incubation and contraction, muscles were treated with vehicle, a NOS inhibitor (L-NMMA) or a non-specific antioxidant (NAC). Contraction increased GU in EDL and soleus muscles of AMPK DN and WT mice to a similar extent (1.6-2.0-fold, P<0.05). In the EDL muscle, both L-NMMA and NAC attenuated the increase in GU during contraction by 50-60% (P<0.05) in AMPK DN and WT muscles. NAC prevented the increase in GU in soleus muscles of AMPK DN and WT (P>0.05 vs basal) but L-NMMA treatment had no effect. Peak force and rate of fatigue of both muscles and genotypes was not effected by any treatment (P>0.05). These results indicate that AMPKα2 is not essential for contraction stimulated GU and that both ROS and NO are involved in regulating contraction stimulated GU via an AMPK-independent mechanism.

22.8

THE EFFECTS OF ENDOGENOUS AND EXOGENOUS CARBOHYDRATE AVAILABILITY ON TRAINING-INDUCED OXIDATIVE ENZYME ADAPTATION OF HUMAN SKELETAL MUSCLE

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The aim of the present study was to examine the effects of training with reduced carbohydrate availability on skeletal muscle adaptations. Following ethical approval three groups of active males performed six weeks of intermittent running. The training protocol consisted of five 3 min bouts at 90% $\dot{V}O_{2max}$ separated by 3 min active recovery periods. Group 1 (n=8; LOW+CHO) and 2 (n=7; LOW) trained twice per day, two days per week and consumed a 6.4% carbohydrate or placebo solution, respectively, immediately before every second training session and at regular intervals throughout exercise. In contrast, Group 3 (n=8; NORM) trained once per day four days per week and consumed no form of beverage throughout training. Muscle biopsies were also obtained from the vastus lateralis and gastrocnemius muscles before and after training and assessed for succinate dehydrogenase (SDH) activity. Training induced similar significant improvements (P<0.05) in $\dot{V}O_{2max}$ (LOW+CHO 10%, LOW 10%, NORM 7%) in all groups. Training also resulted in significant increases (P<0.05) in SDH activity of both the gastrocnemius (LOW+CHO 34%, LOW 76%, NORM 50%) and vastus lateralis (LOW+CHO 16%, LOW 70%, NORM 43%). The largest increases were for subjects who trained in the LOW condition (P<0.05). These data suggest that intermittent training under conditions of reduced carbohydrate availability enhances the oxidative adaptations of skeletal muscle. The research was supported by GlaxoSmithKline.

22.9

DEVELOPMENTAL CHANGES OF MCTS IN THOROUGHBREDS

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The purpose of this study was to investigate the longitudinal changes of lactate metabolism and monocarboxylate transporters (MCTs) in Thoroughbreds. MCT1 is involved with taking up lactate into myocyte, whereas MCT4 is involved with extruding lactate. We previously suggested that MCT1 and MCT4 play key roles in sustaining high intensity exercise in Thoroughbreds. It has been reported that MCTs can be changed by training, but it is not known about developmental changes of MCTs. Six thoroughbred horses were used for the analysis. Middle gluteus muscles were obtained at the age of 2,6,12 and 24 months old. The average body weight at 24 months old reached approximately same value as adults. MCT1 protein content was significantly increased from 2 to 24 months old. On the other hand, MCT4 protein content was not changed through 2 to 24 months old. Citrate synthase (CS) activity was significantly increased from 6 to 24 months old investigated in a crosssectional manner, while Phosphofructokinase (PFK) activity was not altered. The percentage of LDH1 isozyme which is involved in lactate oxidation was increased from 2 to 24 months old. These results about the changes of lactate metabolism might reflect the changes of fiber type composition. In conclusion, the results show that Thoroughbreds would get oxidative capacity as they grow up, with keeping glycolytic capacity unchanged.

22.10

SUBCELLULAR LOCALIZATION OF MUSCLE GLYCOGEN – FIBER-TO-FIBER HETEROGENEITY AND EFFECT OF FASTING

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The role of glycogen in skeletal muscle function is most often evaluated by measures of whole muscle glycogen. However, transmission electron microscopy reveals that glycogen is located both (I) between the myofibrils (intermyofibrillar glycogen) and (II) inside the myofibrils (intramyofibrillar glycogen). Little is known about the functional role of these glycogen pools as well as the effect of fasting. Using EDL single fibers of normal fed (N) (n = 10) and 24 hrs fasted rats (F) (n = 9) we investigated the effect of fasting on the distribution of glycogen in these two distinct pools. Data is presented as medians (upper;lower quartiles). In spite of lower total glycogen volume fraction in F (0.28% (0.52;0.01)) compared with N (0.63% (0.78;0.54)) (p = 0.05) the two groups showed an equal relative distribution of glycogen with 75% (78;65) and 77% (85;59) (F and N, respectively) of the total glycogen volume located in the intermyofibrillar space. The amount of glycogen in the two populations was not related (r = 0.3, p = 0.25) indicating different mechanisms regulating the contents. In conclusion, the relative distribution of glycogen in the inter– and intramyofibrillar space was equal in muscle fibers from normal fed and 24 hrs fasted rats. However, there was a great heterogeneity between fibers emphasizing the importance of measuring glycogen content and distribution at the single fiber level.

22.11

ROLE OF LOCAL MUSCLE CONTRACTILE ACTIVITY IN THE EXERCISE-INDUCED INCREASE IN NR4A RECEPTORS MRNA EXPRESSION

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Exercise upregulates the expression of NR4A receptors which are involved in the regulation of fatty acids utilization genes in skeletal muscles. The purpose of this study was to elucidate the role of local muscle contractile activity and AMPK activation on exercise-induced increases in NR4As mRNA expression. Rats were subjected to an acute 3h low-intensity swimming (LIS) or 3h low-intensity treadmill running (LIR). LIS increased NR4A1 and NR4A3 mRNA in triceps but not in soleus muscles. Conversely, LIR increased NR4A1 and NR4A3 mRNA in soleus but not in triceps muscles. NR4As mRNA increased concomitantly with reduced post-exercise muscle glycogen, suggesting that gene expression of NR4As occur in muscles recruited during exercise. Furthermore, both NR4A1 and NR4A3 mRNA in epitrochlearis muscle were increased after 6h incubation with 0.5mM 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) which activates AMP-activated protein kinase (AMPK). These results suggest that 1) local muscle contractile activity is required for increasing expression of NR4A1 and NR4A3 mRNA following exercise and 2) exercise-induced increase in NR4A1 and NR4A3 mRNA is possibly through, at least in part, an AMPK activation. This research was supported by the Nakatomi Foundation (Tosu, Japan) and a Grant-in-Aid for Scientific Research (KAKENHI) (C) No. 18500518 from the Japan Society for the Promotion of Science.

22.12

HYPERGLYCEMIA DURING MAXIMAL EXERCISE OCCURS IN TRAINED, BUT IS PREVENTED IN UNTRAINED INDIVIDUALS BY THE DIRECT EFFECT OF INSULIN ON LIVER

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Objective: To determine whether insulin attenuates hyperglycemia during maximal exercise. Research Design and Methods: Healthy young people matched for, sex, age, and body composition, but either untrained (n=8), or endurance trained (n=8) were examined before and at the end of maximal graded treadmill exercise. This model allows for the extreme stimulation of hepatic glucose production. Blood samples were drawn at rest and maximal exercise for counterregulatory hormones, IL-6, insulin, c-peptide, glucose and lactate. The c-peptide/insulin ratio was used to reflect insulin's direct effect on the liver, via the portal vein. Results: Insulin resistance (HOMA-IR) was low, and similar between groups 2.2 ± 0.7 (untrained) and 2.1 ± 0.4 (trained). Exercise hyperglycemia however, only occurred in the trained individuals (p=0.01). Lactate concentrations increased similarly in both groups. Despite equivalent increases in drive for glucose production (similar counterregulatory hormone and IL-6 levels), there was significantly greater direct hepatic effects of insulin in the untrained compared to the trained group (c-peptide/insulin ratio: 29 ± 5 (untrained) versus 14 ± 2 (trained), p=0.01). Conclusions: Insulin still modulates glucose homeostasis during maximal exercise. While classic hyperglycemia occurs in the trained individuals, it was prevented in untrained individuals by the strong direct restraining effects of insulin on liver. Funding Support: John. B. Pierce Laboratory.

22.13

POST-GAME CYCLING DOES NOT ENHANCE BLOOD LACTATE REMOVAL IN COLLEGIATE HOCKEY PLAYERS

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The effectiveness of active recovery on blood lactate clearance in collegiate hockey players is unclear. We hypothesized that post-game submaximal cycling would: 1) expedite lactate removal and 2) attenuate blood lactate accumulation during the subsequent game. Eleven male division III college hockey players volunteered for testing. Subjects were randomly assigned to the post-game exercise group (Ex) during one weekend series and the non-exercise group (NonEx) during another weekend series. Blood lactate was similar for the Ex and NonEx groups pre-game and immediately after each period. Blood lactate was also similar for the Ex and NonEx groups at 10 minutes (2.7±0.2 vs. 3.1±0.4 mmol/L), 20 minutes (2.0±0.3 vs. 2.3±0.3 mmol/L), and 30 minutes (1.9±0.4 vs. 1.8±0.2 mmol/L) post-game. Heart rate was similar for each group following each period and 10 minutes post-game, but was significantly higher 20 and 30 minutes post-game for the Ex group due to cycling (p<0.01). Both groups had similar ratings of perceived exertion, number of shifts, and shift duration for each period. Finally, post-game exercise did not alter blood lactate accumulation in the subsequent game. In conclusion, submaximal cycling after a collegiate hockey game does not enhance blood lactate removal and does not appear to affect blood lactate levels during the subsequent game. This project was funded by Portage Sports Medicine Institute.

22.14

CERAMIDE CONTENT IN HUMAN MUSCLE FIBERS

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Objective: To investigate the influence of muscle glycogen and exhaustive one-leg exercise on total muscle and individual fiber type ceramide content in man. Methods: Ten healthy males (26.4±0.9 yrs, BMI 24.4±0.7 kg m-2 & VO2max 57±2 ml-1 O2 min kg-1) participated in the study that adhered to the Helsinki declaration principles. The day before one-leg was glycogen depleted (DL) by exhaustive intermittent exercise followed by a low CHO diet. Next day in the overnight fasted condition muscle biopsies were excised from vastus lateralis before and after exhaustive one-leg exercise in both DL and control leg (CL). Muscle glycogen was analyzed conventionally, total muscle ceramide by a 2D quantitative lipidomic approach and fiber type

ceramide content by fluorescence confocal microscopy (N=4). Results: Muscle glycogen was decreased (P<0.05) 50±6 % in DL vs. CL. After exhaustive exercise muscle glycogen was similar in CL and DL 125±24 mmol kg-1. Total muscle ceramide 58±1 pmol mg-1 was not influenced by glycogen or exercise. Muscle fiber type ceramide content was always higher (P<0.05) in type I than type II (75±7%). Before exercise fiber type ceramide content (arb. Values) was 61% higher (P<0.05) in DL than CL but at exhaustion values were similar Conclusion: Ceramide content is higher in type I than type II muscle fibers. The effects of muscle glycogen and exhaustive exercise on ceramide content are less clear and need further investigation. Supported by: Frk. P. A. Brandts Legat.

22.15

EVIDENCE FOR METABOLIC INFLEXIBILITY IN RESPONSE TO DIETARY LIPID WITH OBESITY

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Excess dietary lipid reportedly increases the expression of genes linked with lipid oxidation in skeletal muscle as well as whole body lipid oxidation in lean humans. We hypothesized that, in contrast to lean subjects, obese are metabolically inflexible when faced with increased dietary lipid, which is evident in terms of the regulation of genes related to lipid oxidation in skeletal muscle. Caucasian men and women (ages 18-27 y) with 7 classified as lean (BMI = 22.4 ± 0.7 kg/m^2) and 7 as obese (BMI = 41.1 ± 1.8 kg/m^2), underwent 5 consecutive days of a high-fat, eucaloric diet (60-65% of energy as fat, HFD). Fasted, Pre- and Post-HFD vastus lateralis biopsies were obtained and analyzed for gene expression using real-time PCR. Repeated measures analysis revealed body size interactions when comparing pre- and post- HFD mRNA content of PDK-4, PGC-1α, and PPAR-α ($P < 0.05$). In the leans PDK4 increased by 5.7-fold following the HFD ($P < 0.05$); in contrast, there was a slight trend for a decrease (-45%) in the obese subjects ($P = 0.07$). Multivariate analysis of all genes studied indicated a body size interaction ($P < 0.05$), with increased mRNA content in the leans and decreased content in the obese (PDK4, CD36, citrate synthase, PPAR-α, PPAR-δ, and PGC-1α. These data indicate that the skeletal muscle of lean individuals responds to increased dietary lipid by upregulating expression of genes involved in lipid metabolism, whereas obese individuals do not. [NIH DK56112].

22.16

ESTROGEN RECEPTOR ALPHA: A POTENTIAL PLAYER IN GLUCOSE REGULATION

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Clinical data suggest that estrogen plays a role in glucose regulation. For example, pregnant women (with high levels of estrogen) and postmenopausal women (with low levels of estrogen) are at an increased risk for diabetes. Despite clinical evidence, the underlying mechanisms for estrogen regulation of glucose homeostasis are not well established. Glucose transporter 4 (GLUT4) is critical for glucose uptake into skeletal muscle, and previous studies suggest that estrogen can modulate GLUT4 expression and translocation. We hypothesize that estrogen regulation of GLUT4 in skeletal muscle occurs through modulation of estrogen receptor α (ERα). In this study, we ovariectomized (OVX) female Sprague Dawley rats and fed them a high fat diet (HFD, 60% of calories) for 6 weeks. OVX females on a HFD had significantly less GLUT4 protein in soleus skeletal muscle (p<0.01) compared with intact, chow-fed rats. GLUT4 levels were restored by treating the HFD rats for 3 days with PPT (10mg/kg s.c.), a selective ERα agonist (p=0.05). In addition, immunohistochemical analyses demonstrated that ERα localization in skeletal muscle varies with estrogen status, which could impact glucose regulation. Our results suggest that estrogen acts through ERα to maintain GLUT4 protein levels and can regulate ERα localization in skeletal muscle. ERα may function as a potential target for modulation of GLUT4 and prevention of insulin resistance in the presence of low estrogen levels.

22.17

DEHYDRATION ELEVATES MUSCLE TEMPERATURE DURING EXERCISE AND MUSCLE GLYCOGENOLYSIS

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This study determined if the elevation of body temperature that is characteristic of dehydration also increases temperature in the exercising muscle as well as rates of muscle glycogenolysis and plasma glucose uptake. Endurance-trained cyclists exercised for 120 min at 63±1% VO2max in a 34±1°C environment. Subjects drank no fluid (NF) in one trial and lost 4.0±0.3% of body weight and drank 2.3±0.2 L of flavored water (F) in the other trial and lost only 0.8±0.3% of body weight. After 120 min of exercise, NF vs. F displayed 0.9±0.1 °C elevations (p<0.05) in both vastus lateralis muscle and rectal temperatures. Total carbohydrate oxidation was increased 12% (i.e.; 24±4 μmol/kg/min; p<0.05) in NF vs. F during the 100-120 min period. However, plasma glucose uptake, determined from primed constant rate infusion of [6,6-2H2]glucose was not significantly elevated. Therefore, muscle glycogen oxidation, calculated as the difference between total carbohydrate oxidation and plasma glucose uptake, was significantly elevated during NF vs. F. In agreement with this observation, muscle glycogen concentration, determine via muscle biopsy, was significantly lower after 120 min during NF vs. F (i.e.; 70.7±7.8 vs. 82.6±6.6 mmol/kg; p<0.05). In summary, dehydration during exercise not only elevates core temperature but also muscle temperature and is associated with an increase in muscle glycogenolysis and total carbohydrate oxidation.

22.18

METABOLIC AND CARDIOVASCULAR RESPONSES TO THE INGESTION OF FRUCTOSE

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The consumption of fructose has increased considerably during the past several decades. While a deleterious role of excess fructose on metabolic and cardiovascular factors exists in a variety of animal species, this relationship in humans is equivocal. The purpose of this study was to assess metabolic and cardiovascular changes following the acute ingestion of a glucose-fructose beverage when compared to an isocaloric glucose beverage. Ten apparently healthy young (27±4 years) male subjects ingested either a glucose (Gluc; 100g/300ml) or a glucose-fructose (Gluc:Fruc; 45:55g/300ml) beverage. Forearm blood flow was measured pre and post-reactive hyperemia prior to and at 30-, 60- and 90-min post ingestion of each beverage. In addition, pulse-wave velocity was recorded prior to and at 45- and 75-min post ingestion. Blood was sampled pre- and every 15-min post-ingestion up to 90 min and assayed for glucose, lactate, fructose, total nitrate/nitrate, uric acid and blood fats (FFA/TG). There was a significant ($p<0.05$) increase in fructose, lactate and uric acid following the ingestion of the Gluc:Fruc beverage when compared to the Gluc beverage and a significant effect of beverage on the area under the blood-flow curve and heart rate responses. In conclusion, significantly different metabolic and cardiovascular responses were observed following the acute ingestion of a Gluc:Fruc beverage compared to an isocaloric Gluc beverage. Funding: Gatorade and S.U. Gerontology Center.

22.19

THE EFFECTS OF ORAL ACETATE SUPPLEMENTATION AFTER PROLONGED MODERATE INTENSITY ON ACETATE METABOLISM AND MUSCLE GLYCOGEN RESYNTHESIS IN HORSES

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We hypothesized that provision of an oral acetate solution with a typical grain and hay meal after glycogen-depleting exercise will result in a rapid appearance of acetate in blood, and rapid skeletal muscle uptake of acetate to be converted to acetyl-CoA (and acetylcarnitine), which will be metabolized to CO2 and water via the TCA cycle, generating ATP within the mitochondria and shuttling muscle glucose to glycogenesis. Gluteus medius biopsies and jugular venous blood was sampled from 9 exercise conditioned horses on 2 separate occasions, at rest and for 24 h following a competitive exercise test (CET). After the CETs horses were allowed water ad libitum and either: 1) 8 L of a hypertonic NaAcetate/acetic acid solution via nasogastric gavage followed by a typical hay/grain meal (NAA trial); or 2) a hay/grain meal alone (Control trial). The CET decreased muscle glycogen concentration by 21% and 17% in the NAA and Control trials, respectively. NAA resulted in a rapid and sustained increase in plasma [acetate], and increases in skeletal muscle [acetyl-CoA] and [acetylcarnitine], suggesting substantial tissue extraction of the supplemented acetate. NAA also resulted in an enhanced rate muscle glycogen resynthesis during the initial 4 h of the recovery period compared to Control, however by 24 h of recovery there was no differences in glycogen replenishent between trials. It is concluded that oral NaAcetate could be a potential alternative energy source in the horse.

22.20

FLUID AND ELECTROLYTE SUPPLEMENTATION AFTER PROLONGED MODERATE INTENSITY EXERCISE ENHANCES MUSCLE GLYCOGEN RESYNTHESIS IN STANDARDBRED HORSES

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We hypothesized that post-exercise rehydration using a hypotonic electrolyte solution will increase the rate of recovery of whole body hydration and that this is associated with increased muscle glycogen and electrolyte recovery in horses. Gluteus medius biopsies and jugular venous blood was sampled from 6 exercise conditioned Standardbreds on 2 separate occasions, at rest and for 24 h following a competitive exercise test (CET) designed to simulate the speed and endurance test of a 3-day event. After the CETs horses were given either water ad libitum (Control) or a hypotonic commercial electrolyte solution (Electrolyte) via nasogastric tube followed by a typical hay/grain meal, or a hay/grain meal alone. The CET resulted in decreased total body water and muscle glycogen concentration of 8.4 ± 0.3 L and 22.6 %, respectively, in the Control trial, and 8.2 ± 0.4 L and 21.9 % in the Electrolyte trial. Electrolyte resulted in an enhanced rate of muscle glycogen resynthesis and faster restoration of hydration (as evidenced by faster recovery of plasma [protein], maintenance of plasma osmolality and greater muscle intracellular fluid volume) during the recovery period compared to Control. There were no differences in muscle electrolyte contents between the 2 treatments. It is concluded that oral administration of a hypotonic electrolyte solution after prolonged moderate intensity exercise enhanced the rate of muscle glycogen resynthesis during the recovery period compared to Control. It is speculated that post-exercise dehydration may be one key contributor to the slow muscle glycogen replenishment in horses.

22.21

REDUCING DIETARY FAT FROM MEALS AFTER EXERCISE ENHANCES MUSCLE GLYCOGEN RESYNTHESIS IN UNFIT ADULTS

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The primary aim of this study was to determine the effect of low-fat/low-calorie meals on glycogen resynthesis after exercise in unfit adults. 5 untrained men exercised at moderate intensity (~65% VO_2peak) to expend 14kcal/kg fat free mass (~700kcal) on 2 separate occasions. The 2 trials differed only by the dietary fat content of the meals ingested after exercise: 1) a high fat content (~100g) to maintain energy balance [EB], and 2) a low fat content (~20g) to induce an energy deficit [ED]. Subjects ingested identical amounts of carbohydrate (~450g) and protein (~70g) during both trials. Despite consuming the same carbohydrate content, skeletal muscle glycogen concentration was greater during ED compared with EB (602±51 vs 428±32 mmol/kg dry wt, P<0.05). Importantly, overnight plasma glucose concentration was lower during ED than EB (area under curve [AUC]: 49.3±1.0 vs 55.6±1.5 mM*h, P<0.05) despite similar plasma insulin concentrations. This suggests that ED may have acutely increased post-absorptive glucose disposal during the overnight hours, which may have contributed to the augmented glycogen resynthesis. Despite the difference in glycogen concentration the next morning, insulin sensitivity (measured via IVGTT) was not significantly different between ED and EB. In conclusion, these data suggest that in unfit individuals dietary fat content and/or energy availability may help regulate post-exercise glycogen resynthesis independently of dietary carbohydrate content.

22.22

INSULIN SENSITIVITY INCREASES IN LEAN BUT NOT OBESE YOUNG WOMEN AFTER 7 WEEKS OF PROGRESSIVE RESISTANCE TRAINING

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Little information exists on the benefit of resistance exercise on insulin sensitivity in women. We examined the effect of body composition on insulin sensitivity response to acute resistance exercise (RE) and 7-weeks progressive resistance training (PRT) in sedentary women. Women were randomly assigned to lean (<26% BF), obese (>30% BF) PRT, or control groups. Experimental groups completed 7-weeks (3x/wk) PRT. Subjects received oral glucose tolerance tests before PRT, following acute RE, and after 7 weeks PRT. Body fat % (BF), android fat % (AF) and gynoid fat % (GF) were determined by dual-energy x-ray absorptiometry. A modified Composite-Insulin Sensitivity Index (C-ISI; Matsuda et al., 1999) estimated insulin sensitivity. C-ISI improved after 7 weeks PRT in the lean group (+77%, p=0.026) but not in obese (+35%) or control (+38%) groups. Acute RE did not affect C-ISI. In sedentary women, there was a significant inverse relationship between C-ISI v. BF and AF (r= -0.57, p=0.01), but not GF (r= -0.39). Acute RE and PRT blunted the differences making only total fat, regardless of location related to C-ISI. PRT did not affect fat distribution in any group, and reduced BF (p=0.006) only in the obese group. Increased BF in women attenuates C-ISI improvement to resistance training. Increased AF but not GF is inversely related to C-ISI in sedentary women. Acute RE and PRT reduce the influence of fat distribution on C-ISI. Funding: WSC Foundation.

22.23

METFORMIN TREATMENT DECREASES FAT UTILIZATION AFTER EXERCISE

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Exercise and the drug metformin are used to prevent/manage Type 2 diabetes. We recently showed that metformin treatment increases fat oxidation during exercise in healthy men and women. Because higher rates of fat oxidation in the resting state are associated with better insulin action, the purpose of this study was to assess the effect of metformin on post-exercise fat metabolism. Using a double-blind, counter-balanced, crossover design, 10 healthy, normal weight individuals (25.0 ± 1.1yr; 69.2 ± 3.3kg, VO_2peak = 47.6 ± 1.7ml/kg/min) received a standard clinical dose (2000 mg/day) of metformin or placebo for 5-7 days. After an overnight fast, participants cycled on an ergometer for 40 min. at workloads from 30-70% of peak work capacity (average 50%). Energy expenditure (EE) and rates of substrate oxidation were measured by indirect calorimetry every 10' for 50' after exercise. Compared with placebo, metformin treatment increased RER (0.73 ± 0.02 to 0.75 ± 0.03; $p < 0.03$) and slightly lowered the relative contribution of fat to EE (90 ± 17 to 83 ± 9%; $p < 0.03$) and total fat oxidation (0.12 ± 0.02 to 0.10 ± 0.02; $p < 0.01$). There was a significant inverse correlation between the rate of fat oxidation during exercise and post-exercise fat oxidation ($r = -0.68$; $p < 0.05$). Metformin treatment slightly lowered fat oxidation in the first hour after submaximal exercise. The reduced fat oxidation post-exercise may be related to higher fat oxidation during exercise. Supported by American Diabetes Association Grant 7-04-JF-10.

22.24

STRIDE LENGTH DOES NOT INFLUENCE SUBSTRATE OXIDATION DURING WALKING WITH ALTERED KINEMATICS IN OBESE WOMEN

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Deviations in stride length (SL) or frequency (SF) from the preferred walking pattern increase metabolic cost. There is little or no research on how metabolic cost or substrate oxidation is affected by altering walking kinematics in obese women. The purpose of this study was to investigate how decreasing SL (at a constant speed) affected fat oxidation during walking in obese women. Ten young, obese (BMI = 33.1 ± 4.2 $kg \cdot m^{-2}$) and ten control (BMI = 22.7 ± 0.9 $kg \cdot m^{-2}$) women walked at a self-selected pace on a treadmill while speed, SL, SF were recorded. Mean SL was then decreased 15% by keeping speed at the preferred mean and pacing SF with a metronome. Energy expenditure and substrate oxidation were assessed by indirect calorimetry. Condition means were compared using repeated measures ANOVA ($\alpha = 0.05$). There was a small but significant increase in metabolic cost when taking short, quick steps vs. preferred SL and SF (5.23 vs. 4.99 kcal/min, $p<0.01$) and the obese group had higher values than the controls ($p<0.01$). There was no significant change in either the percent energy derived from fat (56.73 vs. 61.00%, p=0.157) or the fat oxidation in grams (0.31 vs. 0.32 g, p=0.544). The 5% increase in metabolic cost with short, quick steps was not large enough to alter the balance between CHO and fat use. However, over the course of thousands of steps per day/month/year, altering walking kinematics could be useful for weight loss or maintenance in obese individuals.

22.25

ALTERATIONS IN LIPID METABOLISM AFTER ONE DAY OF OVEREATING ARE REVERSED BY A SINGLE SESSION OF EXERCISE

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The purpose of this study was to assess alterations fatty acid [FA] metabolism in response to acute overeating and exercise. Five obese women performed 3 separate, two-day trials in which they: 1) consumed a weight-maintaining diet [Control], 2) consumed a hypercaloric diet (+700kcal) [HC] and 3) ingested the same hypercaloric diet, but exercised to expend 700kcal [EX]. The morning after each treatment, we measured whole-body FA oxidation [FAO] and calculated non-oxidative FA disposal as the difference between FA uptake (measured using isotope dilution methods) and FAO. A muscle biopsy was also performed to measure intramyocellular triglyceride concentration [IMTG] and glycerol-3-phosphate acyltransferase [GPAT] activity, which catalyzes the first step in IMTG synthesis. The morning after the different treatments, HC suppressed FAO below control levels (187±30 vs. 237±23 umol/min; $P<0.05$), while EX increased FAO (293±36 umol/min; all $P<0.05$). Non-oxidative FA disposal was not different among trials, but the fate of these fatty acids was likely different between trials because IMTG concentration was similar in the morning after all treatments despite an expected exercise-induced reduction in IMTG during EX. We also found a direct correlation between FA uptake and muscle GPAT activity (P=0.02). Therefore, acute exercise reverses the suppressed resting FAO found with acute overeating and may repartition fatty acid uptake toward IMTG resynthesis.

23.0: REGENERATION

23.1

EFFECTS OF UNLOADING ON PROTEIN EXPRESSION DURING THE REGENERATION OF INJURED SOLEUS MUSCLE OF MICE

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The current study was performed to investigate the effects of gravitational unloading on the regeneration of injured mouse soleus muscle by using proteome analysis. Male mice (C57BL/6J), aged 8 weeks, were randomly divided into 4 groups; normal cage control (CC), cardiotoxin (CTX)-injected (CX), hindlimb suspended (HS), and HS+CX (SX) groups. HS, as the preconditioning, was performed for 2 weeks in group HS and SX. And then, CTX was injected into soleus muscles in CX and SX groups. HS was continued for additional 4 weeks in group HS and SX. Unloading, as well as CTX-injection, resulted in a rapid loss of soleus protein contents. Recovery of muscle protein content was observed in CTX-injected soleus after 4 weeks in ambulatory control group. However, there was no gain of protein content in group SX. Profiles of proteins were analyzed by two-dimensional gel electrophoresis. Twenty five spots were significantly altered in group SX compared with group CX. This study was supported, in part, by Grant-in-Aid for Scientific Research (B, 20300218, KG; A, 18200042, TY; S, 19100009, YO) from Japan Society for the Promotion of Science, Ground-based Research Program for Space Utilization from Japan Space Forum (KG), and Research Grant from KAO Health Science Research (KG).

23.2

INTENSE TRAINING AND PHYSICAL EXERCISE DOES NOT MODIFY HUMAN SKELETAL MUSCLE REGENERATION

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Exercise might be an excellent therapeutic strategy to limit the loss of muscle function and mass observed with age. In this study, we have investigated the influence of intense exercise and regular training as practised by adults regularly participating in a competitive sporting activity on regenerative capacity. We have evaluated two in vivo parameters: i) variation in telomere length which was used to evaluate the in vivo turn-over of satellite cells and ii) the proportion of satellite cells, the adult muscle stem cells involved in muscle repair and adaptation to various stimuli. To complete the evaluation of the regenerative capacity of exercised muscles, we have also determined the proliferative capacity and telomere shortening rate of satellite cells isolated from muscles of exercised people. Our results show that in the group of individuals practicing regular training and exercise there was a slight decrease of the minimum telomere lengths compared with sedentary people. However, the mean telomere lengths remained the same. The number of satellite cells calculated as a proportion of nuclei present in a muscle fiber was significantly higher in muscle of exercised individuals, as was the mean number of myonuclei per cross-section. More importantly, we show for the first time that the observed augmentation in satellite cell proportion in vivo did not reduce significantly their in vitro proliferative capacity nor did it increase the rate of in vitro telomere shortening.

23.3

NOTCH AND WNT TEMPORAL RELATIONSHIP FOLLOWING DOWNHILL RUNNING

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Objective: The objective of this study is to characterize the temporal expression time course of traditional muscle development regulators, Notch and Wnt signaling relative to muscle regeneration following downhill running (DHR) in mice. Methods: 43 mice (C57BL/J6) were exposed to either a DHR protocol or normal cage activity. The soleus and gastrocnemius muscles were excised from mice exposed to DHR protocol at 1, 2, 3, 4, 5 and 7 days post-DHR and immunofluorescence or western blot analysis were performed. Muscle-associated cells were isolated from the remaining hindlimb muscles and prepared for FACS analysis. Results: H&E staining showed muscle injury were significant at 4 days and 5 days post-DHR samples. Western blot of gastrocnemius show increased Desmin expression at 3 days to 5 days post DHR. Significantly increased Delta1 protein expression was observed in soleus muscle at 3 days to 5 days post-DHR using immunofluorescence. FACS analysis of isolated muscle-associated cells resulted in significant increases of Delta1 protein and Notch1 protein expression at 5 days post-DHR. Western blot analysis of gastrocnemius did not show any changes in GSK3β nor β-catenin expression during 5 days following DHR, however, Wnt 3a protein expression is elevated at 2 days to 5 days post DHR. Conclusion: DHR upregulates Notch however Wnt signaling expression does not appear to be activated at 5 days post DHR and is proposed to be upregulated following Notch activation.

23.4

THE IMPAIRED INFLAMMATORY RESPONSE TO MUSCLE DAMAGE CONTRIBUTES TO THE IMPAIRED MUSCLE REGENERATIVE CAPACITY AND TO INCREASED MUSCLE ADIPOSITY WITH AGING

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Adiposity in skeletal muscle has been widely recognized as one of the hallmarks of sarcopenia. Adult skeletal muscle has a remarkable regenerative capacity, largely mediated by myogenic stem cells, termed satellite cells (SCs). However, skeletal muscle regeneration is markedly impaired with age. We demonstrated that old rats exhibited impaired muscle regeneration and increased intermuscular adipocytes post-injury. During muscle regeneration, some SCs (M-cadherin positive-cells) were located inside basal lamina and co-expressed C/EBPalpha, which is a master transcriptional factor for adipocyte. We indicated that SCs from old rats were multipotent cells that were able to undergo not only myogenic, but also adipogenic differentiation in vitro. Our data in vivo and vitro suggest that SCs in old muscle have adipogenic potential. In addition, our DNA chip data has indicated that the expression of genes including inflammatory cytokines, chemokines, and growth factors was attenuated during the regeneration of aged skeletal muscle. We also demonstrated that the number of activated

macrophages (ED1 positive-cells) within skeletal muscle was lower in old rats compared with young rats after muscle damage. These data suggest that the impaired inflammatory response to muscle damage that occurs with aging may contribute to the impaired muscle regenerative capacity and to increased muscle adiposity, both characteristic of aged muscle.

23.5

TREADMILL TRAINING ENHANCES AXON REGENERATION IN CUT PERIPHERAL NERVES WITHOUT AFFECTING TOPOGRAPHIC SPECIFICITY OF REINNERVATING MOTONEURONS

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We investigated the effects of continuous (CT) and interval (IT) treadmill training on axon regeneration after sciatic nerve injury. Beginning on the third post-operative day, one group of mice was exercised using a CT strategy and another group was exercised using an IT strategy. Exercise was conducted five days per week for two or four weeks. Counts of retrogradely labeled motoneurons were made from serial histological sections of the spinal cords and both CT and IT group results were compared to unexercised controls. After two weeks of CT, significantly more motoneurons could be labeled from application of tracer to the common fibular and tibial nerves than in controls. The number of labeled cells was not significantly different from the maximal number of labeled neurons encountered at longer survival times (4 weeks) in unexercised animals. After four weeks of CT, the enhancement persisted: nearly twice as many labeled motoneurons were found as unexercised controls. A similar increase in the number of labeled motoneurons was found after two weeks of IT. Topographic specificity of reinnervating motoneurons was not different. Thus axons of more motoneurons regenerate into the branches of the sciatic nerve in both groups of exercised mice with a loss of neuromuscular specificity comparable to that observed in untrained mice.

23.6

VASCULOGENESIS, AN EXERCISE-INDUCED PROCESS?

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In the present study the aim was to investigate the circulating level of EPCs defined by expression of VEGFR2 following an acute bout of exercise, as well as plasma levels and skeletal muscle gene expression of factors hypothesized to be involved in homing of EPCs. 10 healthy, moderately active males performed 1 h of cycle exercise. Blood samples for flow cytometric measure of EPC numbers and ELISA measurements of plasma protein levels were retrieved before, directly after, 30 minutes after and 2 h after the exercise bout. Muscle biopsies from the m. vastus lateralis of both legs were obtained before, directly after and 2 h after the exercise bout. The circulating level of EPCs increased robustly after the exercise bout. The plasma level of G-CSF was significantly increased directly after the bout when adjusted for plasma albumin concentration. ICAM-1 and VCAM-1 mRNA levels were increased 2 h post exercise. The present results indicate that exercise induces recruitment of EPCs to the circulation and prepares the tissue for homing of these cells.

23.7 Withdrawn.

23.8

SWIMMING EXERCISE REVERSES TACTILE STIMULUS-INDUCED HYPERSENSITIVITY FOLLOWING PERIPHERAL NERVE INJURY

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Exercise-induced synaptic plasticity in the spinal cord, may help to recover motor and sensory function following nerve injury. We investigated whether a chronic forced swimming activity influences tactile stimulus-induced neuropathic pain hypersensitivity. Adult Balb/C male mice (20-25 g) were used. Neuropathic pain was induced by partial sciatic nerve ligation whereas sham operated mice were used as control. Chronic exercise activity was performed by swim training which lasted 40 min/day, 5 days/week for 6 weeks. Control animals swam for 30 s over the same period. The development of tactile hypersensitivity following nerve lesion was monitored by von Frey filaments. After nerve injury, animals showed a marked hypersensitivity to mechanical stimuli which lasted for at least 6 weeks ($p < 0.01$, Wilcoxon test, n= 8). However, under moderate swim exercise training, injuried mice showed a progressive recovery of the sensory abnormality from the second week of training ($p < 0.01$, Wilcoxon test, n= 8). By the end of six weeks of training no difference was observed in the mechanical threshold of injuried and sham-operated animals ($p > 0.05$, Mann-Whitney test). Our data indicate that a moderate swimming exercise has a remarkable beneficial effect on tactile stimulus-induced neuropathic pain hypersensitivity. In addition, the results suggest that the exercise effect on chronic pain is reliant on a time-dependent plasticity in the sensory system. Supported by FAPESP (grant # 07/03757-4).

23.9

SIMVASTATIN REDUCES HUMAN PRIMARY SATELLITE CELL PROLIFERATION IN CULTURE

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Statins, 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors cause adverse side effects in skeletal muscle which are heightened with higher doses and physical activity. Understanding the effects of statins on satellite cell (SC) proliferation and regeneration is necessary due to the essentiality of SC for skeletal muscle repair and the anti-proliferative capabilities of statins. The objective of this study was to determine the proliferative capacity of SC exposed to varying concentrations of simvastatin. Human primary SC were isolated from vastus lateralis biopsies. SC were grown to approximately 70% confluency and seeded onto 96-well plates with growth media and simvastatin (0, 0+DMSO, 0.05, 0.1, 1.0, 10, or 100μM) for 48 h. Satellite cell viability (SCV) was determined with MTT cytotoxicity assay and reported as percent of DMSO control. There was a dose dependent decrease in SCV with 1.0, 10, 100μM of simvastatin (~20-60% decrease), but no change in SCV at 0.05 or 0.1μM. Concentrations of statins which lead to decreased SCV equate to what is physiologically available in circulation at higher prescribed doses of simvastatin (e.g., 40 and 80mg/d). These results indicate serious adverse effects that may alter the ability of skeletal muscle to repair and regenerate. Exacerbated muscle toxicity following exercise coupled with statin drugs could be a result of the inability of skeletal muscle to repair/regenerate due to the anti-proliferative effects of statins.

23.10

O-LINKED-β-*N*-ACETYLGLUCOSAMINE MODIFICATION AFFECTS C2C12 CELL CYCLE REGULATION AND DIFFERENTIATION

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O-linked-β-N-acetylglucosamine (O-GlcNAc) is a ubiquitous and dynamic post-translational modification that has been proposed to 1) act as a nutrient sensor protecting against an abundance of fuel and 2) play a vital role in virtually all cellular processes. Mechanical stress and muscle injury activate quiescent satellite cells, inducing proliferation followed by differentiation and fusion. In humans undergoing 16 wk of progressive resistance training, total O-GlcNAc protein modification increased in non-responding patients and remained unchanged in extreme responders. To determine if O-GlcNAc modification can affect normal myoblast physiology, we explored the effect of 10mM glucosamine (GlcN) induced increase in total protein O-GlcNAc modification on C2C12 cell cycle regulation and differentiation. Western blot analyses demonstrated that total O-GlcNAc increased 65% (24h) and 24% (48h) compared to untreated controls, while O-GlcNAc transferase (OGT) expression remained unchanged. MyoD expression was lower in treated vs. controls by 54% (24h) and 42% (48h). Interestingly, myogenin was 41% higher after 24h and 48% lower after 48h of GlcN addition compared to controls. Cells cultured in growth media showed increased expression (76%) of cyclin D1 with 24h GlcN treatment compared to untreated control. MTT cytotoxicity assay over a range of GlcN doses revealed greater cell viability with GlcN compared to untreated controls. These data suggest that increasing total O-GlcNAc modification affects cell cycle regulation and abrogates myoblast differentiation in a manner that is not toxic to the cell.

24.0: REACTIVE OXYGEN SPECIES: CONSEQUENCES ON CELLULAR METABOLISM

24.2

DISRUPTION OF MITOCHONDRIAL REDOX CIRCUITRY IN OXIDATIVE STRESS

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Oxidation-reduction (redox) reactions generate ATP and also function in signaling and control to integrate biologic functions. Mitochondria account for most of the metabolic fuel and oxygen utilization through high flux pathways and for generation of superoxide anion radical and its dismutation product, H_2O_2, to support low-flux signaling and control processes. Redox signaling and control occurs through a subset of the cysteine residues in proteins which undergo reversible modification by disulfide formation, S-glutathionylation or S-nitrosylation. Redox states of mitochondrial proteins are measured with the redox-western blot and show that the mitochondrial antioxidant thioredoxin-2 (Trx2) is not in redox equilibrium with GSH or the reductant NADPH. Because the latter are components of low-flux pathways, enhanced generation of superoxide anion radical and hydrogen peroxide due to inhibition of the high-flux mitochondrial electron transport chain can result in significant oxidation and disruption of normal redox signaling and control. Disruption of these redox systems in mitochondria appears to be a critical factor in oxidative stress as a cause of toxicity and disease. (NIH ES009047). REFERENCES: Jones, D. P. Disruption of mitochondrial redox circuitry in oxidative stress. Chemico-biological interactions 163:38-53; 2006. Kemp M, Go YM, and Jones DP. Nonequilibrium thermodynamics of thiol/disulfide redox systems: a perspective on redox systems biology. Free Radic Biol Med 44: 921-937, 2008.

24.3

LINKING MITOCHONDRIAL ROS TO INSULIN RESISTANCE

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The impact of metabolic imbalance resulting from over nutrition and/or low metabolic demand is only beginning to be understood at the cellular level. Mitochondrial respiratory capacity and content are reduced in skeletal muscle of obese/diabetic individuals, implying that obesity, or more likely the metabolic imbalance that leads to obesity, causes a progressive decline in mitochondrial function. Inherited and/or acquired mitochondrial dysfunction has also been implicated in the etiology of insulin resistance; however, the underlying mechanism leading to impaired mitochondrial function and its potential link to the development of insulin resistance, particularly in the context of metabolic imbalance, is unknown. Data will be presented showing that high dietary fat intake increases mitochondrial H2O2 emission, shifts the redox environment to a more oxidized state, and decreases the redox buffering capacity in the absence of any change in respiratory function or capacity. Using both transgenic and pharmacological approaches, we have found that antioxidants targeted to the mitochondria prevent the development of insulin resistance during a high fat diet. These findings place the consequences of cellular metabolic imbalance in the context of mitochondrial bioenergetics by establishing that H2O2 emission serves as both a gauge of energy balance and regulator of redox state within myofibers, linking cellular metabolic balance to the control of insulin sensitivity.

24.4

HOW DOES EXERCISE AFFECT ROS AND RNS IN SKELETAL MUSCLE?

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The effect of contractile activity on generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) has been studied since the late 1970's although with increasing sophistication of the approaches used. New techniques permit the analysis of specific ROS and RNS both within muscle fibres, released from the fibres or generated outside of the fibres. Current data indicate that isometric or concentric contractions induce an increase in intracellular nitric oxide from nNOS enzymes and superoxide from several potential sources in addition to release of both species from the plasma membrane to the interstitial space. Superoxide and nitric oxide are the primary species generated and lead to the formation of secondary species such as hydrogen peroxide, hydroxyl radicals and peroxynitrite. Most initial data indicated that the major effects of these species were to induce oxidative damage to critical cell components, but recent studies indicate that during normal use of muscles, these species are crucial to physiological adaptive responses to contractile activity. Supported by the Wellcome Trust, Medical Research Council and NIA. REFERENCE: Jackson MJ. (2008). Free radicals generated by contracting

muscle: By-products of metabolism or key regulators of muscle function? Free Rad. Biol. Med. 44: 132-141.

24.5

EXERCISE TRAINING AND ANTIOXIDANT THERAPY AS TREATMENT OF INSULIN RESISTANCE AND TYPE 2 DIABETES

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Impaired insulin-stimulated glucose transport activity in skeletal muscle is a critical defect leading to the development of type 2 diabetes. A major cause of insulin resistance is the defective function of proximal insulin signaling elements, including the insulin receptor (IR) and IR substrate-1 (IRS-1). One important condition associated with insulin resistance is oxidative stress, the imbalance between the production of reactive oxygen species and antioxidant defenses. Exposure of skeletal muscle to an oxidant stress leads to impaired IRS-1-dependent insulin signaling and reduced muscle glucose transport. Treatment of insulin-resistant animal models and human subjects with antioxidants, including α-lipoic acid (ALA), enhances whole-body glucose tolerance and insulin action on the glucose transport system in skeletal muscle. Endurance exercise training is also effective in ameliorating the insulin resistance of skeletal muscle glucose transport. Combining endurance exercise training and ALA in insulin-resistant obese Zucker rats produces an interactive effect resulting in a greater improvement in insulin action on skeletal muscle glucose transport than either intervention individually, highlighted by enhancements of IRS-1 protein expression and functionality. These results underscore the potential of combining endurance exercise training and antioxidants for improving defective insulin action in insulin-resistant skeletal muscle. REFERENCE: Henriksen EJ. Exercise training and the antioxidant alpha-lipoic acid in the treatment of insulin resistance and type 2 diabetes. Free Rad Biol Med 40: 3-12, 2006.

25.0: REMODELING OF THE EXTRACELLULAR MATRIX OF TENDON AND SKELETAL MUSCLE IN RESPONSE TO EXERCISE

25.3

REMODELING OF THE EXTRACELLULAR MATRIX OF TENDON AND SKELETAL MUSCLE IN RESPONSE TO EXERCISE

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The extracellular matrix (ECM) of muscle is thought to play an important role in laterally transmitting the force produced within muscle fibers, while within the tendon ECM serves to transfer force from the muscle to the bone. Both of these properties play an important role in improving movement economy and decreasing contraction-induced injury. Therefore, changes in the composition of the ECM could lead to changes in force transmission resulting in altered contraction-mediated muscle damage. How these important ECM structures adapt dynamically to changes in loading is poorly understood largely because of the difficulties in isolating cellular material from the dense collagen network. Recent advances in isolating both protein and mRNA from these structures is changing the way that we think about how these tissues change with exercise. For example, inactivity decreases the expression of collagen I (76±1.6%), collagen III (73±2.3%), and lysyl oxidase (83±3.2%) mRNA in the ECM of muscle. This occurs in spite of the fact that there is an increase in the concentration of the ECM of muscle. These data suggest that during inactivity the breakdown of collagen is rapidly decreased leading to decreased turnover. Work from other labs has shown that exercise increases the expression of collagens, lysyl oxidase, as well as metalloproteinases suggesting that exercise increases turnover in the ECM. While these data suggest that exercise regulates ECM turnover, data to date is from mRNA and might not be translated into changes in protein or more importantly mechanics of the tissue.

25.4

EXPRESSION AND FUNCTION OF MATRIX METALLOPROTEINASE-9 IN SKELETAL MUSCLE

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Changes in skeletal muscle connective tissue degradation are thought to underlie numerous muscle adaptive states. Matrix metalloproteinases or MMPs are secreted proteases that degrade extracellular matrix. Our research has focused on the expression and function of the inducible gelatinase MMP-9. Secretion of MMP-9 from muscle cells in vitro is dramatically increased by treatment with the growth factors fibroblast growth factor-2 or tumor necrosis factor-alpha (TNF-α). Treatment of C2C12 myoblasts with TNF-α also significantly increases activity of an MMP-9 promoter-reporter construct, suggesting that the increase in MMP-9 secretion in response to TNF-α is regulated at least in part by transcriptional mechanisms. We have also demonstrated that two polymorphisms in the human MMP-9 upstream promoter region, a CA microsatellite repeat at –90 and a –1562C/T single nucleotide polymorphism, alter both basal and TNF-α -induced MMP-9 promoter activity in skeletal muscle cells in vitro. Functionally, over-expression of MMP-9 in primary mouse myoblasts resulted in a significant increase in their ability to migrate in chamber assays. Currently we are evaluating the role of MMP-9 in muscle damage and repair by comparing the extent of exercise-induced damage and repair in control mice and in mice lacking the MMP-9 gene, as well as the effects of eccentric exercise on serum MMP-9 levels in humans in vivo. In summary, expression of the MMP-9 gene is regulated by secreted factors as well as by genetic mechanisms, and this MMP may play a role in the migration of myoblasts and other cells during muscle repair following injury.

26.0: SIGNALING MECHANISMS REGULATING METABOLIC AND TRANSCIPTION PROCESSES IN SKELETAL MUSCLE

26.2

SIGNALING MECHANISMS THAT COORDINATE MITOCHONDRIAL PROGRAMMING AND INTRAMUSCULAR LIPID DROPLET METABOLISM

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Intramuscular triacylglycerol (IMTG) droplets have gained widespread attention as a paradoxical hallmark of both obesity and exercise training. In the context of obesity, IMTG have been implicated as a principal diabetogenic culprit due to their strong positive correlation with the development of insulin resistance. By contrast, endurance trained athletes remain highly insulin sensitive despite abundant IMTG stores. We reason that the physiological role and regulation of IMTG in the trained state might prove relevant to the mechanisms that underlie insulin resistance in deconditioned muscles. The notion that IMTGs benefit physically active muscles by serving as a local source of oxidative fuel is supported by the following observations: 1) IMTG content is highest in red muscles enriched with mitochondria, 2) IMTG utilization during exercise is enhanced by endurance training, and 3) IMTGs reside in close proximity to interfibrillar mitochondria. Additionally, we have found that the programs of mitochondrial genesis, β-oxidation and IMTG biosynthesis are coordinately regulated by the exercise-inducible transcriptional coactivator, PGC-1α. Together, these findings establish a strong connection between elevated IMTG content and mitochondrial selection of lipid substrate. Fitting with these data, recent evidence suggests that the development of muscle insulin resistance stems from excessive β-oxidation, owing both to transcriptional activation of the pathway as well as increased substrate supply. In sedentary animals this induction occurs absent a coordinated increase in TCA cycle activity, resulting in "incomplete" fat oxidation and production of incompletely oxidized lipid intermediates that are thought to reflect mitochondrial stress. Our emerging model predicts that IMTG accumulation provokes insulin resistance in sedentary muscles by fueling high rates of β-oxidation at a time when workload, and thus ATP consumption, is low. (This work is supported by grants from the American Diabetes Association and NIH RO1-AG028930).

26.4

MOLECULAR SIGNALING MECHANISMS LEADING TO EXERCISE-INDUCED CHANGES IN TRANSCRIPTION

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Both endurance and resistance exercise have been shown to alter gene transcription in skeletal muscle, with the former generally believed to promote mitochondrial biogenesis, oxidative capacity and angiogenesis, while the latter increases contractile protein synthesis and muscle mass. The molecular signaling events mediating these adaptive responses have been well studied in recent years (Baar, 2006; Bassel-Duby & Olson, 2006). Our recent interests have focused on the role of class IIa histone deacetylases (HDAC) in mediating endurance exercise effects on metabolic gene expression. These transcriptional repressors interact with myocyte enhancer factor 2 (MEF2) to modulate transcription of key muscle-specific genes. Phosphorylation of HDACs (specifically HDAC4 and HDAC5) results in their nuclear export and activation of metabolic gene transcription. Exercise reduces nuclear HDAC5 and MEF2-associated HDAC5 and increases MEF2 DNA binding and GLUT4 mRNA in human skeletal muscle (McGee & Hargreaves, 2004). We have also recently observed that exercise reduces nuclear HDAC4 in human skeletal muscle. Putative upstream HDAC kinases include calcium/calmodulin kinase II, protein kinase D and AMP-activated protein kinase. The HDAC5-MEF2 axis also regulates the expression of peroxisome proliferator-activated receptor γ coactivator -1α (PGC-1α), which plays a central role in mitochondrial biogenesis. Exercise-induced activation of AMP-activated protein kinase and p38 mitogen activated protein kinase can also directly modify PGC-1α localization and/or expression. The calcium dependent phosphatase calcineurin appears to regulate muscle fibre type in the longer term. A key future challenge is to dissect the temporal and spatial contributions of these various signaling pathways as they "decode" numerous exercise stimuli (eg. calcium, energy charge, metabolite and oxygen levels, redox state, muscle length/tension) and mediate appropriate adaptive responses. **References:** Baar, K. Training for endurance and strength: lessons from cell signaling. Med. Sci. Sports Exerc. 38: 1939-1944, 2006. Bassel-Duby, R. & Olson, EN. Signaling pathways in skeletal muscle remodeling. Ann. Rev. Biochem. 75: 19-37, 2006. McGee, SL. & Hargreaves, M. Exercise and MEF2 regulation in human skeletal muscle. Diabetes. 53: 1208-1214, 2004.

26.5

SIGNALING MECHANISMS CONTROLLING POST-EXERCISE INSULIN SENSITIVITY IN CONTRACTING HUMAN SKELETAL MUSCLE

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Insulin sensitivity to stimulate glucose uptake in skeletal muscle is markedly enhanced by exercise. Studies in both human and rodent models have provided evidence that this effect is local in nature and restricted to the contracted muscle per se rather than being mediated by systemic factors. The mechanism in exercise training-induced insulin sensitivity involves changes in muscle quality i.e. changes in expression of a range of metabolic proteins e.g. Glut4, hexokinase and glycogen synthase. The marked change observed in the period (up to 48 hrs) after a single bout of exercise is however also an important contributor to the overall improvement of the insulin sensitivity in a period of exercise training. The mechanism for this latter effect of exercise is largely unresolved. AS160 "Akt Substrate of 160 kDa" has been characterised as a GTPase activating protein (GAP) and is thought to positively regulate the GTPase activity of certain Rab proteins to regulate GLUT4 translocation to the plasma membrane. AS160 has been shown to be involved in both insulin-mediated and exercise/contraction-mediated glucose uptake. In addition, there is evidence to suggest that insulin signalling to AS160 is impaired in human subjects with decreased insulin sensitivity and interestingly, that medical treatment reversing insulin sensitivity may act via a mechanism involving AS160. These findings have given rise to the idea that AS160 is a point of convergence for the insulin signalling pathway and the pathway initiated by exercise to increase glucose uptake. As a consequence we and others have hypothesised that interaction between these signalling pathways at the level of AS160 mediates the enhanced glucose uptake in previously exercised muscles. This idea will be discussed.

27.0: ROLES OF BIOMECHANNICAL SIGNALING IN CARDIAC AND SKELETAL MUSCLE

27.2

DECIPHERING THE MECHANISMS OF ACTIN FILAMENT ARCHITECTURE IN CARDIAC MYOCYTES

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Efficient contractile activity in striated muscle requires that the actin-containing thin filaments precisely assemble with the correct polarity and spacing, and maintain specific lengths. The barbed ends of actin filaments in striated muscle are anchored within the Z-disc and capped by CapZ, a protein that blocks actin polymerization and depolymerization in vitro. The mature lengths of the thin filaments are likely maintained by the giant "molecular ruler" nebulin, which spans the lengths of the thin filaments. We found that CapZ specifically interacts with the C-terminus of nebulin (modules 160-164) in several biochemical assays. Binding of nebulin modules 160-164 to CapZ does not affect the ability of CapZ to cap actin filaments in vitro, consistent with our observation that the C-terminal actin-binding regions of CapZ are not necessary for its interaction with nebulin. Knockdown of nebulin in chick skeletal myotubes using siRNA results in a reduction of assembled CapZ and, strikingly, a loss of the uniform alignment of the barbed ends of the actin filaments. These data suggest that nebulin restricts the position of thin-filament barbed ends to the Z-disc via a direct interaction with CapZ. We propose a novel molecular model of Z-disc architecture in which nebulin interacts with CapZ from a thin filament of an adjacent sarcomere, thus providing a structural link between adjacent sarcomeres.

27.3

MECHANO-SENSING FROM WITHIN THE Z-DISK OF CARDIAC

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Prolonged hemodynamic overload results in cardiac hypertrophy and heart failure. Mechanosensing in myocytes necessary for maintaining adaptation is thought to become impaired as a result of the prolonged overload. However, the mechanisms by which chronic overload leads to these changes are poorly understood. Cardiac muscle LIM protein (MLP) is a mechanosensor and relays signals from the myofibrils to the nucleus. Using the techniques of biochemical subcellular fractionation and immunocytochemistry, we found MLP exhibits oligomerisation in cultured cardiac rat neonatal myocytes. MLP translocated to the nucleolus in response to cyclic stretch. Adenoviral over-expression of MLP resulted in a 2 fold increase in ribosomal S6 protein suggesting that MLP can activate ribosomal protein synthesis in the nucleolus. Inhibition of MLP nuclear translocation prevented increased protein synthesis in response to phenylephrine treatment and decreased total MLP expression. These data suggest that MLP can regulate its own expression and myocyte hypertrophy through nuclear translocation. Furthermore, when myocytes were cyclically stretched for 48hrs in the absence of nuclear MLP, the sarcomeres lost their integrity suggesting that MLP is required for maintenance and remodelling of the myofilaments in response to mechanical stretch. These findings suggest that MLP plays an important role in the regulation of the myocyte remodelling. (AHA-0630307N and P01 HL-62426). Boateng SY, Berlin JB, Geenen DL, Margulies KB, de Tombe PP and Russell B. Cardiac dysfunction and heart failure are associated with abnormalities in the subcellular distribution and amounts of oligomeric muscle LIM protein. Am J Physiol-Heart Circ Physiol 292(1):H259-69 (2007).

27.4

MECHANICAL REGULATION OF MUSCLE AND STEM CELLS

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Cell organization and the mechanical force play important roles in regulating the functions of muscle and stem cells. Here we used micropatterning techniques to guide cell organization and investigated cellular responses to spatial pattern and mechanical strain. On the surfaces with aligned nanofibers or microgrooves, skeletal myoblast aligned, fused efficiently and formed more and longer striated myotubes. Similar micropatterning strategy was used to pattern vascular smooth muscle cells (SMCs) and show that aligned SMCs had elongated spindle shape and were less proliferative. The decrease of proliferation in elongated SMCs was partially recovered by PDGF, but was further suppressed by cyclic uniaxial mechanical strain. By micropatterning SMCs on matrix islands with different shapes, we showed that cell shape directly regulated SMC proliferation. Furthermore, we extended our studies to bone marrow mesenchymal stem cells (MSCs), a potential cell source for muscular and vascular tissue engineering. To simulate the cell alignment in muscular and vascular tissues and investigate the anisotropic mechanical sensing by MSCs, we cultured MSCs on elastic membranes with parallel microgrooves, and subjected MSCs to cyclic uniaxial strain in the alignment direction. We showed that uniaxial strain increased smooth muscle markers and decreased cartilage markers, and these effects were diminished when cells were aligned perpendicularly to the axis of mechanical strain. The differential cellular responses to micro and nano scale topographic cues and anisotropic mechanical environment have important implications in muscular and vascular tissue remodeling and tissue engineering. (NIH HL078534).

28.0: SIGNALING

28.1

THE ROLE OF PI3K/PKB AND PHOSPHATIDIC ACID IN THE ACTIVATION OF MTOR SIGNALING FOLLOWING RESISTANCE EXERCISE

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Resistance exercise (RE) induces a hypertrophic response in skeletal muscle and recent studies have begun to shed light on the molecular events involved in this process. For example, signaling by mTOR has been shown to be necessary for the hypertrophic response. Furthermore, it has been proposed that RE activates mTOR via an upstream pathway involving PI3K/PKB; however, this hypothesis has not been thoroughly tested. To test this hypothesis, we first evaluated the temporal dynamics of signaling through PI3K/PKB and mTOR following a bout of RE with eccentric contractions (EC). It was determined that the activation of signaling through PI3K/PKB is a transient event (<15 minutes), while the activation of mTOR signaling is sustained for a long duration (> 12 hours). Furthermore, pharmacological inhibition of PI3K/PKB did not prevent the activation of mTOR by EC, indicating that PI3K/PKB is not part of the upstream pathway. These observations led us to investigate the role of phospholipase D (PLD) and phosphatidic acid (PA) in the activation of mTOR signaling. Our results demonstrate that EC induce a sustained elevation in [PA] and blocking the PLD-dependent synthesis of PA prevented the EC-induced activation of mTOR signaling. Furthermore, exogenous PA activated mTOR signaling and this occured through a PI3K/PKB-independent mechanism. Combined, these results indicate that activation of mTOR following RE is elicited through a PI3K/PKB-independent pathway that requires PLD and PA.

28.2

HIGHER LEUCINE CONTENT IN AN ESSENTIAL AMINO ACID SOLUTION ENHANCES MTOR SIGNALING IN HUMAN SKELETAL MUSCLE

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Essential amino acid (EAA) ingestion stimulates mammalian target of rapamycin (mTOR) signaling in humans. This effect appears to be largely due to the branched-chain amino acid leucine. We hypothesized that increasing the leucine content of an EAA solution would stimulate mTOR signaling to a greater extent as compared to an EAA solution with a leucine content typical of high quality proteins. Seven young subjects were randomized into two groups, each ingesting 10 grams of EAA but with differing amounts of leucine. Leucine composition was 18% for the EAA group (n=4) and 35% for the LEU group (n=3). Muscle biopsies were taken at baseline, 1-, 2- and 3-hr post-ingestion, and blood was sampled throughout. mTOR signaling was assessed by immunoblotting of muscle biopsies. The phosphorylation of mTOR was increased 1-hr following nutrient ingestion in both groups ($P<0.05$), however, the increase tended to be higher in the LEU group. mTOR signaling to its downstream effectors, S6K1 and 4E-BP1 was also increased in both groups at 1-hr ($P<0.05$) with a slightly higher increase in the LEU group. This suggests translation initiation was activated to a larger extent in the LEU group. The phosphorylation of eEF2 tended to decrease more at 1-hr post-ingestion in the LEU group indicating further enhancement of translation elongation. We conclude that increasing the content of leucine in an EAA solution appears to enhance skeletal muscle mTOR signaling in young human subjects. Supported by NIH/NIAMS grant RO1 AR049877.

28.3

EXERCISE TRAINING DOES NOT REVERSE AND EVEN PROMOTES THE UNFOLDED PROTEIN RESPONSE INDUCED BY A HIGH-FAT DIET IN MICE SKELETAL MUSCLE

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The endoplasmic reticulum (ER) is a key organelle where the folding and post-translational modifications of proteins occur. Certain stress conditions disrupt ER homeostasis and lead to the activation of a signal transduction referred to as the unfolded protein response (UPR). When the UPR fails, cell death occurs, usually in the form of apoptosis. The purpose of the present study was to test if a high-fat diet (HFD) for 6 weeks activates the UPR in mice skeletal muscle and if concomitant exercise training limits this response. HFD ingestion for 6 weeks increased the expression of UPR components in the soleus muscle of mice whereas the tibialis was slightly affected. Glucose regulated-protein 78, inositol-requiring enzyme α, membrane-bound transcription factor peptidase site 2 and protein kinase R-like ER protein kinase expressions were increased by 5-fold in the soleus ($P<0.05$) of HFD mice and exercise training did not reverse these up-regulations. UPR stimulation may lead to chronic inflammation via c-Jun N-terminal kinase activation and apoptosis via caspase 12 clivage. The combination of exercise training and HFD increased these two events in soleus ($P<0.05$) as compared to sedentary controls mice fed normal or HF diet. We show for the first time that a HFD increases UPR components expression in soleus muscle of mice and that exercise does not reverse and even promotes the HFD-induced UPR. Whether this phenomenon is a compensatory mechanism or not remains to be elucidated.

28.4

NEUREGULIN SIGNALING IN SKELETAL MUSCLE FOLLOWING DENERVATION-INDUCED INACTIVITY

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Neuregulin is a member of the epidermal growth factor family, is expressed in motor neurons and exerts multiple physiological effects on skeletal muscle. We have observed that NRG increases protein synthesis and decreases protein degradation in rat diaphragm muscle (DIAm) in a PI 3-kinase/Akt dependent manner. NRG signaling is predicted to be reduced following phrenic nerve denervation of DIAm. We hypothesize that NRG is an important regulator of muscle mass and that following denervation, a reduction in nerve-derived neuregulin is partially responsible for the loss of muscle cross-sectional area and muscle mass. We have previously reported that DIAm cross sectional area and muscle mass is reduced following 14 days of denervation. In this study, we investigated the phosphorylation of the neuregulin receptor, ErbB3, following 14 days of phrenic nerve denervation. In denervated animals, we observed a dramatic decrease in ErbB3 phosphorylation suggesting a reduction in neuregulin signaling. These results support the proposed role of neuregulin as a nerve-derived regulator of skeletal muscle mass.

28.5

RAPAMYCIN PREVENTS THE POST-EXERCISE INCREASE IN PROTEIN SYNTHESIS IN HUMAN SKELETAL MUSCLE

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Resistance exercise stimulates mTOR signaling and muscle protein synthesis (MPS) during post-exercise recovery in humans. Rapamycin is a specific inhibitor of mTOR and is often used to inhibit protein synthesis in rodent muscle. We hypothesized that the administration of rapamycin to human subjects prior to a bout of resistance exercise would prevent the increase in MPS during post-exercise recovery. We studied young men that received rapamycin treatment (12mg)

2 hr prior to exercise (Rapamycin; N=7) and a Control group without rapamycin (N=7). Rapamycin and Control subjects performed a single bout of resistance exercise and muscle biopsies were sampled immediately, 1 and 2hr post-exercise. Stable isotope and immunoblotting techniques were used to determine MPS and mTOR signaling. We found that MPS increased post-exercise in Control subjects ($P<0.05$) but was unchanged in the Rapamycin subjects ($P>0.05$). Furthermore, phosphorylation of several cellular signaling molecules (mTOR and ERK pathways) were blunted in the Rapamycin group as compared to the Control group. We conclude that the increase in MPS following an acute bout of resistance exercise appears to be rapamycin dependent indicating that mTOR signaling is playing an important role in regulating the post-exercise protein anabolic response. Supported by NIH/NIAMS grant # RO1 AR049877.

28.6

CHARACTERIZATION OF OXIDATIVE CAPACITY IN PRIMARY HUMAN SKELETAL MUSCLE CELLS: A SYSTEM FOR STUDYING METABOLIC DISEASE

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Skeletal muscle metabolism plays an important role in metabolic syndrome, obesity, and diabetes. Muscle oxidative capacity and insulin sensitivity is compromised in obese patients (Kiens, 2006) and can improve with weight loss (Corpeleijn, 2008). Insulin sensitizing drugs like AMPK activators (Thompson, 2007) and PPAR agonists increase muscle oxidative metabolism (Lefebvre, 2006). Understanding the obesity/muscle metabolism axis may help us identify novel therapeutic strategies for metabolic disorders. For screening purposes, relevant human cell models need to be established. Common tissue culture practice involves culturing cells in glucose rich media, which renders cells to derive ATP predominantly through glycolysis. In contrast, low glucose or galactose/glutamine containing media, force cells to generate ATP through mitochondrial OXPHOS (Marroquin et al., 2007). This knowledge encouraged us to establish a robust system to study oxidative capacity in primary human skeletal muscle cells. Cells grown in media containing 10 mM galactose as the energy source yielded high rates of oxygen consumption as compared to cells that where cultured in 25 mM glucose media, where respiration was very low. Cells grown in 5 mM glucose with 10 mM galactose yielded an intermediate result. This assay system will be used for exploring drug targets in muscle that could potentially improve whole body metabolism and weight control.

28.7

THE IMPACT OF OVARIAN HORMONE STATUS ON FUNCTIONAL AND CELLULAR CHARACTERISTICS OF SKELETAL MUSCLE

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To determine the impact ovarian hormones have on contraction-induced activation of signaling proteins thought to affect skeletal muscle metabolic function, C57/Bl6 female mice underwent bilateral ovariectomy (OVX) or SHAM surgery. Eight weeks later, mice were subjected to in situ or in vitro contractile protocols and AMPK, ERK 1/2, p38 and JNK phosphorylation was measured in control and fatigued limbs. Functionally, OVX mice were significantly more resistant to fatigue than SHAM mice using the in situ model, but, in vitro, no difference was observed between groups. AMPK phosphorylation was 30% higher in SHAM than OVX mice at rest, and contraction increased phosphorylation only in OVX mice using the in situ model. In vitro contraction significantly increased AMPK phosphorylation in SHAM and OVX mice with no difference between groups. In situ muscle contraction increased normalized ERK 2 phosphorylation to a greater degree in OVX compared to SHAM mice. The in vitro model produced similar increases in normalized ERK2 phosphorylation, with no difference between groups. Contraction significantly increased phosphorylation of p38 and JNK in SHAM and OVX mice using in situ and in vitro models, with no differences between groups. These data suggest that ovarian hormone status can impact the ability of contraction to activate cellular signaling processes in skeletal muscle. This work was supported by NIH Grant AR051396 (EES), AR053318 (CWW), K01AR053235 (RML) and MDA 4278 (RML).

28.8

HSP27 OVEREXPRESSION IS SUFFICIENT TO INHIBIT NF-KB ACTIVATION DURING SKELETAL MUSCLE DISUSE

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Heat shock protein 25 (Hsp25) and Heat shock protein 70 (Hsp70) are significantly decreased in skeletal muscle during disuse and are speculated to play a role in the loss of muscle mass. We have recently shown that overexpression of Hsp70 is sufficient to inhibit disuse-induced NF-kB and Foxo3a transactivation, and prevent muscle atrophy. However, it is currently unknown whether Hsp25 can also regulate these two major signaling pathways in skeletal muscle, which are required for disuse muscle atrophy. We therefore co-injected, and electrotransfered, a control or Hsp27 (human equivalent to murine Hsp25) expression plasmid plus an NF-κB or Foxo3a reporter plasmid into the soleus muscle of rats that were then assigned to weight bearing or 3-day hind limb immobilization groups. Hsp25 mRNA expression was decreased by 40% and protein level by 24%, following 3 days of immobilization. As expected, Foxo3a and NF-kB activities were increased in immobilized muscles, by 2.5-fold and 2.2-fold, respectively. Although overexpression of Hsp27 had no effect on Foxo3a activity, it completely abolished the disuse-induced increase in NF-kB activity. These findings show, for the first time, that overexpression of Hsp27 is sufficient to inhibit disuse-induced NF-kB activity in skeletal muscle, and therefore suggest that Hsp27 may attenuate disuse muscle atrophy.

28.9

HSP70 INHIBITS FOXO3A-DEPENDENT TRANSCRIPTION OF ATROPHY GENES IN SKELETAL MUSCLE

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Degradation of skeletal muscle protein through the ubiquitin proteasome pathway (UPP) is largely responsible for the skeletal muscle wasting that accompanies both systemic diseases, such as cancer and diabetes, as well as disuse. Activation of the UPP is mediated through the Foxo transcription factors, which regulate the transcription of atrophy genes, including the ubiquitin E3 ligases atrogin-1 (MAFbx) and MuRF1. However, other than Akt, the upstream regulators of Foxo-dependent transcription in skeletal muscle are largely unknown. We have recently shown that Hsp70, which is significantly downregulated during skeletal muscle atrophy, is sufficient to inhibit Foxo3a reporter activation and muscle fiber atrophy when overexpressed prior to disuse. To determine if Hsp70 can directly regulate Foxo3a, we injected and electrotransfered a WT Foxo3a expression plasmid plus either a control or an Hsp70 expression plasmid. WT Foxo3a induced a 3-fold increase in the transcription of a Foxo3a reporter plasmid, which was completely inhibited in muscles co-expressing Hsp70. Furthermore, Hsp70 prevented Foxo3a-induced promoter transactivation of both atrogin-1 (MAFbx) and MuRF1. Levels of phosphorylated Foxo3a were significantly increased in muscles co-expressing Hsp70, which suggests Hsp70 may inhibit Foxo3a by maintaining its phosphorylated (inactive) state. In conclusion, we identify Hsp70 as a novel repressor of Foxo3a-dependent transcription with vast therapeutic potential.

28.10

CAFFEINE ACTIVATES P38 MAPK VIA A CA^{2+} INDEPENDENT PATHWAY

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The mitogen-activated protein kinase p38 (p38) has been indicated as a downstream target of Ca^{2+} signaling, resulting in phosphorylation and increased activity of the myocyte enhancer factor 2. The aim of this study was to investigate the phosphorylation of p38 after acute caffeine treatment in the presence and absence of dantrolene, an inhibitor of sarcoplasmic Ca^{2+} release. C2C12 myotubes were incubated with 5mM caffeine for 30 and 60 minutes and harvested at time 0, 1 and 2 hours, post caffeine treatment. Western blot analyses showed a 1.6 and 1.9 fold increase ($P < 0.01$) in p38 phosphorylation after 30 and 60 minutes at time 0 hours, respectively, with values returning to baseline after 1 hour. Myotubes, pre-incubated with 10mM dantrolene 30 minutes prior to caffeine stimulation revealed the same profile in p38 phosphorylation as without. These results show that p38 may be activated by a Ca^{2+} independent pathway, but warrants further investigation to elucidate the upstream mechanisms.

28.11

GLUCOCORTICOIDS ACTIVATE UBIQUITIN TRANSCRIPTION IN MUSCLE BY SUPPRESSING PI3-KINASE: IMPLICATIONS FOR MUSCLE ATROPHY

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Muscle atrophy is a consequence of chronic systemic diseases (e.g., diabetes) that results from muscle-specific activation of the ubiquitin-proteasome (UbP) pathway. Glucocorticoids are required for these transcriptional responses. We previously demonstrated that glucocorticoids increased the transcription of the Ubiquitin C (UbC) gene in L6 myotubes by a mechanism involving MEK1 and the Sp1 transcription factor. Presently, we examined how glucocorticoids activate MEK1 and UbC transcription. Dexamethasone (Dex; 100nM) increased UbC promoter-driven luciferase activity by 205±7 % after 24 h and by 310±6% after 48 h (both are $P<0.05$ vs control). In the time course requiring > 24h, Dex increased MEK/ERK signaling, induced Sp1 phosphorylation and suppressed PI3-kinase (PI3K)/Akt signaling. To test if inhibition of the PI3K pathway reroutes cell signaling to the MEK/ERK pathway, cells were infected with an adenovirus encoding the PI3K p85 subunit to suppress PI3K activity. MEK1/2 phosphorylation and UbC promoter activity were increased. Thus, we propose that glucocorticoids increase MEK signaling and UbC transcription by an indirect mechanism involving suppression of the PI3K pathway. Our findings underscore the multifaceted role that glucocorticoids play in muscle atrophy due to chronic systemic diseases associated with increased glucocorticoid production, insulin resistance and muscle wasting. Supported by NIH DK61521.

28.12

ALTERATIONS IN AKT-FOXO3A SIGNALING BEFORE AND AFTER 12 WEEKS OF RESISTANCE EXERCISE IN YOUNG (24 YR) AND OLD WOMEN (85 YR)

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Skeletal muscle displays reduced size and function with increasing age, which is associated with reciprocal alterations in anabolic and catabolic processes. Resistance exercise (RE) has been shown to attenuate these changes in aging muscle, but little is known about the contributing signaling events. The purpose of this study was to examine the Akt-FOXO3a signaling pathway in response to acute and chronic RE. Six young (YW; 24±2y, 67±6kg) and 6 old women (OW; 85±1y, 67±3kg) completed 12 wks of progressive resistance training (PRT); 3 x 10 knee extensions at 70% of 1-RM,3 days/week. Prior to (acute) and following (chronic) the PRT, biopsies were taken from the vastus lateralis muscle before and immediately after a bout of RE under fasted conditions for Western analysis of phosphorylated (P) and total protein expression. Both groups displayed increases ($p<0.05$) in (P)Akt Thr308 with acute and chronic RE, with no change on Ser473 site. There was a surprising decrease ($p<0.05$ main time effect; driven by YW) in (P)FOXO3a Ser253 with acute and chronic RE in YW and OW. Prior to the PRT, OW displayed lower ($p=0.05$) resting (P)FOXO3a than YW, but both YW and OW trended ($p=0.14$) towards an increase in (P)FOXO3a after PRT. OW also had a greater ($p=0.06$) nuclear to cytosolic FOXO3a ratio after PRT. These data suggest that the communication of Akt with FOXO3a or FOXO3a alone may be altered in aged muscle at rest and in response to RE, attenuating the overall training adaptation in OW.

28.13

FOXO1 INHIBITS SKELETAL MUSCLE HYPERTROPHY

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To examine the role of FoxO1 in the regulation of skeletal muscle hypertrophy, wildtype (WT) and FoxO1overexpressing mice (FoxO1+/-) were exposed to synergist ablation (SA) or control (CT) surgery. After 14 days of CT or SA, plantaris muscles were assayed for changes in mass, protein content, cross-sectional area (CSA) and expression of total and phospho-Akt and -p70s6k via western blot analyses. Changes in MAFbx gene expression were assessed via qPCR. Although both strains exhibited significant increases in mass, protein content, and CSA after SA, increases were significantly greater in WT vs. FoxO1+/- (~60% vs. ~20%). SA resulted in increased total Akt in both strains; however, total Akt levels were higher in FoxO1+/- CT and SA vs. WT. Phospho-Akt (Ser473) was significantly greater in CT muscles of FoxO1+/- vs. WT mice. After SA, WT mice exhibited significant increases in phospho-Akt vs. CT, but FoxO1+/-

mice exhibited no further gains in phospho-Akt. Total p70s6k was not different between CT muscles of WT and FoxO1+/- mice and although total p70s6k increased after SA in both strains there was no significant difference between strains. Phospho-p70s6k (Th389) was elevated in both strains after SA; however, WT mice exhibited greater phospho-p70s6k than FoxO1+/-. MAFbx gene expression was elevated in FoxO1+/- vs. WT mice and was suppressed in both strains after SA. Thus, FoxO1 inhibits skeletal muscle hypertrophy through the suppression of anabolic cell signaling.

28.14

ENDURANCE TRAINING, INDEPENDENT OF WEIGHT LOSS, IMPROVES MITOCHONDRIAL OXIDATIVE CAPACITY AND ENHANCES INSULIN SIGNAL TRANSDUCTION IN LEAN AND OBESE MEN

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Background: Enhanced glucose uptake and improvements in insulin sensitivity associated with endurance exercise training are associated with changes in insulin signal transduction and mitochondrial proteins in skeletal muscle. Objective: In this study, we examined the effects of endurance training on insulin signaling and mitochondrial capacity in sedentary lean and obese men in the absence of weight loss. Methods: Eighteen sedentary lean (n = 9) and obese (n = 9) volunteers participated in a 16-week endurance training intervention. Insulin resistance was assessed using $HOMA_{IR}$. We measured cytochrome c oxidase (COX) activity, Akt/phospho-Akt, AMPK and GLUT-4 protein content in muscle biopsies before and after the intervention. Results: Endurance training improved aerobic capacity ($P < 0.001$) in both groups with no weight loss. IR improved non-significantly by 9.1% in obese men and 13.4% in lean men. COX ($P < 0.05$) and citrate synthase ($P < 0.001$) activity, Akt ($P < 0.01$), phospho-Akt ($P < 0.05$), AMPK ($P = 0.06$) and GLUT-4 ($P < 0.05$) protein content also increased following the exercise intervention. Conclusions: Endurance exercise training enhanced oxidative capacity and increased insulin signal transduction in the absence of weight loss and tended to improve insulin sensitivity in both lean and obese men. Research supported by CIHR.

28.15

RHOA REGULATION IS TRANSCRIPTIONALLY ACTIVE IN SKELETAL MUSCLE FOLLOWING ACUTE ECCENTRIC EXERCISE

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Skeletal muscle gene expression patterns are altered by the stimulus of eccentric exercise. Rho GTPases are involved in cytoskeletal organization and actin remodeling. These molecular signals switch between an active and inactive state via guanidine exchange factors (GEFs), GTPase activating proteins and a recently discovered transducer named striated muscle activator of Rho signaling (STARS). We measured skeletal muscle expression of mRNA in healthy males following 150 eccentric contractions. Muscle biopsies were collected before, 3 and 48 hours post exercise. Quantification of mRNA expression was determined using Affymetrix Gene Chips and protein quantified by Western Blotting. Three hours post exercise activators of Rho signaling: RhoGEF7, RhoGEF12, RND3 and STARS, were elevated by 1.3, 1.2, 5.4 and 10.1 fold respectively. RND3 protein levels were significantly increased 1.7 fold 48 hours post exercise. As well, a negative regulator Rho GTPase activating protein 24 was down regulated 0.8 fold. Genes downstream of RhoA involved in transcription (c-fos), actin remodeling (α-actinin) and stress fibre formation (DIAPH1) were elevated 14.8, 1.4 and 1.9 fold respectively. All genes returned to baseline expression at 48 hours after exercise. These findings indicate an early temporal pattern in steady-state mRNA content for genes involved in regulation of RhoA activity following a single bout of eccentric exercise. This research was funded by NSERC.

28.16

MULTIPLE SIGNALING PATHWAYS REGULATE THE CONTRACTILE ACTIVITY-MEDIATED INDUCTION OF PGC-1α TRANSCRIPTION IN SKELETAL MUSCLE CELLS

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Contractile activity of skeletal muscle is associated with cross-bridge cycling, increased ATP turnover, and ROS production. The expression of PGC-1α is also induced during contractions. The intent of this study was to investigate signaling mechanisms which may be responsible for the contraction-induced increase in PGC-1α expression. C_2C_{12} myoblasts were transfected with a 2.1 kb PGC-1α mouse promoter, and subsequently myotubes were stimulated (2 hrs, 5 Hz, 9 V) to elicit contractile activity. To assess the role of contraction-induced signaling, BTS (150 μM), Compound C (40 μM), and NAC (20 mM) were employed to inhibit myosin ATPase, AMPK activation, and ROS production, respectively, during stimulation. PGC-1α mRNA increased by 2-fold at 2 hrs of stimulation, with levels returning to baseline after 24 hrs of recovery. PGC-1α promoter activity was also increased by 40% following contractions. BTS completely attenuated the contraction-induced increase in promoter activity, despite electrical activation of the cells, and presumably calcium release. Inhibition of AMPK phosphorylation with Compound C had no effect on the contractile activity-induced increase in PGC-1α promoter activity. However, NAC abolished the contraction-elicited increase in PGC-1α transcription and mRNA expression. Thus, multiple signals, including cross-bridge cycling and ROS, play a role in regulating the contraction-induced transcription of PGC-1α in skeletal muscle.

28.17

MARK4 IS A NOVEL CAMKKα- AND CONTRACTION- REGULATED KINASE IN MOUSE SKELETAL MUSCLE

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Ca^{2+}/calmodulin-dependent protein kinase kinase α (CaMKKα) regulates AMP-activated protein kinase (AMPK) and contraction-induced glucose uptake in skeletal muscle. Importantly, we have shown that AMPK is not necessary for CaMKKα-mediated uptake. Thus, the mechanism by which CaMKKα regulates glucose uptake is unknown. Microtubule affinity regulated kinase (MARK) isoforms 2, 3 and 4 are highly homologous to AMPK, however no studies have assessed MARKs as CaMKKα substrates. Our goal was to determine if CaMKKα or contraction regulate MARKs in skeletal muscle. Plasmids containing constitutively active CaMKKα (caCaMKKα) or empty vector were transfected into mouse muscle by in vivo electroporation. After 2 wks, caCaMKKα protein was increased ≥20-fold over endogenous CaMKKα. caCaMKKα increased MARK4 activity 2-fold, but did not alter MARK2/3 activity. To determine if caCaMKKα regulated MARK4 independent of the other muscle AMPK kinase, LKB1, LKB1 knockout mice were transfected with caCaMKKα. In knockout mice, basal MARK4 activity was decreased 80%, and caCaMKKα increased MARK4 activity 10-fold over the contralateral leg. To determine if MARK4 is regulated by contractile activity, muscles were contracted in situ for 1, 2, 5 or 10 min. After 5 and 10 min, MARK4 activity was increased 2- and 3-fold, respectively. In conclusion, caCaMKKα and muscle contraction activate MARK4, implicating MARK4 as a novel CaMKKα- and contraction-regulated kinase in skeletal muscle. SUPPORT: NIH R01AR4670.

28.18

TIME COURSE AND DOSE RESPONSES OF MYOFIBRILLAR PROTEIN SYNTHESIS AND INTRACELLULAR SIGNALLING TO RESISTANCE EXERCISE BETWEEN 20 AND 90% 1 REPETITION MAXIMUM IN YOUNG AND ELDERLY MEN IN THE POSTABSORPTIVE STATE.

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To delineate the time-course and effects of exercise-intensity on muscle protein synthesis and anabolic signaling in the overnight fasted state we made measurements of myofibrillar protein synthesis (MPS, by incorporation of [1,2-$^{13}C_2$] leucine) and the phosphorylation state of p70S6K, eiF4BP1 and eEF2 (by immunoblotting) in groups (4-6) of young (25±5 y) and elderly men (69±5y) at rest, immediately post-exercise, and at 1-4 h afterwards. The subjects performed isotonic unilateral leg extension at 20-90% of 1 repetition maximum (RM) with similar total work outputs. In the young there was a curvilinear dose relationship of MPS with %RM at 1-2 h post-exercise after a 1 h lag; exercise at 75-90% caused increases of ~4 fold in MPS. In older subjects the responses were blunted by ~50%. In all subjects MPS fell 2-4 h post-exercise. The immediate post-exercise biopsies were characterized (irrespective of intensity or age) by a depression (~50%) of eIF4BP1 phosphorylation which rebounded to basal values by 1 h post-exercise, remaining steady thereafter; the pericontractile depression in MPS may be due to this depression of anabolic signaling. There were no significant changes in eEF2 phosphorylation at any time, casting doubt on its putative role in modulating MPS during and after resistance exercise. Post-exercise increases in P70S6k activity were significant only in the young subjects in whom they paralleled increases in MPS at 1-2 h then fell at 2-4 h post exercise.

28.19

P70S6K SIGNALING INDUCES EIF2B-EPSILON PROTEIN EXPRESSION IN RESPONSE TO MECHANICAL LOAD

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We have previously reported that the translational signaling response in skeletal muscle to unaccustomed mechanical load was different in those humans that ultimately experienced hypertrophy after 16 wk training (extreme responders, XR) vs. those that did not (non-responders, NR). Specifically, XR increased p70S6k phosphorylation and eIF2B-ε protein content, while NR did not. Since p70S6k signaling and eIF2B-ε content followed similar trends, and since p70S6k is known to control the translation of specific subsets of mRNAs, we hypothesized that mechanical load-induced p70S6k signaling could induce protein expression of eIF2B-ε. Western blotting of C2C12 myoblasts exposed to 1 h of 15% cyclical stretch at 1 Hz exhibited a 47% increase in eIF2B-ε content that occurred within 6 h of the cessation of stretch, which was preceded by a 106% increase in p70S6k phosphorylation (T389) that peaked 1 h post-stretch. Transfection of un-stretched myoblasts with wild type p70S6k resulted in a 216% increase in rpS6 phosphorylation and a 62% increase in eIF2B-ε content relative to un-transfected controls. Together these data suggest that p70S6k signaling can increase eIF2B-ε content and that this response may at least partially underlie mechanical load-induced myofiber hypertrophy. Ongoing experiments will determine the response of eIF2B-ε protein and mRNA levels to constitutively active and dominant negative p70S6k mutants both with and without mechanical load. F30AG031623, R01AG017896.

28.20

THE EFFECT OF HEAT SHOCK ON ACUTE HYPERTROPHIC SIGNALING FOLLOWING SKELETAL MUSCLE DAMAGE

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Heat shock proteins (Hsp's) have been implicated in reducing muscle damage and inhibiting muscle hypertrophy. The aim of this study was to determine if heat shock will inhibit hypertrophic signaling in muscle following eccentric exercise. Forty-eight hours prior to a bout of downhill running (18 m/min, -16% grade), Wistar rats were randomized into two treatment groups: eccentric only group (EE - core temp: 35.4°C + downhill running) and a heat stressed + eccentric group (HS+EE- core temp: 41°C, 20 min + downhill running). Soleus (Sol) and red vastus lateralis (VLR) muscles were assessed for Hsp70, Akt, p70s6k, and JNK 150 min following exercise. Both treatment groups were compared to a non-exercise / non-heat shock control to elucidate the effect of both eccentric actions and heat shock. The Sol muscle showed no differences ($p > 0.05$) between groups (Con, EE and HS+EE) for Akt & JNK, however both EE and HS+EE increased ($p < 0.05$) beyond controls for p70s6k and Hsp70. Further, in the Sol Hsp70 was found to be significantly higher ($p < 0.05$) in the HS+EE group as compared to the EE group. In the VLR both EE and HS+EE groups showed significant elevations ($p < 0.05$) over controls in the phosphorylation of Akt, p70s6k and Hsp70. There was no difference ($p > 0.05$) between the groups for JNK phosphorylation. Contrary to previous literature, our data suggests that the induction of Hsp's does not impair the acute hypertrophic signaling response in skeletal muscle.

29.0: FATIGUE

29.1

IMMOBILIZATION-INDUCED INCREASES IN FATIGUE RESISTANCE IS NOT EXPLAINED BY CHANGES IN THE MUSCLE METABOREFLEX

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Immobilization has been reported to enhance fatigability, which is paradoxical in light of the metabolic and molecular alterations that occur in atrophied muscles. We examined whether the immobilization-induced enhancement in fatigability was associated with attenuation in the muscle metaboreflex response. Ten subjects completed 3-wks of hand-forearm immobilization, and the time to task failure of a handgrip contraction (20% intensity) was determined along with heart rate and mean arterial pressure (MAP) at rest, during the task and during a 2-min post-exercise muscle ischemia (PEMI) test that continues to stimulate the metaboreflex. Immobilization decreased strength 25% ($p<0.01$), and increased the time to task failure 21% ($p=0.03$). However, no changes were observed for the HR and MAP responses to the exercise task or during PEMI ($p>0.05$). These findings indicate that the augmentation of time to task failure with immobilization is not associated with changes in the pressor or metaboreflex responses.

29.2

RELATIONSHIP BETWEEN MOOD PROFILES AND PLASMA TRYPTOPHAN RATIO DURING THE COMPETITION PERIOD IN ELITE FEMALE WRESTLER

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This study investigated the relationship between mood profiles and the ratio of plasma tryptophan to other neutral amino acids (plasma tryptophan ratio) during the competition period in elite female wrestlers. Eleven female elite wrestlers participated in this study. Subjects were determined the mood profile by profile of mood status (POMS) test and collected blood samples for amino acids determination one month before, just before, and one month after the competition. The body weight was reduced 1.8 kg (3%) just before the competition. Mean value of each t-scores of POMS (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor, Fatigue, and Confusion) and total mood disturbance (mean value of t-scores without Vigor; TMD) were not changed during experimental period. However, subjects were categorized into two groups by means of the value of TMD. The value of TMD in high TMD group (>50) was significantly higher than low TMD group (<50) through the experimental period. Furthermore, the value of TMD seemed to be increased at just before the competition in high TMD group. Although characteristic change of each amino acid in the plasma was not observed during experiment, tryptophan ratio in high TMD group was increased at just before the competition. Because it was suggested that increase in plasma tryptophan ratio induce central fatigue, the increase of TMD observed in high TMD group might be responsible for the increase of tryptophan ratio just before the competition.

29.3

GLYCOGEN HAS A STRUCTURAL ROLE IN MAINTAINING NORMAL EC COUPLING IN ELITE CROSS COUNTRY SKIERS, BY MODULATING SR CA2+ RELEASE RATE

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Skeletal muscle glycogen (Gly) content is closely related to fatigue. However, little is known about the precise mechanism of Gly on muscle function. In vitro studies, has proposed a structural role of Gly, affecting events in the excitation-contraction coupling. The aim of the present study was to examine the effect of Gly content on sarcoplasmic reticulum (SR) function in arm and leg muscles of elite cross country skiers (n=10, VO2max 72 ml kg-1 min-1), before, immediately after, and 4 h and 20h after a fatiguing 15-km race. During the first 4 hrs recovery, skier received either water or carbohydrate (CHO), thereafter having the same CHO enriched food. Arm muscle Gly was reduced to 31±4% and SR Ca2+ release rate decreased to 85±2% of initial level, directly after the race. 4h recovery with CHO, fully normalized SR Ca2+ release rate and Gly was noticeably recovered (59±5% initial). However, in the absence of CHO during the first 4h recovery, the muscle Gly and SR Ca2+release rate remained low and reduced (29±2% and 77±8%, respectively), with both parameters being normalized after remaining 16h recovery with CHO. Leg muscle Gly was decreased to a lesser extent (71±10% initial) and there were no effects on SR Ca2+ release rate. There were no effect on SR Ca2+ uptake in both arm and leg muscle. These observations strongly indicate that Gly content modulates the SR Ca2+ release rate, which is in agreement with the emerging concept of a structural role of Gly. ®

29.4

FATIGUE ALTERS IN VIVO FUNCTION WITHIN AND BETWEEN LIMB MUSCLES DURING RUNNING

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Although much is known about whole-limb force generation and muscle activation patterns in relation to fatigue under controlled conditions, we know little about the effects of whole-body fatigue on the in vivo dynamics of limb muscles. Here we show that limb kinematics and contractile function in the lateral (LG) and medial (MG) gastrocnemius of helmeted guinea fowl (Numida meleagris) are significantly altered with fatigue during steady running at 2 m s^{-1} on a level treadmill. Stride frequency was significantly lower in the fatigued trials (2.8±0.04 Hz) compared with the non-fatigued trials (3.1±0.03 Hz). Related to this was a decrease in the time to peak force for both the LG and MG with fatigue, suggesting selective fatigue of the fast-twitch fibers. Variation in peak force measured directly from the muscles' distal tendons increased significantly with fatigue, leading to higher peak muscle forces, and likely indicating that the limb bones were loaded with higher peak forces. This could help explain the increased susceptibility to bone injury that is associated with fatigue. Negative work increased in all muscles with fatigue, revealing the dynamic changes that can occur within muscles during fatigue. Fascicle shortening in the proximal MG, but not the distal MG, decreased significantly with fatigue. This is surprising given that muscles are often thought to function uniformly. This work was funded by an NIH grant (R01-AR047679).

29.5

FATIGUE IN A HILL-BASED MUSCLE MODEL OF HUMAN TIBIALIS ANTERIOR

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Computer simulations are useful for investigating variables that cannot easily be studied in vivo, such as the mechanics of individual human muscles during force production. The Hill muscle model is widely used in computer modeling, but its basic formulation cannot account for the effects of fatigue. Previous investigators have modified the Hill model to include fatigue by damping its active state or force output. However, a more realistic method of simulating fatigue is through alteration of basic muscle mechanical properties, as has been suggested by many experimental studies. Therefore, our purpose was to simulate fatigue in a Hill muscle model through adjustments of known muscle mechanical properties. A 4-min maximum voluntary isometric contraction (MVIC) of human tibialis anterior was simulated and its force output compared to in vivo data reported previously. When series elastic stiffness (K) and the range of lengths at which the muscle could develop force (W) were decreased as functions of time, the simulated force output declined during MVIC. A combination of limiting maximum neural excitation (central fatigue) and adjusting K and W nonlinearly (peripheral fatigue) matched both the magnitude and time course of fatigue seen in the literature. The nonlinear adjustments in K and W necessary to match experimental data suggest these parameters may be related to metabolite concentrations that follow similar time courses during a fatiguing MVIC.

30.0: MECHANOTRANSDUCTION

30.1

FUNDAMENTAL CHARACTERISTICS OF THE MECHANO-SENSING MACHINERY IN SKELETAL MUSCLE

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Mechanical signals play a central role in the regulation of skeletal muscle mass; however, even the most elementary properties of the mechano-sensing machinery have yet to be defined. Thus, the purpose of this study was to simply characterize how skeletal muscles respond to progressively higher magnitudes of mechanical stimulation (MS). To accomplish this, we subjected C2C12 myoblasts to progressively higher magnitudes of strain, strain rate, and strain time integral, and then evaluated the signaling responses of various molecules implicated in the regulation of skeletal muscle mass. Our results identified three distinct response patterns, i) linear increase in signaling as the magnitude of MS increased (P-p70(389) and P-ERK1/2), ii) non-linear (threshold) activation of signaling as the magnitude of MS increased (P-JNK2), and iii) maximal activation of signaling at all of magnitudes of MS (P-p70(421/424)). These distinct response patterns suggest that skeletal muscles posses multiple mechano-sensing machines, and these machines are activated by different types of mechanical information. Our current studies are now aimed at determining whether each response pattern is elicited specifically by changes in the magnitude of strain, the strain rate, or the strain-time integral. The results from these studies will provide fundamental biophysical information about the mechano-sensing machines and will facilitate future studies aimed at elucidating their molecular identity.

30.2

COSTAMERES ARE NODAL POINTS OF MYOFIBRE DIFFERENTIATION AND FORCE TRANSMISSION *IN VIVO*

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Sarcolemmal focal adhesions (costameres) have been hypothesized to integrate the contractile apparatus with the sarcolemma during lengthening and shortening of the muscle cells. Using a system approach we provide first evidence for a functional implication of costameres in mechano-transduction in fully-differentiated muscle fibres. Both, muscle-targeted overexpression of the focal adhesion modulators, focal adhesion kinase (FAK) and Tenascin-C, by gene electrotransfer of rodent muscle promoted the slow fibre expression program. Signal transduction to slow muscle transcript expression was under physiological control by muscle loading and functionally important as shown by fast-to-slow transformation of FAK-transfected muscle and fibres. FAK-overexpression also enhanced specific force in whole muscle but not single fibres due to the promotion of repair in damaged fibres after electrotransfer. The observations support the concept of a double role of costameres in lateral force transmission and chemical mechano-transduction upstream of slow fibre transformation. The load-dependence of costamere's control over muscle function has major implications for effective gene therapy of striated muscle. Supported by the 'Région Rhône-Alpes', the 'Association Française contre les myopathies' and the Swiss National Science Foundation.

30.3

DEPOLARIZATION OF MUSCLE CELLS FOLLOWING ECCENTRIC CONTRACTIONS CAN BE REVERSED

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The purpose of this study was to test the hypothesis that gadolinium (Gd^{3+}) treatment following the completion of eccentric contractions (EC) would reverse the depolarization known to occur trough the opening of stretch activated ion channels (SAC). The tibialis anterior muscles of rats were exposed to a single acute bout of 24 total EC. The resting membrane potential (RMP) was measured in-situ immediately following EC and compared to non-exercised contra lateral control muscles. TA muscles exposed to EC were significantly depolarized (-72.7 mV) compared to control (-82.3 mV). Gd^{3+} treatment by i.v. infusion (80μM/kg) resulted in a significant

repolarization of the muscle cells towards control values (-78.9 mV). Previously it has been shown that pre-treatment with Gd^{3+} prior to EC prevented the depolarization associated with the opening of SAC and significantly reduced the phosphorylation of proteins in the Akt/mTOR pathway. Experiments are currently underway to determine if blocking SAC following the completion of EC results in a similar significant decrease in the Akt/mTOR response. All procedures involving animals were approved by the IACUC of CSUB and followed APS guidelines.

31.0: GENOMICS/PROTEOMICS

31.1

FTO GENOTYPE IS ASSOCIATED WITH EXERCISE TRAINING-INDUCED CHANGE IN ADIPOSITY: THE HERITAGE FAMILY STUDY

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FTO gene is the first obesity-susceptibility gene identified by genome-wide association scans and confirmed in follow-up studies in Caucasians. Homozygotes for the risk allele (A/A) have 1.67 times greater risk of obesity than those who do not have the allele. However, it is not known if exercise training-induced changes in body composition are modified by the FTO genotype. The purpose of our study was to test if the FTO genotype is associated with training-induced changes in adiposity. Body composition was derived from underwater weighing before and after a 20-week endurance training program in 476 white subjects of the HERITAGE Family Study. FTO SNP rs8050136 was genotyped using Illumina GoldenGate assay. In sedentary state, the A/A homozygotes were significantly heavier and fatter than the heterozygotes and the C/C homozygotes in men ($p=0.004$) but not in women ($p=0.331$; gene-by-sex interaction $p=0.0053$). The FTO genotype was associated with body fat responses to training ($p<0.005$; adjusted for age, sex, and baseline value of response trait): carriers of the C-allele showed three times greater fat mass and %body fat losses than the A/A homozygotes. The FTO genotype explained 2% of the variance in adiposity training responses. Our data suggest that the FTO obesity-susceptibility genotype influences the body fat responses to training. Resistance to exercise training-induced reduction in total adiposity may represent one mechanism by which FTO A allele promotes weight gain.

31.2

MECHANISMS OF DECREASED FATTY ACID OXIDATION IN SKELETAL MUSCLE OF MORBIDLY OBESE INDIVIDUALS

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In lean individuals, exposure of skeletal muscle to increased lipid, such as during a high fat diet, results in changes to gene expression that promote lipid oxidation. The ability of skeletal muscle to oxidize lipid is compromised with obesity, an effect for which mechanisms are unknown. Our aim was to determine if the lipid-induced transcriptional regulation of genes involved in lipid oxidation is impaired in skeletal muscle from obese individuals. Satellite cells were isolated from lean (L; N=8) and morbidly obese (Ob; N=8) women. Myotubes were incubated for 24h in no lipid, oleate (O) or oleate:palmitate (O:P). mRNA content was analyzed via microarray analysis. 318 genes were different ($P<0.01$) at baseline between groups. Many of these genes are part of the retinoic acid receptor (RXR) pathway, with differences in SR-B1 (+5.9 fold) and P2RY2 (-3.6 fold) in Ob vs. L groups. 1023 genes were different between groups after O treatment, including the attenuation of lipid-induced CPT1B upregulation (+1.6 fold in L) in the OB group. 323 genes were different between groups after O:P treatment, including downregulation of NCOA1 (+2.9 fold in L; -2.6 fold in Ob). These findings suggest that the skeletal muscle of obese and lean individuals respond differently to lipid exposure. Many of the differentially expressed genes are associated with RXR pathways. These data suggest that RXR and related pathways may affect the capacity of skeletal muscle to adapt to increased lipid availability.

31.3

PHOSPHORYLATION OF HEAT SHOCK PROTEIN 20 AT SERINE 16 IS INDUCED IN THE RAT HEART IN RESPONSE TO ENDURANCE EXERCISE

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A proteomics approach was used to further understanding of the adaptation of the heart in response to a standardised regimen of endurance exercise. Rats (~280 g) performed exercise tests on a motorised treadmill to measure their peak oxygen uptake (VO2peak) and were prescribed 6 weeks of endurance exercise (75 % VO2peak for 30 min, 4 days per week). Left ventricles were isolated from weight-matched control and exercised animals (n = 6, in each group) 4 h after the final exercise test. Homogenates were resolved using 2-dimensional electrophoresis and gene products identified by searching tryptic peptide- and fragment-ion spectra against the Swiss-Prot database using Mascot. Twenty-three gel spots were differentially expressed ($P<0.05$) in exercise-trained hearts. The expression of myofibrillar proteins (e.g. alpha-myosin heavy chain and cardiac alpha-actin), and proteins associated with fatty acid metabolism (e.g. heart fatty acid binding protein, acyl-CoA dehydrogenase and mitochondrial thioesterase-1) was increased. In addition, endurance training induced a shift in the gel pattern of heat shock protein 20 indicative of phosphorylation, and analysis of fragment ion spectra mapped this modification to serine 16. Phosphorylation of heat shock protein 20 at serine 16 is associated with improved cardiomyocyte contractility and protection against apoptosis, and is a therapeutic target against heart disease. These data show that endurance exercise is able to induce this modification.

31.4

PROTEOMIC IDENTIFICATION OF SEX-SPECIFIC DIFFERENCES IN MUSCLE HEAT SHOCK PROTEIN EXPRESSION IN RESPONSE TO INTERVAL TRAINING

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Proteomics techniques were used to provide a broad assessment of the adaptation of human muscle in response to interval exercise training. Recreationally active men and women (n=5, each) completed a six-week training programme involving 3 sessions per week, utilising six 1-minute bouts at 100 % maximum oxygen uptake (VO2max) interspersed with 4 minutes at 50 % VO2max. The vastus lateralis was biopsied at standardised times before, and after, the training intervention. Proteins were resolved using 2-dimensional electrophoresis and gene products identified by searching tryptic peptide-and fragment-ion spectra against the Swiss-Prot database using Mascot. Interval training increased average VO2max by 8 % in men and 7 % in women ($P=0.001$). In males, the expression of 7 gene products was significantly different after interval training. For example, muscle creatine kinase increased 50 % ($P=0.022$) and fast troponin T by 60 % ($P=0.032$). In contrast, slow troponin T decreased 115 % ($P=0.008$), suggesting a transition toward a faster contracting muscle phenotype. In women, only the expression of heat shock protein 27 was significantly ($P=0.032$) increased (35 %), whereas, in men significant increases in the expression of heat shock proteins 70 (8 %; $P=0.012$) and 20 (31 %; $P=0.009$) was detected. Thus, a standardised regimen of interval training induced greater adaptation in men than women and resulted in sex-specific adaptations in muscle heat shock protein expression.

31.5

SKELETAL MUSCLE CAPILLARITY AND EXERCISE CAPACITY IS INCREASED IN THROMBOSPONDIN-1 KNOCK-OUT MICE

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Thrombospondin-1 (TSP-1) is a multifunctional matrix glycoprotein found in many body tissues, including skeletal muscle. TSP-1 has been shown to inhibit and regulate angiogenesis under a number conditions, such as tumor growth, wound healing, retinal angiogenesis and during the menstrual cycle. We have previously reported the 1-hour acute exercise increases skeletal muscle TSP-1 mRNA, yet the importance of TSP-1 in regulating skeletal muscle angiogenesis is still not yet known. Therefore, the purpose of this study was to examine exercise capacity and skeletal muscle capillarity in 4-month old global (whole-body) TSP-1 knock-out (KO, n=6) mice compared to wild-type (WT, n=5) mice. The results indicated significant ($p < 0.05$) increases in maximal running speed (mean ± SEM, 37.6±1.2 vs 34.7±1.0 m/min), time to running fatigue (60±1 vs 36±5 min), capillarity-to-fiber ratio (plantaris m. 1.25±0.05 vs 0.68±0.08; solues m. 1.34±0.03 vs 0.89±0.04) and body mass (27.6±1.5 vs 21.3±0.5 g) in KO compared to WT, respectively. There were no significant differences in muscle (plantaris, soleus and gastrocnemius) mass between KO and WT. These data provide evidence that TSP-1 is an important negative angiogenic regulator involved in the basal regulation of skeletal muscle capillarity. Support by NIH 5R24-HD050537, TRDRP #16FT-0060 and Parker B. Francis Fellowship.

31.6

RELATIONSHIPS BETWEEN CHANGES IN CIRCULATING METABOLIC INTERMEDIATES AND INSULIN SENSITIVITY WITH SIX MONTHS OF AEROBIC EXERCISE TRAINING OR INACTIVITY.

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Exercise training can improve insulin sensitivity, but the mechanisms by which these improvements occur remain unclear. Here, we explored the potential for a targeted mass-spectrometry based platform to provide insight into the mechanisms by which exercise training mediated improvements in insulin action. This investigation was performed in 72 sedentary, dyslipidemic individuals randomized to six months of continued inactivity or supervised aerobic training. Insulin sensitivity (S_I) was derived from a frequently sampled intravenous glucose tolerance test. Plasma concentrations of 75 circulating amino acids, acylcarnitines, free fatty acids, and conventional metabolites were measured at baseline and after six months of training or inactivity. Principal components analysis followed by linear regression was used to explore relationships between changes in metabolite concentrations and change in S_I. The 75 metabolite changes clustered into 19 retained factors. A factor comprised of changes in 8 free fatty acids and ketones was inversely related to change in S_I ($P<0.0001$). A factor containing changes in citrulline and glycine was positively related to improvements in S_I ($P<0.005$). Both of these relationships were independent of one another, age, gender, and waist circumference ($P<0.0001$, $r^2=0.35$). These finding suggest that changes in fatty acid, citrulline, and glycine concentrations might serve as a metabolic signature of changes in insulin action induced by exercise training.

31.7

ANALYSIS OF THE EFFECT OF HIGH PROTEIN-CARBOHYDRATE NUTRITION ON GLOBAL MRNA EXPRESSION IN SKELETAL MUSCLE DURING RECOVERY FROM HIGH-INTENSITY ENDURANCE EXERCISE

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Novel pathways in skeletal muscle responding to the ingestion of high protein-carbohydrate nutrition following exercise were identified using Illumina®BeadArrays. In a crossover design, 8 cyclists completed 1.75h of high-intensity cycling followed by ingestion of protein-rich (1.2/0.4/0.2 $g \cdot kg^{-1}$ carbohydrate/protein/fat) or control (1.6/0/0.2)food. Biopsies were collected from V. lateralis at 3 and 48h post exercise. Global error assessment was used to identify differentially expressed genes (detection threshold $P<0.01$), which were then assigned into over or under expressed biological pathways using Panther. Overall, 158 genes were found to be differentially expressed at 3h, and 103 genes at 48h. Protein lead to over expression of muscle contraction followed by immunity and defence genes at 3h, and carbohydrate metabolism and transport mechanism genes at 48h. Genes expressed at both time points but differentially regulated included: protein complex assembly, stress response, immunity and defence, protein folding (regulated up at 3h and down at 48h); and lipid and fatty acid transport; lipid and steroid metabolism, and muscle contraction (regulated down at 3h and up at 48h). Within this subset, over expressed genes were those involved in Hsp70 chaperone, chaperone, and nucleic acid binding at 3h, and transporter processes and apolipoprotein at 48h. The protein component of post-exercise nutrition facilitates targeted adaptive responses to high-intensity exercise stress.

31.8

DOES DNA METHYLATION OF THE MYOSIN HEAVY CHAIN IIB GENE PROMOTER REGULATE EXPRESSION DURING SKELETAL MUSCLE DIFFERENTIATION?

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DNA methylation regulates gene expression through attachment of methyl groups to cytosine at CpG sites often located in the promoter region of the gene. We sought to determine if genes encoding the contractile proteins that characterize differentiated skeletal muscle cells are regulated by DNA methylation. DNA or RNA was isolated from C2C12 myoblasts or 4, 8, 12, 24, 48, and 72hrs after the induction of the differentiation process. RT-PCR was used to determine the expression patterns of DNA methyltransferase I (DNMT1) and myosin heavy chains (Myh) perinatal and types I, IIa, IIb and IIx in the muscle cells, as well as liver (control). Myh type IIb RNA was first expressed after 48hrs of differentiation; Myh type IIb was not expressed in liver cells. DNMT1 was expressed in all tissues and at all time points. DNA methylation of CpG sites within the Myh IIb promoter was examined by bisulfite treatment followed by direct DNA sequencing. Bisulfite treatment revealed minimal methylation of the CpG sites in the Myh IIb promoter region (-3235 to -3025) across all time points in the C2C12 cells, while liver cells exhibited consistent CpG methylation in the IIb promoter. Promoter DNA methylation in Myh type IIb does not appear responsible for the regulation of transcription in C2C12 cells during differentiation, but methylation of the promoter may ensure that promoter activation does not occur in non-muscle tissue. We are currently confirming these results across the other Myh genes.

31.9

MIRNA-MEDIATED REGULATION OF METABOLIC CONTROL AND MUSCLE DIFFERENTIATION FOLLOWING ACUTE ENDURANCE EXERCISE

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MicroRNAs (miRNAs) are evolutionarily conserved, genomically encoded, small non-coding RNA species involved in post-transcriptional gene regulation by controlling translation or stability of mRNA. In vitro studies have identified a small number of muscle-specific miRNAs that play a crucial role in myoblast proliferation and differentiation. In skeletal muscle, an acute bout of endurance (END) exercise results in up-regulation of transcriptional networks involved in regulating mitochondrial biogenesis, glucose and fatty acid metabolism, and skeletal muscle maintenance. The objective of this study was to assess the expressional profile of muscle-specific miRNAs following an acute bout of END exercise, which may correlate with previously observed transcriptome networks. Equal numbers of C57Bl/6J wild-type mice (N = 7/group) were randomly assigned to either sedentary (SED) or forced-endurance (END) exercise bout group (treadmill run @ 15 m/min for 90 min). We analyzed quadriceps femoris for miR- 181, 1, 133, 23, and 107 expression (TaqMan® miRNA Assays) that have been predicted to regulate Hox-A11/MyoD/myogenin/MHC, HDAC4, SRF, PGC1α, and PDK4/PANK expression, respectively. END exercise increased miR-181, miR-1, and miR-107 expression by 37%, 40%, and 56%, respectively, and reduced miR-23 expression by 84% ($P \leq 0.05$ for all), with no change in miR-133. We conclude that miRNA-mediated post-transcriptional regulation is integrally involved in the complex regulatory networks that govern END exercise-mediated physiological adaptations. (This research was supported by NSERC).

31.10

EFFECTS OF DIETARY FOLATE INTAKE AND PHYSICAL ACTIVITY ON THE INTERACTION BETWEEN THE PLASMA HOMOCYSTEINE AND MTHFR GENOTYPE

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PURPOSE: Elevated plasma homocysteine concentration has been identified as an independent risk factor for future cardiovascular disease. The C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) enzyme gene had reduced enzyme activity and higher homocysteine. The purpose of this study was to examine the effect of physical activity or folate intake on the association of plasma homocysteine level and the MTHFR C677T genotype. METHODS: The MTHFR C677T was genotyping 751 Japanese men and women aged 18-85 years. Fasting plasma concentration of homocysteine was determined. Amount of physical activity was measured by accelerometer, and dietary folate intake was estimated using a food-frequency questionnaire (BDHQ). RESULTS: Plasma homocysteine level in the subjects with 677TT genotype was significantly higher than that with CC and CT genotype. Dietary folate intake was also significantly associated with the plasma homocysteine. In the TT genotype, the plasma homocysteine in the subjects with higher folate intake was significantly lower than that with lower folate intake. However, there were no effects of physical activity on the interaction between the plasma homocysteine and MTHFR genotype. CONCLUSION: These results suggest that dietary folate intake is associated with the interaction between plasma homocysteine level and the MTHFR genotype, but physical activity was not. This study was supported by grants from the JSPS and MHLM in Japan.

31.11

PLASMA METABOLIC PROFILING OF ACUTE EXERCISE IN HUMANS

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Emerging metabolic profiling tools have raised the possibility of establishing metabolic signatures of exercise. We applied metabolic profiling to subjects with normal exercise capacity undergoing treadmill ETT (N=26, Age 51±11, 62% male) and bicycle ergometry CPET (N=16, age 52±12, 60% male). Peripheral plasma samples were obtained at baseline, peak exercise, and 60 min. post-exercise. Plasma was fractionated by liquid chromatography and measurement of metabolites was performed using a high-sensitivity electrospray triple quadrupole mass spectrometer under selected reaction monitoring conditions for 210 human metabolites. We identified previously reported changes in plasma metabolites reflecting adenine nucleotide catabolism, protein catabolism (phenylalanine and tyrosine), and heightened TCA cycle anapleurosis (alanine, pantothenic acid) in both cohorts. Changes in plasma levels of TCA cycle span 2 intermediates at peak exercise (i.e. succinic acid +313%, malic acid +172%, and fumaric acid +176%, all P<0.005 vs. baseline in both cohorts) closely mirrored previously reported intramuscular changes in these metabolites during exercise and persisted for 60 min. Finally, metabolic profiling demonstrated novel changes in bioactive molecules not previously known to be modulated by exercise. In conclusion, metabolic profiling identifies plasma signatures of alterations in intramuscular metabolic pathways and elucidates novel metabolic changes associated with exercise.

31.12

THE ARG16GLY POLYMORPHISM OF THE BETA-2 ADRENERGIC RECEPTOR AND MUSCULAR EFFICIENCY DURING EXERCISE

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The efficiency of a muscle during exercise is the ratio of power output to the rate of energy expended. The β2-adrenergic receptors (ADRB2) are associated with oxidative capacity in skeletal muscle, and are found in higher numbers in those muscles that have the greatest contractile potential. One variant of the ADRB2 is a substitution of Arginine for Glycine at amino acid 16. Given that the ADRB2 plays a role in muscular function, we sought to determine if there were differences in muscle efficiency during exercise between Arg16Arg (n=16), Arg16Gly (n=17), and Gly16Gly (n=31) subjects (age=29±6, 28±6, and 29±6yrs, BMI=23±3, 24±3, and 25±4kg/m2, VO2peak=32±6, 37±7 and 35±8ml/kg/min for Arg16Arg, Arg16Gly, and Gly16Gly respectively, mean±SD). We measured power output and VO2 across the genotype groups during light exercise (work=71±20, 86±21, and 82±27watts, p<0.05: VO2=17±3.4, 18±2.3, and 18±3.4ml/kg/min) and heavy exercise (Work=140±42, 170±43, and 164±57watts, p<0.05: VO2=27±5, 31±5, and 30±7ml/kg/min). Muscular efficiency was calculated by dividing the work by the energy expended (light ex eff = 16.3±2.8, 15.8±1.7, and 15.8±2.6: heavy ex eff=17.6±2.0, 16.8±1.7, and 16.7±1.7, p<0.05). Change in efficiency (from light to heavy exercise) was then calculated (Δeff=18.1±3.3, 17.8±3.6, 17.8±3.7). These results suggest that genetic variation of the ADRB2 does not influence muscular efficiency with short-term exercise in healthy young adults.

31.13

EXERCISE PROTEOMICS: ALTERATIONS IN THE HUMAN VASTUS LATERALIS MUSCLE PROTEOME AFTER ECCENTRIC EXERCISE

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This descriptive screening study aimed at discovering changes in expression of human skeletal muscle proteins after eccentric exercise using proteomics. Ten male subjects (mean age 31, range 21-58) years completed 45 min of downhill (8¢X) running at approximately 60% of their VO2max. A matched group non-runners served as controls. Biopsies from the vastus lateralis muscle were taken 48 h after running. Physiological measurements and muscle soreness were recorded before and during the exercise. Muscle samples were analyzed using immunohistochemistry, 2-dimensional difference gel electrophoresis (DIGE) and mass spectroscopy. A total number of 2458 individual spots were identified which after filtration was reduced to 612 protein spots used for statistical calculations. Compared to controls the expressions of 7 spots were higher (actin, desmin, Ubiquinol-cytochrome-c reductase complex core protein I), 7 were lower (Calsequestrin-1, Splics Isoform 2 LIM domain-binding protein 3, Ras-related protein Rab-35 and Haemoglobin) and 10 were correlated to physiological variables. Correlations included: max heart rate and age to ATP synthase; CK activity in the blood to CK expression in muscle; DOMS and Pain to Rab 35; CD3 in muscle to Four and a half LIM domains protein 1 and Myoglobin; CD11b in muscle to Peroxiredoxin-6 and Four and a half LIM domains protein 1; CD163, IL-1beta and VO2max were correlated to unidentified proteins. It is concluded that voluntary eccentric exercise in humans increased cyoskeletal proteins and decreased proteins related to calcium storage. Physiological variables such as age, heart rate and VO2max were related to differential protein expression in skeletal muscle.

32.0: MOLECULAR REGULATORY MECHANISMS

32.1

CAMK ACTIVATION BY CAFFEINE INCREASES NRF-1 BINDING TO THE MEF2A PROMOTER AND THE EXPRESSION OF BOTH MEF2A AND GLUT4 IN C2C12 MYOTUBES

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Studies have consistently shown that skeletal muscle mitochondrial proteins and GLUT4 are up-regulated by exercise (Boirie et al., 2001) or caffeine in a CaMK-dependent manner (Ojuka et al., 2003) but the signal that coordinates these responses remain elusive. Expression of many mitochondrial proteins are regulated by Nuclear Respiratory Factor (NRF)-1 whereas of GLUT4 by MEF2. Recently, Baar et al (2003) overexpressed NRF-1 in mice and observed increases in a number of mitochondrial proteins, MEF2A and GLUT4. These observations prompted us to hypothesize that NRF-1 might be the signal that coordinates GLUT4 expression and mitochondrial biogenesis. Our hypothesis is that CaMK activation increases the binding of NRF-1 to its cis elements on the mef2A promoter to increase MEF2A content and binding to the glut4 gene. Differentiated C2C12 cells were treated with 10 mM caffeine to activate CaMK in the presence or absence of 25 μM KN93. Quantitative RT PCR and Western blot were used to measure MEF2A and GLUT4 mRNA and protein levels, respectively. Chromatin immunoprecipitation (ChiP) assay was used to assess the binding of NRF-1 to the mef2 and Ala synthase (Alas) promoters and MEF2A to the glut4 promoter Compared to controls, caffeine increased the expression of GLUT4, MEF2A and ALAS ~1-2 fold. The amount of NRF-1 that was bound to Mef2A and Alas promoters and that of MEF2A to the Glut4 promoter was increased 1.8 - 2.2 fold. The above effects of caffeine were abolished when CaMK activity was inhibited by KN93. These results support the hypothesis that NRF-1 mediates the coordinated expression of ALAS and GLUT4 genes in response to CaMK signalling.

32.2

FUNCTIONAL INTERACTION OF REGULATORY FACTORS WITH THE PGC-1α PROMOTER IN RESPONSE TO EXERCISE BY *IN VIVO* IMAGING

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Real-time optical bioluminescence imaging is a powerful tool for studies of gene regulation in living animals. To elucidate exercise-induced signaling/transcriptional control of the peroxisome proliferator-activated receptorγ coactivator α (Pgc-1α) gene in skeletal muscle, we combined this technology with electric pulse-mediated gene transfer to co-transfect Pgc-1α reporter gene with plasmid DNA encoding mutant/deletion forms of putative regulatory factors to assess the responsiveness of the promoter to motor nerve stimulation. We show here that each of the MEF2 sites on the Pgc-1α promoter is required for contractile activity-induced Pgc-1α transcription. The responsiveness of the Pgc-1α promoter to contractile activity could be completely blocked by overexpression of dominant negative form of activating transcription factor 2 (ATF2), signaling-resistant form of histone deacetylase 5 (HDAC5) or protein kinase D (PKD), but not by that of HDAC4. These findings provide in vivo evidence for functional interactions between PKD/HDAC5 and ATF2 regulatory factors and the Pgc-1α gene in adult skeletal muscle.

32.3

ENDURANCE EXERCISE AFFECTS TRANSCRIPTION OF UBIQUITIN PROTEASOME PATHWAY COMPONENTS

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Studies examining acute effects of exercise on transcriptional markers of protein turnover in human skeletal muscle have been limited to resistance exercise. Molecular regulation of protein turnover during endurance exercise is not well-characterized. We examined alterations in transcription factors associated with protein turnover in muscle following 60 min of cycling exercise. Muscle biopsies obtained from 10 men (23±3yr, 176±4cm, 79±7kg) 120, 280 and 300 min after rest or exercise (60±5% VO2 peak), were analyzed for mRNA levels of UPP components, FOXO transcription factors, and myogenic regulatory factors. Compared to the corresponding resting time points, MuRF and Atrogin-1 mRNA was upregulated ($p<0.05$) 4.7-, 5.8-, and 5.7-fold and 1.2-, 3.0-, and 3.2-fold, respectively, at 120, 280, and 300 min post-exercise. FOXO3, a transcription factor for inducing Atrogin-1, was upregulated ($p<0.05$) 2.6-fold 120 min post-exercise, with values returning to baseline by 280 min post-exercise. Exercise had no effect on mRNA abundance for UPP components (E3 Alpha, PSMA1), FOXO transcription factors (FOXO1, FOXO4), or myogenic regulatory factors (Myostatin, IGF-I). These observations are the first to document alterations of regulators of the UPP in humans in response to endurance exercise, expanding our understanding of the transcriptional response to endurance exercise.

32.4

APOPTOSIS RESISTANCE OF DIFFERENTIATED MYOTUBES IS ASSOCIATED WITH ENHANCED ANTI-DEATH MECHANISMS

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Apoptosis is associated with skeletal muscle atrophy, while differentiation often results in increased apoptosis resistance. The objective of this study was to investigate mechanisms underlying apoptosis susceptibility in myoblasts and differentiated myotubes. C_2C_{12} myoblasts and myotubes were treated with H_2O_2 (1mM) or staurosporine (Stsp, 0.5uM) to induce apoptosis. H_2O_2 and Stsp induced apoptosis in more than 50% myoblasts, but only less than 10% myonuclear death in myotubes was observed. Mitochondrial membrane potential transition was detected in myoblasts with H_2O_2 and Stsp, while this response was greatly diminished in myotubes. Caspase-3 activity was 20-fold higher in myotubes, than myoblasts, and Stsp caused a significant caspase-3 induction in both. However, exposure to H_2O_2 did not lead to caspase-3 activation in myoblasts, and only to a modest induction in myotubes at higher concentrations. Caspase-2, -8 and -9 responded similarly to differentiation and apoptosis induction as caspase-3. Gene expression of apoptosis repressor, ARC, and of Hsp70 and -27, caspase-inhibitors, was significantly higher in myotubes compared to myoblasts, and ARC was suppressed by H_2O_2 or Stsp. Interestingly, protein abundance of endonuclease G was higher in myotubes than myoblasts. These results suggest that apoptosis resistance in myotubes may be mediated by enhanced anti-caspase mechanisms, and caspase-independent pathways may have evolved for myonuclear apoptosis. Supported by AG028925

32.5

HIGH ACTIVE C57L/J MICE HAVE DIFFERENT DOPAMINERGIC PROFILES COMPARED TO LOW ACTIVE C3H/HEJ MICE

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This study investigated differences in expression of seven dopamine genes (Drd1, Drd2, Drd3, Drd4, Drd5, Tyrosine Hydroxylase (TH), and Slc6a3) between high active C57/LJ (n=5) male mice and low active C3H/HeJ (n=20) male mice, and between mice with access to a running wheel (RW) and without RW access (non-RW) within strain. RW mice were housed with running wheels interfaced with a bike computer for 21 days with distance and duration recorded every 24 hours. On day 21, the nucleus accumbens and striatum were removed during the active period (~9pm) for dopaminergic analysis. All procedures were approved by IACUC. C57L/J mice ran 99% farther, 98% longer, and 65% faster than the C3H/HeJ mice. No differences in gene expression were found between RW and non-RW mice within strain. Relative expression for 4 dopamine genes was significantly lower in the C57L/J mice compared to the C3H/HeJ mice [Drd1 ($p=0.027$), Drd2 ($p=0.026$), Drd4 ($p=0.001$), and TH ($p=0.05$)]. These results support previous work which suggests decreased dopaminergic functioning is correlated with increased activity levels in mice. This research was supported by NIH Grant NIAMS AR050085.

32.6

RAPID INCREASES IN SKELETAL MUSCLE PGC-1α AND PPAR CONTENTS PRECEDE INCREASES IN MITOCHONDRIAL ENZYMES DURING HIGH-INTENSITY INTERVAL TRAINING IN MEN

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The PGC-1 and PPAR isoforms are believed to mediate transcription of metabolic genes during exercise-induced mitochondrial biogenesis. Mitochondrial fusion may also facilitate training-induced increases in oxidative capacity. To determine the time-course that transcriptional and mitochondrial proteins respond throughout high-intensity interval training, 9 male subjects completed 7 training sessions over 2 weeks. Resting biopsies of the vastus lateralis were obtained before training and 4 and 24 hrs after the 1st, 3rd, 5th and 7th sessions. The protein contents of PGC-1α (23%), PPARα (25%) and PPARγ (16%) were greater 24 hr after the initial training session. Increases in citrate synthase and β-hydroxyacyl CoA dehydrogenase maximal activities were observed 24 hrs after session three. PGC-1β (18%) and PPARβ/δ (21%) contents were increased 24 hr after three and five sessions, respectively. PGC-1α and PPARα continued to increase whereas PGC-1β returned to baseline after 7 sessions. Training increased the mitochondrial fission proteins Fis-1 (73%; 5th session) and DRP-1 (32%; 3rd session) and the fusion protein MFN-1 (27%; 7th session), but not MFN-2. Increased PGC-1α and PPAR contents precede the increases in mitochondrial enzymes and likely amplify the early stages of training-induced mitochondrial biogenesis in human skeletal muscle. Mitochondrial fusion and fission may occur early during training to re-model the mitochondrial network. Supported by NSERC, Canada and CIHR.

32.7

TUMOR SUPPRESSOR P53 DETERMINES AEROBIC EXERCISE CAPACITY

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Tumor suppressor p53 regulates mitochondrial respiration by transactivating the Synthesis of Cytochrome c Oxidase 2 (SCO2) gene, an important component of the cytochrome c oxidase (COX) complex (Matoba et al, Science 312, 1650-3, 2006). In preliminary tests we reported decreased swimming endurance in p53-deficient (p53-/-) mice although morphometric analyses revealed no significant differences in comparison to wild-type counterparts. The effect of p53 on aerobic exercise capacity remains to be elucidated. We examined various cardiovascular and skeletal muscle characteristics of p53-/- mice, that could influence their exercise performance. The exercise capacity of p53-/- mice were significantly reduced by treadmill testing as well, and no motor coordination abnormalities were detected. Biochemical studies revealed increased blood lactate levels in p53-/- mice after submaximal exercise indicating aerobic insufficiency compared to p53+/+ mice. Substantial defects in physiological adaptation to aerobic exercise training were also observed in p53-/- mice. Molecular mechanisms by which p53 may regulate exercise capacity and mitochondrial function will be presented. Insights from our studies may allow the development of new strategies for modulating bioenergetic abnormalities through a tumor suppressor pathway with potential implications for improving health.

32.8

ACTIVITY OF THE ANTISENSE BETA MYOSIN HEAVY CHAIN GENE PROMOTER DEPENDS ON THE NF1/CTF1 BINDING SITE IN RAT HEARTS

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The rat heart expresses two MHC isoforms: beta (b) and alpha (a); these genes are arranged in tandem on the chromosome. We have reported that an antisense (AS) b RNA starts in the intergenic (IG) region between b and a genes and extends to overlap the b gene. We propose that in adult rats, both b sense and IG AS b RNA promoter are activated, but the transcription of AS bRNA interferes with the accumulation of sense b, resulting in low levels of b mRNA. We reported that 1340bp and 559bp sequences of the b AS IG promoter injected into rat ventricle were activated in control heart and decreased greatly in response to hypothyroid (PTU) and diabetes (STZ) and increased in hyperthyroid (T3) rats, similar in pattern to the endogenous AS b RNA. This indicates that STZ and PTU responsive regulatory elements are within the 559 (-2285/-1726) promoter region. Mutation of either an RAR element or a nuclear factor 1/CAAT box TF 1 (NF1/CTF1) binding site nearly abolished promoter activity in control, STZ and PTU rats. These two element sequences overlap in this promoter region. Clearly this region (-1944/-1955) containing overlapping RAR and NF1 sites is significant in the regulation of the AS b promoter. EMSA analysis shows that ventricular nuclear proteins are binding the NF1/CTF1 site, and not the RAR element, indicating that NF1/CTF protein is relevant in the regulation of this promoter. Support: American Diabetes Assoc; NIHLB.

32.9

POSSIBLE INVOLVEMENT OF LIPIN-1 IN MITOCHONDRIAL ENZYME ADAPTATIONS TO ENDURANCE EXERCISE IN RAT SKELETAL MUSCLE

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Endurance exercise induces mitochondrial biogenesis in skeletal muscle. However, the precise mechanisms by which this adaptation occurs are not known. It has been shown that lipin-1 acts as a transcriptional coactivator in liver, and amplifies the expression of peroxisome proliferator-activated receptor (PPAR)α/PPARγ coactivator-1α (PGC-1α) target genes involved in fatty acid oxidation. Furthermore, lipin-1 is shown to be expressed at higher level in skeletal muscle. These findings led us to consider the possibility that lipin-1 is involved in endurance exercise-induced mitochondrial biogenesis in skeletal muscle. In the present study, we first assessed the effect of acute bout of endurance exercise on lipin-1 expression in skeletal muscle, and found that lipin-1 mRNA in triceps muscle of 5-week-old male Sprague-Dawley rats was increased by approximately 2-fold after a 6-h low-intensity swimming exercise. Second, enhanced lipin-1 expression in L6 myocyte by lipofection-mediated transfer of human lipin-1 gene resulted in increases in mCPT-1 and ALAS mRNA. Finally, lipin-1 mRNA expression in triceps muscle was significantly increased 6-h after subcutaneous injections of AICAR (AMP-activated kinase (AMPK) activator) and Clenbuterol (β2 adrenergic receptor (AR) activator). In conclusion, these results may suggest that enhanced expression of lipin-1 is involved in endurance exercise-induced mitochondrial enzyme adaptations in skeletal muscle possibly through, at least in part, AMPK-and β2 AR-related mechanism.

32.10
EXERCISE INDUCES HYPER-ACETYLATION OF HISTONES AT THE MEF2 BINDING SITE ON THE GLUT4 PROMOTER BY A CAMK-DEPENDENT MECHANISM
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Regular exercise protects against type II diabetes in part by increasing GLUT4 content. Previous work from our laboratory has established that GLUT4 expression is mediated by CaMK-dependent binding of MEF2A to its cis element on the GLUT4 promoter. To further investigate how MEF2A binding to the GLUT4 gene is regulated, we injected rats with KN93 to inhibit CaMK II activation and measured; 1) MEF2A binding to, and histone H3 acetylation of, the MEF2 site on the GLUT4 gene by ChIP assay, 2) nuclear HDAC5 and GLUT4 contents by Western blot and 3) GLUT4 mRNA by RT-PCR after exercise. Exercise increased CaMK II activity ~50%, H3 acetylation and MEF2A binding to DNA ~2-fold and GLUT4 expression significantly. All the above increases by exercise were attenuated by KN93. Our data show that CaMK II activity modulates chromatin structure to increase MEF2A binding to the GLUT4 gene during exercise and suggests that drugs that mimic these effects might be worthy targets for controlling diabetes.

32.11 Withdrawn.

32.12
INFLUENCE OF A CYCLOOXYGENASE-2 INHIBITOR ON CYCLOOXYGENASE MRNA EXPRESSION AFTER RESISTANCE EXERCISE IN HUMANS: IMPLICATIONS FOR MUSCLE PROTEIN SYNTHESIS
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We have previously shown that consumption of a cyclooxygenase (COX)-2 inhibitor amplifies the muscle protein synthesis response following resistance exercise. This study attempted to clarify these unexpected findings by examining the expression levels of the known COX isoforms and variants (COX-1v1, COX-1v2, COX-2, COX-1b_1, COX-1b_2, COX-1b_3). Sixteen males (23±1y) were randomly assigned to one of two groups that received three doses of either a COX-2 specific inhibitor (celecoxib; 200 mg per dose, 600 mg total) or a placebo in double-blind fashion during the 24h following a single bout of knee extensor resistance exercise. At rest and 24h postexercise muscle biopsies of the vastus lateralis were taken for the measurement of COX mRNA expression levels using real-time RT-PCR. Similar to the muscle protein synthesis response (206% greater increase vs placebo), COX-2 mRNA induction was greater (170%, $P<0.05$) in the COX-2 inhibitor group (3.0±0.9 fold) than placebo (1.3±0.3 fold), while the response of the COX-1 variants was not different ($P>0.05$) between the two groups. It appears the greater postexercise muscle protein synthesis response with cyclooxygenase-2 specific inhibition is manifested through a compensatory increase in the cyclooxygenase-2 isoform. These findings further highlight the importance of cyclooxygenase in the regulation of human skeletal muscle protein synthesis after resistance exercise. NIH R01 AG020532.

32.13
FOXO1 INDUCES APOPTOSIS IN SKELETAL MYOTUBES
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We recently demonstrated that the transcription factor FoxO1 promotes atrophy of skeletal myotubes in vitro, which was independent of DNA binding. The purpose of this study was to examine mechanisms of FoxO1-mediated muscle atrophy via gene expression analysis for genes associated with protein ubiquination (MAFbx, Murf-1), apoptosis (Bim) and autophagy (BNip3). FoxO1-estrogen receptor fusion proteins (FoxO1AAA and FoxO1215 [DNA-binding deficient]) that are activated by treatment with 4-hydroxytamoxifen (4-OHT) were stably transfected in C2C12 skeletal myoblasts using the pBABE retroviral system and grown into 4-day-old skeletal myotubes. Non-transfected C2C12 cells served as controls. After 24 hour treatment with vehicle or 4-OHT, total RNA was isolated and gene expression performed using qPCR. Activation of FoxO1AAA resulted in a significant increase in MAFbx (~33 fold), and Bim (~4 fold) gene expression, with no significant increase in Murf-1 or BNip3 gene expression. Whereas, activation of the FoxO1215 resulted in a significant increase in Murf-1 (~2 fold), and BNip3 (~2.5 fold) gene expression, with no significant increase in MAFbx or Bim gene expression. No change in gene expression was observed in the control cells. These findings demonstrate that muscle atrophy induced via FoxO1 activation is associated with the induction of genes responsible for regulating ubiquination, apoptosis and autophagy, via DNA binding dependent and independent mechanisms.

32.14
INHIBITION OF CASEINE KINASE Iα INCREASES NUCLEAR NFAT IN C2C12 CELLS
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Casein Kinase Iα (CKIα) has been shown to be an important kinase in the rephosphorylation and nuclear export of NFAT, however its role in skeletal muscle is not clear. We hypothesized that CKIα is important in maintaining NFAT in an inactive phosphorylated state in the cytoplasm and that inhibition of CKIα would result in increased nuclear NFAT. C2C12 cells were transfected with an NFAT-GFP reporter with siRNA duplexes directed against CKIα or a control duplex. CKIα siRNA duplexes reduced CKIα expression by 70-80% at the mRNA level. NFAT nuclear localization was assessed using the Cellomics Array Scan assay system with an activated form of calcineurin (CnA*) used as a positive control. Activation with CnA* resulted in a 2.6 –fold increase in the nuclear:cytoplasmic ratio of NFAT. Co-transfection with CKIα siRNA also increased the NFAT nuclear:cytoplasmic ratio 1.8 and 2.6 –fold but the control duplex did not alter NFAT localization. Concurrent activation with CnA* and CKIα siRNA did not further increase nuclear NFAT (2.3 –fold increase) implicating calcineurin and CKIα in the same signaling pathway. These data support the idea that CKIα is an important kinase in the rephosphorylation and inactivation of NFAT and suggest that it may play a role in silencing the calcineurin-NFAT pathway in non-activated skeletal muscle.

32.15
AMINO ACID INFUSION ALTERS GROWTH RELATED GENE EXPRESSION IN HUMAN SKELETAL MUSCLE
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Amino acid (AA) infusion acutely stimulates protein synthesis and creates a net anabolic environment in human skeletal muscle. However, the underlying regulatory factors that mediate this response are largely unexplored. The aim of this study was to determine the influence of AA infusion on the expression of myogenic (MRF4, myogenin, and MyoD), proteolytic (FOXO3A, MuRF-1, and atrogin-1), cytokine (IL-6, -8, -15), and myostatin mRNA. Eight male subjects (26±2 yr) underwent muscle biopsies from a predominantly slow twitch muscle (soleus [SOL]) and a mixed fiber type muscle (vastus lateralis [VL]) before and after a 4 hr AA infusion and mRNA expression was determined using real time RT-PCR. AA infusion reduced ($P<0.05$) FOXO3A expression in both the SOL and VL. MRF4, IL-6, and IL-15 expression was increased ($P<0.05$) in only the SOL in response to AA. MyoD expression displayed a trend ($P=0.06$) toward increasing with AA infusion in both muscles. Myostatin, MuRF-1, atrogin-1, myogenin, and IL-8 expression were not altered by the AA infusion. These data suggest that the acute net anabolic effect of AA provision may be attributed to alterations in the expression of select myogenic and proteolytic/catabolic genes. NASA Grant NNJ06HF59G.

33.0: INFLAMMATION

33.1 **Witdrawn.**

33.2
EICOSAPENTAENOIC ACID IS MORE EFFECTIVE THAN DOCOSAHEXAENOIC ACID IN INHIBITING PRO-INFLAMMATORY MEDIATOR PRODUCTION AND TRANSCRIPTION FROM LPS-INDUCED HUMAN ASTHMATIC ALVEOLAR MACROPHAGE CELLS
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Background: Fish oil has previously been shown to reduce airway inflammation in individuals with exercise induced bronchoconstriction. Aim: The purpose of this study was to determine which of the active constituents of fish oil, eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), is most effective in suppressing proinflammatory mediator generation and cytokine expression from LPS-stimulated human asthmatic alveolar macrophages (AMφ). Methods: The AMφ were obtained from twenty one asthmatic adults using fiberoptic bronchoscopy. Cells were pretreated with DMEM, pure EPA, an EPA-rich media (45% EPA/10% DHA), pure DHA, a DHA-rich media (10% EPA/50% DHA) or Lipovenos^{R} (n-6 PUFA), and then exposed to DMEM (-) or LPS (+). Supernatants were analyzed for leukotriene (LTB_4, prostaglandin (PGD_2, tumor necrosis factor (TNF)-α and interleukin (IL)-1β production. Detection of TNF-α and IL-1β mRNA expression levels were quantified by reverse transcriptase polymerase chain reaction. Results: 120 μM pure EPA and EPA-rich media significantly ($p<0.05$) suppressed TNF-α and IL-1β mRNA expression and the production of LTB_4, PGD_2 and TNF-α and IL-1β in LPS-stimulated primary AMφ cells obtained from asthmatic patients to a much greater extent than 120 μM pure DHA and DHA-rich media respectively. Conclusions: This study has shown for the first time that EPA is a more potent inhibitor than DHA of inflammatory responses in human asthmatic AMφ cells.

33.3
β2 INTEGRINS CONTRIBUTE TO SKELETAL MUSCLE HYPERTROPHY IN MICE
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We tested the contribution of β2 integrins, which are important for normal function of neutrophils and macrophages, to skeletal muscle hypertrophy after mechanical loading. Using the synergist ablation model of hypertrophy and mice deficient in the common β subunit of β2 integrins (CD18-/-), we found that overloaded muscles of wild type mice had greater myofiber size, dry muscle mass, and total protein content compared to CD18-/- mice. The hypertrophy in wild type mice was preceded by elevations in neutrophils, macrophages, satellite cell/myoblast proliferation (BrdU+desmin+ cells), markers of muscle differentiation (MyoD1 and myogenin gene expression and formation and size of regenerating myofibers), signaling for protein synthesis (phosphorylation of Akt and p70S6k), and reduced signaling for protein degradation (decreased gene expression of MAFbx/atrogin-1). The deficiency in β2 integrins however, altered the accumulation profile of neutrophils and macrophages, disrupted the temporal profile of satellite cell/myoblast proliferation, reduced markers of muscle differentiation, and impaired p70S6k signaling, all of which could serve as mechanisms for the impaired hypertrophy in overloaded CD18-/- mice. In conclusion, our findings indicate that β2 integrins contribute to the hypertrophic response to muscle overload by temporally regulating satellite cells/myoblast proliferation and by enhancing muscle differentiation and p70S6k signaling.

33.4
EXERCISE INDUCES A CARDIOPROTECTIVE, ANTI-INFLAMMATORY PHENOTYPE IN THE RAT HEART THAT IS BLOCKED BY DELTA OPIOID RECEPTOR ANTAGONISTS
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OBJECTIVE: The objective of this study was to characterize the effects of exercise on cardiac expression of inflammation- and apoptosis-related genes and to determine whether exercise-induced changes in gene expression were mediated by opioid receptors. METHODS: Rats were exercised using a 5-day exercise protocol or served as sham exercise controls. For opioid receptor antagonist studies, animals were subcutaneously injected with saline (control) or with saline plus naltrexone (1 mg/kg) on days 4 and 5 just prior to exercise. Twenty-four hours after the last exercise period, hearts were harvested. One set of hearts then underwent a period of ischemia (25 min) and reperfusion (30 min) (I/R). Total RNA was isolated from hearts before and after I/R, and gene expression was assessed using real-time PCR microarrays. RESULTS: Exercise induced an anti-inflammatory, anti-apoptotic phenotype in the rat heart that was blocked by naltrexone. Interestingly, naltrexone-treated controls showed increased baseline

expression of pro-inflammatory genes. This suggests that release of endogenous opioids during exercise might prevent stress-induced changes in gene expression. CONCLUSIONS: Exercise-induced increases in cardiac ischemic tolerance may be due in part to opioid receptor-dependent changes in gene expression that reduce inflammation and apoptosis following ischemia and reperfusion. FUNDING: Funding was provided by the Department of Emergency Medicine, The University of Iowa.

33.5

THE EFFECT OF COMBINED STATIN THERAPY AND EXERCISE TRAINING ON MEDIATORS OF INFLAMMATION

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Physically inactive hypercholesterolemic subjects were randomly assigned to Rosuvastatin (R, n=17) and Rosuvastatin/Exercise (RE, n=16) groups. Physically active hypercholesterolemic subjects served as a control (AC, n=16). R and RE groups received Rosuvastatin (10 mg/d) for 20 weeks. From week 10 to 20, the RE group completed an exercise training program, while the R group remained sedentary. The AC group received no treatment. Fasting blood samples were obtained after 20 minutes seated rest at baseline, week 10 and week 20. Measurements included: TLR4 expression on CD14+ monocytes, CD14+CD16+ percentage, serum CRP, and serum oxLDL. TLR4 expression on CD14+ monocytes was higher in the R group at week 20 compared to baseline (1.74 vs. 1.51 MFI). oxLDL was lower in the R and RE groups at week 10 (R; 56 U/L, RE; 52 U/L) and 20 (R; 63 U/L, RE; 48 U/L) compared to baseline (R; 89 U/L, RE 83 U/L). At week 20, RE had lower oxLDL than R (48 U/L vs. 63 U/L). Inflammatory monocyte percentage was lower in the RE group at Post compared to Pre (2.3% vs. 3.7%). CRP was lower in the RE group compared to the R group at the post time point (1.63 mg/L vs. 0.99 mg/L). In conclusion, Rosuvastatin decreased oxLDL and increased monocyte TLR4 expression. The addition of exercise training decreased inflammatory monocyte percentage, oxLDL and CRP, suggesting an additive anti-inflammatory benefit. Supported by a grant from the Investigator-Sponsored Study Program of AstraZeneca.

33.6

STATIN PLUS EXERCISE TRAINING: MARKERS OF INFLAMMATION, LIVER FUNCTION, AND MUSCLE DAMAGE

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After baseline measurements, 33 physically inactive hypercholesterolemic subjects were randomized to either a 20 wk 10 mg/day Rosuvastatin treatment (R, n=17) or 20 wk Rosuvastatin treatment and 10 wk of exercise training (RE, n=16) initiated at midpoint. A hypercholesterolemic physically active (PA, n=16) group served as a comparison (no treatment). Inflammatory markers were measured at 0, 10, and 20 wk. At 0, 5, and 10 wk creatine kinase (CK) and alanine aminotransferase (ALT) were measured in RE and R and again in RE 48 hr after 1st and 5th exercise sessions. Results: Mean [ALT] did not significantly change. Mean [CK] was elevated ($p<0.0001$) 48 hr after the 1st exercise session but returned to baseline levels 48 hr after 5th session. Baseline RE and R VO_2max (est.) was correlated with total cholesterol (TC, r=-0.43, p=0.02) and LDL (-0.53, 0.002). Baseline CRP was correlated with body fat % (0.51, 0.01), and HDL was negatively correlated with BMI (-0.65, <0.0001). HDL and BMI were not correlated at 20 wk in either treatment group. In PA subjects, CRP was correlated with BMI (0.74, 0.002) and TC (-0.59, 0.02); inflammatory (CD14+/CD16+) monocyte % correlated with triglycerides (TG, 0.74, 0.002) and TC (-0.57, 0.03). Conclusion: [CK] elevation was transient and similar to previous exercise-only studies. [ALT] was not changed. Inflammatory monocytes were correlated with TG in PA only. Supported by a grant from the Investigator-Sponsored Study Program of AstraZeneca.

33.7

MACROPHAGE DEPLETION DOES NOT AFFECT MDX MOUSE TOTAL BODY STRENGTH

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The inflammatory response that occurs in patients with Duchenne Muscular Dystrophy (DMD) contributes to the pathology of the disease. Yet macrophages have not been examined in this regard. Therefore, the objective of this study is to elucidate the role of macrophage inflammation in the pathology of DMD.(Procedures conducted in accordance w/ APS guidelines for animal use) Twenty-four 4-week old male mice (mdx, n=12 and C57BL/10, n=12) were randomly assigned to macrophage depletion (n=12) or control (n=12, PBS) injection groups. Baseline measures of total body strength (TBS, N/g of body weight) and neuromuscular coordination (rota-rod) were made. To deplete macrophages, mice received IP injections (100ul) of either liposome encapsulated Clodronate or liposomes and PBS every third day for 5 weeks. After two weeks of treatment all mice underwent TBS measures. After 5 weeks of treatment, baseline measures are repeated and mice killed. Tissues are frozen and stored for histopathologic assessment. Results: After two weeks of treatment, TBS was not significantly different (P=0.12) between mdx macrophage depleted (5.30E-02 N/g ± 0.55E-2) and mdx PBS/control (6.04E-02 N/g ± 0.34E-02). Conclusion: Here we report the preliminary findings for two weeks of macrophage depletion in mdx mice. Though a slight decrease in TBS in the macrophage depleted group was noted, it was not significant. Final results at study conclusion should provide definitive findings.

34.0: AGING

34.1

SIX-MINUTE WALK DISTANCE IN INDIVIDUALS WITH PARKINSON DISEASE: A REGRESSION MODEL

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Background: Based on reference equations utilizing age and anthropometric measures for healthy adults, individuals with Parkinson disease (PD) walk less than half of their predicted six-minute walk distance (6MWD). We hypothesized that in addition to clinical features of PD, balance performance and susceptibility to falling may explain a significant amount of variance in this population. Our aim was to determine 6MWD and to identify predictors using a hierarchical regression approach in individuals with PD. Methods: Seventy-five individuals with PD (65 ± 9.5 yrs) of mild to moderate severity, as defined by a HY stage of 2 ± 0.4, completed all tests in one visit. Subjects were administered the motor subsection of the UPDRS and completed the following tests in a randomized order; Berg balance scale (BBS), timed up-and-go (TUG), and 6MWD. In addition, they also provided self-reports of freezing of gait and number of falls in the past six months. Results: Average 6MWD was 391.6 ± 99.9 m. All of the aforementioned tests correlated significantly with 6MWD (range r = -0.64 – 0.55). Using a block-entry regression model, we entered age, HY, and UPDRS motor score into the first block to represent Parkinsonian characteristics which explained a significant amount of variability in 6MWD (R^2 = .196, $P < .001$). The second block entered (e.g. functional measures scores, self-reports) explained a significant amount of additional variability (R^2 change = 0.355, $P < .0001$). The TUG, BBS, and number of falls contributed independently in the presence of all predictors. Conclusion: 6MWD in individuals with PD is explained, in part, by disease specific characteristics and perhaps to a greater extent by impaired balance and predisposition to falling.

34.2

GENETIC BACKGROUND INFLUENCES DAILY RUNNING WHEEL DURATION ACROSS THE LIFESPAN IN THREE GENERATIONS OF MICE

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Recent evidence suggests voluntary activity is influenced by genetic background. The purpose of this study was to determine the broad-sense heritability of daily physical activity in three generations of mice across the lifespan. We monitored the daily duration of running wheel activity of DBA/2J mice (8 mice), SWR/J mice (8 mice), their first generation crossbred offspring (F1, 36 mice), and their second generation crossbred offspring (F2, 231 mice) from 8 weeks of age to the end of life. All procedures were performed in conformance to the APS guidelines and approved by the University's IACUC. Mice were housed separately at age 8 weeks with a running wheel and computer. Duration of physical activity was measured every 24 hours. All data were calculated into two week averages throughout the lifespan. Across the lifespan, daily running wheel activity decreased after week 46 ($p < 0.0001$). The F0 mice exhibited a greater decrease in daily running duration across the lifespan than the remaining mice ($p < 0.0001$). There were no differences in broad-sense heritability (h2) between generations ($p = 0.30$) and across the lifespan ($p = 0.10$). The h2 across the lifespan ranged from 0.2 to 0.8. Genetic influence upon daily duration of activity was variable depending upon the age suggesting that genetic background influences the decline of activity with aging. Supported by NIA-AG022417, NIAMS-AR050085, NIDDK-DK61635, and NIEHS.

34.3

ARE THERE MUSCLE-SPECIFIC EFFECTS OF TRAINING STATUS OR OLD AGE ON OXIDATIVE CAPACITY AND INTRAMYOCELLULAR LIPIDS *IN VIVO*?

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Magnetic resonance spectroscopy was used to measure muscle oxidative capacity and intramyocellular lipids (IMCL) in vivo, in tibialis anterior (TA) and vastus lateralis (VL) in 44 men and women. Runners (n=12, 27±1 yrs, mean±SE), activity-matched sedentary young (n=16, 26±1 yrs) and sedentary older (n=16, 69±1) adults performed brief maximal voluntary isometric contractions of the TA and VL, while intracellular phosphocreatine ([PCr]) was measured by ^{31}P-MRS. The rate constant of post-contraction PCr recovery (k_{PCr}) was determined from a mono-exponential fit and used as an index of the rate of mitochondrial oxidative phosphorylation. In a subset of subjects (n=23), IMCL was measured in TA and VL using localized ^{1}H-MRS. Studies were conducted in accordance with the Declaration of Helsinki. In young, k_{PCr} was higher in VL than TA ($p=0.01$), and higher in both muscles in trained than untrained ($p<0.001$). In sedentary young and older groups, there was a muscle-by-age interaction ($p=0.006$) such that k_{PCr} of TA was higher in old than young ($p=0.02$), and k_{PCr} of VL was higher in young than old ($p=0.10$). There were no effects of muscle ($p\geq0.09$), training status ($p\geq0.53$) or age ($p\geq0.58$) on IMCL, and IMCL was not associated with k_{PCr}. This study provides novel evidence of muscle-specific effects of training status and old age on oxidative capacity, but not on IMCL levels, in vivo. Support: NIH/NIA R01 AG21094, K02 AG023582; ACSM Research Grant (RGL).

34.4

AGING DIFFERENTIALLY AFFECTS HUMAN SKELETAL MUSCLE MICRORNA EXPRESSION AT REST AND FOLLOWING A PROTEIN ANABOLIC STIMULUS

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Sarcopenia, the loss of skeletal muscle during aging, is associated with increased falls, fractures, morbidity, and loss of independence. MicroRNAs (miRNA) are novel post-transcriptional regulators. It is unknown what role miRNAs play in size regulation after an anabolic stimulus in human skeletal muscle. The expression of muscle-specific miRNAs in skeletal muscle of young and old men was measured using real-time PCR before and after a potent anabolic stimulus (ingestion of essential amino acids (EAA) following a bout of resistance exercise). Muscle biopsies were sampled at rest, and 1, 3 and 6h post-exercise. Leucine-enriched EAA (20g) were ingested after the 1h post-exercise biopsy. At rest, we found pri-miRNA1-1, 1-2, 133a-1, and 133a-2 expression elevated in old compared to young ($P<0.05$). Pri-miRNA1-2, 133a-1, and 133a-2 were reduced at select time points post-exercise only in the young compared to baseline whereas levels of pri-miRNA206 were elevated at 3h and at 6h post-exercise in the old and young, respectively ($P<0.05$). In the young, miR1 was reduced at 3 and 6h points while miR206 was elevated at 1h post-exercise as compared to baseline. We conclude that skeletal muscle primary and mature miRNAs expression in young men is readily altered by an acute protein anabolic stimulus. However, aging is associated with higher basal skeletal muscle pri-miRNA expression and a dysregulated miRNA response following resistance exercise and essential amino acid ingestion. Supported by NIH grant # RO1 AR049877 (NIAMS), AR053641 (NIAMS), AR45617 (NIAMS), and AG024832 (NIA).

34.5

EFFECT OF RESISTANCE EXERCISE WITH BLOOD FLOW RESTRICTION ON MUSCLE PROTEIN SYNTHESIS AND MTOR SIGNALING IN OLDER MEN

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Recent studies have shown that low-intensity (20~50% of 1-repetition maximum) resistance training combined with a moderate reduction of vascular flow to working muscles produces similar increases in muscular size and strength as compared to traditional high-intensity resistance training. Three male subjects (age > 60 years) were randomized to either a Control (n=3) or blood flow restriction (BFR) (n=3) group. Subjects performed low intensity resistance exercise on separate days with or without a blood flow restriction cuff placed proximally on each leg. Blood samples were obtained throughout the study and muscle biopsies were taken at baseline, immediately, 1 and 3hr post-exercise. Mammalian target of rapamycin (mTOR) signaling was assessed using immunoblotting methods. mTOR phosphorylation tended to increase post-exercise in both groups. S6K1 phosphorylation was increased from baseline at 3hr post-exercise in the BFR group only ($P<0.05$). 4E-BP1 phosphorylation was higher 1hr post-exercise in the BFR vs. Control ($P<0.05$). The increase from baseline for muscle protein synthesis during post-exercise recovery was ~80% in the BFR group and only ~10% in the Control group. We conclude that blood flow restriction during low intensity resistance exercise appears to enhance muscle protein synthesis and mTOR signaling in older men which may be an effective strategy to counteract sarcopenia. Supported by NIH/NIAMS grant RO1 AR049877 and the UTMB Center for Rehabilitation Sciences.

34.6

SKELETAL MUSCLE GENE EXPRESSION IS STRONGLY CORRELATED WITH STRENGTH AND SIZE GAINS AFTER RESISTANCE EXERCISE TRAINING IN ELDERLY ADULTS

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We previously reported differential expression of a number of gene products hypothesized to function in skeletal muscle growth in response to resistance exercise (EX) in v. lateralis biopsies from elderly and young adults both pre- and post-acute EX (Exp Gerontol 41(3):320-327, 2006; Physiol Genomics 32(3):393-400, 2008). The current study examined a group (N=8) of healthy elderly adults (68±6yrs) to determine if gene expression levels are correlated pre- or post-acute EX, or after 12 weeks of EX training with the training induced changes in muscle size (MS), or leg extension (LE) or leg press (LP) strength. After training, MS, LE, and LP increased (Avg±SD) 7±6%, 30±16%, and 20±8%, respectively. LE was positively correlated with mRNA levels for IGF1, MMP2, TIMP1, and CNTF pre-EX and inversely correlated with change for these mRNAs after training ($P\leq0.003$ and $R^2\geq0.8$). Levels of these and other mRNAs were also strongly correlated with MS but not LP, both pre-EX and after training. However, changes in mRNA levels post-acute EX and cytokine mRNA levels at any time were, for the most part, not correlated with training outcomes. These results suggest that muscle size and strength gains can be predicted prior to EX training by quantifying specific muscle mRNAs. Confirmation of these results using larger sample sizes may facilitate the design and prescription of more effective exercise and rehabilitation routines. Supported by AG012411.

34.7

EXOGENOUS ANTIOXIDANTS MIMIC THE EFFECTS OF EXERCISE TRAINING ON ENDOTHELIAL FUNCTION IN ARTERIES PERFUSING SKELETAL MUSCLE OF AGED RATS

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Exercise training increases extracellular superoxide dismustase (ecSOD) protein content and reverses age-induced endothelial dysfunction in soleus muscle feed arteries (SFA). This suggests that exercise improves endothelium-dependent dilation (EDD) in aged arteries, in part, by improving vascular antioxidant capacity. We hypothesized that exogenous antioxidants produce exercise-like effects on EDD in senescent arteries. SFA were isolated and cannulated from young (4 mo, n=13) and old (24 mo, n=13) male Fischer 344 rats. EDD to flow or acetylcholine (ACh) was assessed in the absence or presence of SOD, an SOD mimetic (TIRON), or SOD+Catalase (CAT). Results indicated that flow- and ACh-induced dilations were impaired in old SFA. Treatment with SOD, TIRON, and SOD+CAT improved flow-induced dilation in old SFA to the extent that dilation was similar to young SFA. ACh-induced dilation was improved in old SFA in the presence of SOD and SOD+CAT, but not in the presence of TIRON. In Young SFA, TIRON treatment resulted in an inhibition of ACh-induced dilation. Antioxidants had no affect on endothelium-independent dilation to sodium nitroprusside in young or old SFA. These data indicate that exogenous antioxidants produce exercise-like effects on EDD in senescent arteries and suggest that increases in vascular antioxidant capacity may play an integral role in exercise-induced improvements in EDD in aged arteries. Supported by NIH AG-00988, AHA Texas affiliate 0765043Y and an ACSM FRG.

34.8

EFFECT OF EXERCISE CAPACITY ON FOREARM VASCULAR RESPONSE TO SYMPATHETIC ACTIVATION IN HEALTHY MIDDLE-AGED SUBJECTS

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The forearm vasoconstrictor response to increases in muscle sympathetic nerve activity (MSNA) during graded lower body negative pressure (LBNP) is diminished with age. Exercise training augments changes in forearm vascular resistance (FVR) during LBNP in young subjects, but its effect on the FVR/MSNA relationship in middle-aged subjects is unknown. We therefore studied 14 middle-aged subjects (age=48±3 years; mean±standard error); 7 trained (119±7% of predicted peak oxygen uptake) and 7 untrained (80±4%). FVR (plethysmography) and MSNA (microneurography) were acquired during 4 minutes each of LBNP at -5, -10, -20, and -40 mmHg, applied in random order. Analysis was by 2-way analysis of variance and linear regression. Heart rate was lower at rest and during LBNP in the trained group ($P<0.001$). There was no difference between groups in baseline MSNA burst incidence nor the increase with LBNP ($P<0.001$). The trained group had a significantly lower forearm blood flow at LBNP-5 ($P=0.03$) and -40 ($P=0.02$). The change in mean FVR was significantly related to the change in mean MSNA burst incidence in the untrained group ($r=0.98$, $P=0.02$) but not the untrained group ($r=0.74$, $P=0.26$). Thus, in middle-aged individuals, neural and vascular responses to LBNP are closely linked in untrained subjects, yet are dissociated in trained subjects, suggesting altered neuro-vascular transduction with training. Funded by the Heart and Stroke Foundation of Ontario.

34.9

RUNNING PERFORMANCE BY AGED FEMALE MICE; EFFECTS OF ESTRADIOL TREATMENT AND RESIDUAL OVARIAN TISSUE

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Estradiol treatment to young adult mice that are estrogen deficient via ovariectomy results in increased voluntary wheel running. We hypothesized that estradiol treatment to aged mice that are estrogen deficient via ovarian-failure would also cause increased running. Plasma estradiol levels and vaginal cytology were analyzed weekly in 17 mo-old C57BL/6 mice; ovarian failure was verified at 19.2±0.2 mo of age. These mice were treated with 17β-estradiol (n=12) or placebo (n=9) and given free access to running wheels for 6 wk. Estradiol-treated mice ran 1.7±0.3 km/24 hr while placebo-treated mice ran 3.7±1.9 km/24 hr ($P=0.03$). This result presented the question, why in the aged, estrogen-deficient mice did estradiol treatment not improve voluntary wheel running as it did in the adult, estrogen-deficient mice? A second study was undertaken in which aged mice were ovariectomized (n=5) or sham operated (n=3). Over a 4-wk period, sham mice ran 56% more than OVX mice ($P=0.04$) indicating that the residual ovary, though not producing estradiol, provoked running. All mice were then treated with estradiol but no running differences were found 1, 2, or 3 wks post-treatment ($P\geq0.23$) suggesting an overall diminished age-related response to estradiol. While estradiol treatment to adult, estrogen-deficient female mice robustly affects wheel running and muscle function, estradiol treatment to aged, ovarian-failed mice is more complicated. Supported by NIH AG20990 and AG2586.

34.10

REDUCTIONS IN GLUT4 PROTEIN CONTENT IN FAST TWITCH MUSCLE WITH AGING ARE PREVENTED BY EXERCISE TRAINING

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Aging is associated with decreasing insulin sensitivity. These changes have been linked to reductions in skeletal muscle GLUT4 (glucose transporter isoform 4) content. We wanted to determine if GLUT4 content decreased between young adult and senescence, and if exercise from late middle age until senescence could prevent these changes. Late middle aged F344BN rats exercised for 5 and 7 mo from late middle age (29 mo) until senescence (34 and 36 mo) by treadmill running (60 min per day, 4 days per week). Body composition was assessed by DEXA and GLUT4 protein content in the plantaris (primarily fast twitch) and soleus (primarily slow twitch) muscles was determined by Western blot. The exercise groups had significantly lower body fat (15 ± 1 %) than the untrained groups (25 ± 1%). In the soleus muscle, GLUT4 content did not decrease with age and was not affected by exercise training. The plantaris muscle showed a modest (14%), but significant, decline in GLUT4 content at senescence compared to young adult. At 36 mo of age the exercise group had a higher GLUT4 content than the sedentary group, with levels similar to young adult. These results show that in senescence GLUT4 is reduced in fast but not slow twitch muscle and that regular endurance exercise initiated at late middle age can prevent this decline. This work has been funded by Alberta Provincial CIHR Training Program in Bone and Joint Health (AB), CIHR (AB, RH), NSERC (MT) and AHFMR (RH, DW, LS).

34.11

AGE-RELATED CHANGES IN THE ENERGY COST OF TWITCH CONTRACTIONS IN HUMAN SKELETAL MUSCLE *IN VIVO*

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Force production by type II muscle fibers has been shown to be more costly than force produced by type I fibers. In humans, senescent muscle often displays a shift toward greater type I composition, as a result of motor unit remodeling. The energetic implications of this shift are unknown. The purpose of this study was to test the hypothesis that the ATP cost of evoked twitch contractions is lower in older skeletal muscle than in young muscle in vivo. Healthy young (Y; n=8, 26±4 years) and older (O n=9, 71±2) men participated after giving written informed consent, and all procedures were in accordance with the Declaration of Helsinki. The ankle dorsiflexor muscles were stimulated supramaximally via the peroneal nerve at 2 Hz for 5 min, and ^{31}P-MRS was used to monitor intracellular PCr and pH during contractions. The ATP cost of a single twitch was calculated from the first derivative of the monoexponential decay in PCr during the contraction protocol. Twitch cost was 0.18±0.02 mM ATP·twitch^{-1} and 0.13±0.02 mM for Y and O, respectively ($p=0.05$), despite nearly identical time-tension integrals (3.9 ±0.7 and 3.8±0.7 N·s for Y and O, respectively, $p=0.96$) across age groups. The ~28% lower twitch cost in O suggests that intramuscular changes have a significant impact on muscle energetics in older adults, and that this change may be an important mechanism for the proposed higher metabolic economy of senescent muscle in vivo. Support: NIA R01AG21094, K02AG023582.

34.12

CHANGES IN EXERCISE TOLERANCE AND PHYSICAL PERFORMANCE IN MYOSTATIN TRANSGENIC MICE

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Skeletal muscle atrophy is associated with decrease in muscle mass in elderly. Myostatin is a one of the growth factors of skeletal muscle; it downregulates the muscle mass. The purpose of this study was to elucidate the role of Mst in muscle performance with age using Mst overexpressing transgenic (Tg), knock out (KO) and wild type (WT) mice. Twelve and 18 months male mice were used (n=5): exercise tolerance was measured repeatedly by incremental tests for 6 weeks on treadmill. Daily activity was measured on running wheel for 8 weeks. Animals were sacrificed and muscle fiber typing was done. Change in gene expression profile was identified by RT-PCR SuperArray technique. In 12 months old Tg mice, Mst overexpression decreased muscle mass (28%), increased fat mass (34%), caused fast-to-slow fiber transition; significantly higher daily activity and exercise tolerance were found as compared to WT (16 J/g vs. 7.9 J/g, respectively) mice. In contrast, physical activity was lowest in Mst KO animals. At age of 18 months, fat mass

was further increased by 11%, daily activity and exercise tolerance declined as compared to the 12 months old Tg mice. Conclusion: The increase in muscle mass of KO animals is not coupled with muscle strength, rather it is associated with weaker muscle. We conclude that this phenomenon is due to muscle transition from slow-to-fast fiber type caused by the lack of Mst gene activity. This study was supported by S06 GM0685510-01, G12RR030262, and P20 MD000545 grants.

34.13

EXERCISE-INDUCED SHEAR STRESS IS ASSOCIATED WITH PLASMA VWF IN OLDER HUMANS

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Exercise induces an increase in plasma vWF in humans, but the relationship between exercise-induced shear stress and changes in plasma vWF following exercise is unknown. The purpose of this study was to determine if the increase in shear stress during exercise correlates with plasma vWF. Young (n = 14) and older (n = 13) individuals performed in 30 min of dynamic handgrip exercise. Brachial artery diameter and blood flow was measured at rest and during exercise using ultrasound Doppler. Shear stress was calculated using Poiseuille's equation. Blood samples were collected before, immediately after, and following 30 min of recovery from exercise. Plasma levels of vWF were quantified using gel electrophoresis. Immediately post-exercise, plasma levels of vWF increased by 6% and 4% in young and older individuals, respectively. Following 30 min of recovery from exercise, plasma levels of vWF returned to baseline in young individuals but remained elevated in older individuals. The change in plasma vWF was linearly correlated with the increase in shear stress during exercise in older individuals (post-exercise: $r = 0.78$, 30 min recovery: $r = 0.77$, $P < 0.01$) but no association was found in young individuals. These results suggest that exercise-induced shear stress is associated with changes in plasma levels of vWF in humans and that aging may influence the relationship between exercise-induced shear stress and endothelial activation. Supported by NIH F31 (HL077996).

34.14

THE ANGIOGENIC RESPONSE TO AEROBIC EXERCISE TRAINING IS PRESERVED IN AGED COMPARED TO YOUNG WOMEN

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Advanced age is associated with fewer capillaries surrounding muscle fibers and an attenuated skeletal muscle angiogenic response to limb ischemia. However, we have recently reported that the angiogenic response to aerobic exercise training is similar in young and aged men. PURPOSE: To determine if the skeletal muscle angiogenic response to aerobic exercise training is attenuated in aged compared to young women. METHODS: Six young (24 ± 1 yrs) and six aged (65 ± 2 yrs) women completed 8 weeks of cycle ergometer exercise training (60 min/day, 4 days/week at 65% of VO2max). Vastus lateralis muscle biopsies were obtained prior to and 16 hrs after the last exercise bout. Standard morphological techniques were used to analyze capillarization. RESULTS: VO2max was lower in aged compared to young prior to training (28%) and was increased in young, but not aged with training (14% vs. 4% increase, respectively). Fiber cross sectional area (FCSA) was similar in young and aged and was unchanged by training. The percentage of type IIb fibers was decreased 7% on average by training in young and aged. Capillary contacts (CC) surrounding type I fibers was 35% greater in aged compared to young. CC surrounding type I, IIa, and IIb fibers were increased similarly by exercise training in young and aged (19%, 28%, and 37%, respectively). CONCLUSIONS: These results suggest that aging does not impair the skeletal muscle angiogenic response to exercise training even when no initial deficit in capillarization was present in aged women. Support: NIH and AHA Mid-Atlantic.

34.15

EXERCISE TRAINING-INDUCED IMPROVEMENTS IN ANTIBODY RESPONSES TO INFLUENZA VACCINATION IN OLDER ADULTS ARE RELATED TO CHANGES IN CARDIOVASCULAR FITNESS

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The purpose of this study was to determine whether cardiovascular exercise training improved the antibody response to influenza vaccination in previously sedentary older adults and, if so, what factors were related to such changes. Previously sedentary older adults (70 ± 0.4 yrs, n=137) were randomly assigned to either a 10 month cardiovascular exercise group (Ex, n=69, 3x/wk, 45-60min/session, 55-70%VO2peak) or a flexibility attention control group (Flex, n=68, 2x/wk, 45-60min/session). Four months into the intervention, both groups received an influenza vaccination (Fluzone™) with serum collected pre-, 3, 6 and 24 wk post-vaccination for hemagglutination inhibition (HI) titer analysis. We found no significant group by time interaction in H1N1 (New Caledonia/20/99) HI antibody titer when analyzing the entire cohort. However, analysis of subjects (n=109) with existing pre-HI titers revealed that Ex resulted in a significant increase in antibody titers at 24 wk compared to the Flex group such that 43% and 19% of subjects were seroprotected in Ex and Flex, respectively ($\chi^2=7.3$; $p=0.007$). This improvement in vaccine protection was related to ($r=0.23$, $p=0.02$) ΔVO2peak but not age, gender, or Δ%fat. In conclusion, regular cardiovascular exercise improves the duration of protection of influenza vaccination in older adults with detectable pre anti-influenza HI titers (suggestive of recent exposure) and this effect is related to changes in cardiovascular fitness. (supported by NIH AG-18861 to JA Woods; G. Munk assisted with HI analysis).

34.16

FIBER-TYPE SPECIFIC EXPRESSION AND AGING-RELATED DECLINE OF SKELETAL MUSCLE NAMPT

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Nicotinamide ribosyl transferase (Nampt) has been suggested to fulfill the role of an 'anti-aging' molecule in mammals by increasing intracellular NAD^+ levels and sirtuin activity. We have found robust Nampt expression in skeletal muscle from young mice; however, the role of Nampt in aging muscle is currently not known. Sarcopenia, an aging-related loss of muscle mass, is characterized by a disproportionate decrease of fast-twitch fiber cross-sectional area. Slow-twitch fibers are relatively protected from this effect. We determined if Nampt levels are higher in slow-twitch (soleus) compared to fast-twitch (gastrocnemius) muscle, and determined if aging alters Nampt protein levels by studying these muscles from 11-, 59-, and 85-week-old mice. Nampt contents were determined by immunoblot and were approximately 2-fold higher in the slow-twitch soleus muscle compared to the mixed gastrocnemius muscle in 11-week-old mice ($p<0.001$). Nampt concentrations remained nearly constant during aging in mouse soleus muscle ($p=n.s.$). In contrast, Nampt concentrations in gastrocnemius muscle declined significantly from 44±5 A.U. in 11-week-old to 19±3 A.U. in 85-week-old animals ($p<0.01$). In conclusion, we report a fiber-type specific expression and aging-related decline in skeletal muscle Nampt protein levels, suggesting a potential role for Nampt in fiber type determination and/or muscle loss with aging. Support: NIH DK068626 (L.J.G.),NIH 5 T32 DK07260-30 (J.B.), Brookdale Foundation (M.H.).

35.0: MUSCLE FUNCTION & ADAPTATION II

35.1

ENDURANCE TRAINING REDISTRIBUTES INTRAMYOCELLULAR LIPIDS FROM THE SUBSARCOLEMMAL TO THE INTRAMYOFIBRILLAR REGION IN SKELETAL MUSCLE OF LEAN AND OBESE MEN

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Elevated intramyocellular lipid (IMCL) content and reduced mitochondrial function have been associated with impaired insulin resistance (IR) in obesity. Endurance training (ET) increases skeletal muscle mitochondrial capacity and IMCL content in young, moderately active men and women. We examined the influence of ET on IMCL content, mitochondrial capacity, IMCL-mitochondrial ultra-structure and physical juxtaposition in sedentary lean (n=9) and obese (n=9) men before and after 16-weeks of endurance exercise training. We measured vastus lateralis mitochondrial and IMCL content, size and IMCL-mitochondrial proximity by electron microscopy, electron transport chain (ETC) and β-oxidation (SCHAD) activity, and IR ($HOMA_{IR}$). Mitochondrial size and density increased (both $P<0.001$) with ET. Although total IMCL size and density remained unchanged, ET reduced IMCL size ($P<0.05$) and density ($P<0.01$) in the subsarcolemmal (SS) region but increased IMCL size ($P=0.08$) and density ($P<0.05$) in the intermyofibrillar (IMF) region. The % IMCL in contact with mitochondria increased ($P<0.05$) after ET as did ETC (cytochrome c oxidase, $P<0.05$; citrate synthase, $P<0.001$) and SCHAD ($P<0.001$) activities, with no significant effect on IR. ET increased oxidative capacity, redistributed IMCL from SS to IMF region of the muscle fiber, and increased IMCL-mitochondria proximity, which may reflect greater IMCL turnover capacity, in lean and obese men. Research supported by CIHR.

35.2

PGC-1α PROMOTES ANTIOXIDANT ENZYME EXPRESSION AND PREVENTS MUSCLE ATROPHY IN CHRONIC HEART FAILURE

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Chronic heart failure (CHF) and many other chronic diseases cause loss of lean body mass (cachexia), which lead to exacerbation of the diseases and death. We have shown that oxidative myofibers are resistant to cachexia due to an inducible antioxidant defense system. It has also been shown recently that expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) protects skeletal muscle from atrophy by repressing transcription of the atrophic genes. We hypothesized that PGC-1α provides protection by upregulating antioxidant enzymes. Here we show in a mouse genetic model of CHF (cardiac overexpression of calsequestrin) that muscle wasting is associated with reduced PGC-1α and mitochondrial enzyme expression, and transgenic overexpression of PGC-1α promotes antioxidant enzyme expression, including superoxide dismutase 2 and catalase, and prevents skeletal muscle from CHF-induced atrophy. These findings suggest the importance of PGC-1α/antioxidant enzyme axis in a protective mechanism against muscle wasting in cachexia.

35.3

HYPERGRAVITY RESISTANCE TRAINING ON A HUMAN POWERED CENTRIFUGE

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Microgravity exposure results in muscular, cardiovascular, and skeletal deconditioning and loss of exercise capacity. The Space Cycle is a human powered centrifuge that can be configured for aerobic or resistance training to offer an integrative countermeasure to microgravity. Healthy male subjects performed 2 weeks of squat resistance training on the space cycle (SC, n=9) or using free weights (FW, n=9). Subjects completed 9 workouts, each consisting of 3 sets of squats at 70-90% of individual 10 repetition maximum (10RM). Space cycle subjects performed squats at 2.3 to 3.9 +Gz (measured at the feet) without additional weights. Squat 10RM and isokinetic knee extension strength were measured before and after the training program. Subjects in both groups increased 10RM and isokinetic knee extension strength. SC subjects improved knee extension strength by 9 ± 4% and squat 10RM by 25 ± 1%. FW subjects improved knee extension strength by 6 ± 4% and squat 10RM by 35 ± 4%. Biopsies were taken from the right vastus lateralis prior to, 4 h after, and 24 h after the first and last workout for evaluation of acute and chronic cellular responses to space cycle training. All subjects completed the training program successfully. Strength improvements support the efficacy of the space cycle as a gravity-independent resistance training device. Supported by NASA MA00403 and NIH M01 RR00827.

35.4

PGC-1α AND β SLOW MUSCLE ATROPHY BY INHIBITING PROTEIN DEGRADATION AND THE INDUCTION OF ATROPHY-SPECIFIC UBIQUITIN LIGASES, ATROGIN1 AND MURF1

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The exercise-induced transcriptional coactivator PGC-1α, and its homolog PGC-1β, both increase mitochondrial content, but do not coactivate identical sets of genes. PGC-1α has been shown to inhibit denervation and fasting induced atrophy of skeletal muscle (Sandri et al. PNAS 2006), but whether PGC1-β functions similarly is unknown. To test if these coactivators influence muscle protein turnover, C2C12 myotubes were infected with adenoviruses expressing

PGC-1α or PGC-1β. At 2.5 days, citrate synthase activity, a marker of mitochondrial content, was twice that in control-infected myotubes. Although PGC-1α or β overexpression did not alter rates of protein synthesis, they significantly reduced overall rates of protein degradation (measured with pulse chase of ^{3}H-tyrosine). During atrophy, proteolysis is stimulated by FoxO transcription factors. Elevated PGC-1α or β levels blocked the ability of activated FoxO3 (and of serum deprivation) to stimulate proteolysis in the myotubes. Furthermore, using promoter luciferase constructs we show that PGC-1α or β inhibited the ability of activated FoxO3 to stimulate the transcription of muscle atrophy-specific ubiquitin ligases, atrogin1/MaFBx and MuRF1. In conclusion, both PGC-1α and β can slow protein degradation via the ubiquitin-proteasome pathway, and PGC-1α production appears to be one mechanism by which exercise retards muscle wasting. Support: NIH 1F32AR054699 (JB), MDA and Ellison Foundation (AG).

35.5

ASSESSMENT OF CUMULATIVE FSR OVER A 24 H PERIOD WITH HINDLIMB UNLOADING AND INTERMITTENT RELOADING IN RATS

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Fractional synthesis rates (FSR) during simulated microgravity has been shown to be depressed with traditional, isotopic methodologies such as flooding dose and primed constant infusions. However, those methods only measure protein synthesis over a relatively short-term, thus making it difficult to assess cumulative protein synthesis (e.g. measured over 24 h, in which feeding and other factors might affect homeostasis). Deuterium oxide (^2H_2O) is currently being investigated as a novel stable isotopic methodology to determine FSR over long periods of time. The purpose of this study was to (i) determine cumulative FSR (over 24h) during hindlimb unloading using deuterium oxide and (ii) examine whether FSR could be recovered during brief, intermittent periods of reloading. Mature male Sprague-Dawley rats were randomly assigned to cage control (CC), hindlimb unloaded (HU) or HU with reloading (HURE). HU were unloaded for five days with reloading occurring for one hour on days 2 and 4. Deuterium oxide was administered over a 24 hour period prior to sacrifice for assessment of FSR. HU demonstrated reduced soleus and plantaris muscle mass when compared to CC ($p<0.05$), and was similar to animals with 2h of intermittent reloading activity ($p>0.05$). Although 24h FSR was depressed with HU ($p<0.05$), reloading returned values similar to that of CC. These results suggest that normalizing FSR with limited reloading (2h) cannot overcome the wasting of skeletal muscle mass during HU.

35.6

A COMPARISON OF ^2H_2O AND PHENYLALANINE FLOODING DOSE METHODOLOGIES TO INVESTIGATE PROTEIN FRACTIONAL SYNTHESIS RATES IN SKELETAL MUSCLE OF RATS

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Flooding dose has traditionally been used for assessing tissue protein synthesis; however, this approach introduces a supra-physiological dose of tracer and only assesses fractional synthesis rates of protein synthesis (FSR) over a short time frame. Recent studies have demonstrated that ^2H_2O can be used to assess protein synthesis, i.e. measure the incorporation of ^{2}H-alanine into tissue and/or specific proteins. We aimed to determine if ^2H_2O would provide similar FSR of skeletal muscle proteins, as compared to the flooding dose method. Rats were assigned to either cage control (Con, n = 6) or resistance exercise (RE, n =6), in which they were operantly conditioned to engage in a single bout of progressive, high intensity, 'squat-like' RE. All rats were given an IP injection of ^2H_2O (20 ul · mg^{-1} body mass) and provided 4.0% ^2H_2O drinking water twelve hours post-RE. In addition, all rats were given a flooding dose of Phe (150 mM, 1ml · 100 g body mass^{-1}) 16 hours post-RE, followed by blood and tissue collection. FSR did not differ ($p>0.05$) between RE and Con in the mixed gastrocnemius, plantaris or soleus (mixed muscle) or mixed gastrocnemius (myofibrillar) when assessed with ^2H_2O or with the flooding dose of Phe. We conclude that the ^2H_2O method and a flooding dose of Phe yield comparable results; however, the ^2H_2O method offers advantages in that (i) it only requires an IP injection of tracer and (ii) FSR can be determined over short-term and prolonged periods.

35.7

MUSCLE DAMAGE OR MYOFIBRILLAR REMODELING IN HUMAN MUSCLE AFTER ECCENTRIC EXERCISE

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Background: Myofibrillar alterations like Z-disc streaming, observed in muscles after unaccustomed eccentric exercise, have generally been considered to represent damage. By contrast our recent studies have shown that these alterations rather reflect myofibrillar remodeling, leading to lengthening of myofibrils by the formation of new sarcomeres. Such areas exhibit increased amount of F-actin, myotilin, desmin and obscurin, whereas alpha-actinin, titin and nebulin are temporarily lacking. Aim: To examine by immunohistochemistry how the Z-disc proteins filamin, Xin, FATZ, ZASP and telethonin are affected by eccentric exercise in relation to the proteins previously investigated, and how they are involved in myofibrillar remodeling and formation of new sarcomeres. The intermediate filament proteins synemin and nestin were also analyzed. Results: We show that the staining of filamin and Xin was increased in lesions with strong actin and myotilin staining. The corresponding areas totally lacked FATZ, ZASP and telethonin staining, whereas synemin staining was, as desmin, present in longitudinally oriented strands. Staining of nestin was generally not seen. Conclusion: Our study confirmed that a profound rearrangement in Z-disc and Z-disc associated proteins occurs in muscles exposed to high force eccentric exercise. Filamin and Xin seem to be involved already at early steps of sarcomerogenesis, whereas FATZ, ZASP and telethonin are incorporated into the Z-disc late in that process.

35.8

MOUSE SKELETAL MUSCLE VOLUME REGULATION BY THE NA+,K+,2CL- COTRANSPORTER DURING EXPOSURE TO HYPERTONIC AND HYPOTONIC SOLUTIONS

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Skeletal muscle cell volume regulation under hyper- and hypo-osmotic stress was investigated. We hypothesized that: a) mammalian skeletal muscle will demonstrate a dose-dependent regulatory volume increase (RVI) during hypertonic stress and (b) regulatory volume decrease (RVD) during hypotonic stress; c) bumetanide, a NKCC inhibitor, and ouabain, a Na^+/K^+ ATPase inhibitor, will inhibit the RVI, and d) slow twitch muscle (SOL) fibres will show a more rapid regulatory volume response than fast twitch (EDL). Muscles loaded with the fluorophore calcein-AM were excited at 491 nm and emissions collected at 521 nm at 10Hz. Cell volume changes were computed from fluorescence. Without drug, both SOL (n=6) and EDL (n=8) demonstrated initial volume loss (SOL = -7.1±5.5%, EDL = -9.5±3.6%) and RVI (SOL = 4.5±2.7% in 387±133s, EDL = 5.1±21% in 641±115s). NKCC inhibition inhibited the RVI response in SOL by 68% ($P<0.05$) and in EDL by 44%. The RVI response was not affected by ouabain. In summary: 1) a dose response relationship was observed between volume recovery and the magnitude of the extracellular hypertonic challenge; 2) SOL showed a faster RVI than EDL; 3) bumetanide had a greater effect on inhibiting the RVI in SOL than EDL; 4) both muscles demonstrated initial swelling and RVD in response to extracellular hypotonic challenge; and 5) the absence of effect of ouabain may be due to the presence of ouabain insensitive Na^+,K^+ ATPase isoforms in murine hindlimb muscle. Supported by the Natural Sciences and Engineering Research Council of Canada.

35.9

SKELETAL MUSCLE VOLUME REGULATION BY THE NA+,K+,2CL- COTRANSPORTER IS IMPAIRED IN MDX MICE DURING HYPERTONIC STRESS

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SOL and EDL muscles excised from wild type (WT) and mdx mice were loaded with calcein-AM, then excited at 494 nm and emissions collected at 520 nm at 10Hz. Cell volume changes were computed from fluorescence. Control muscles (CON) were exposed to a 35% increase in extracellular tonicity (+125 mosm/L using NaCl). WT muscle initially lost volume (SOL = -10.4±2%, EDL = -20±1%) then showed a regulatory volume increase (RVI) (SOL = 20.1±1.2% in 1031±91s, EDL = 24.1±1% in 1142±83s). Mdx muscle did not lose more volume (VL) than WT. Within EDL, mdx took more time to recover volume (Tr;1521±85s) than WT (1142±83s). NKCC inhibition (1.43mM bumetanide) increased time to peak volume loss (Tp) in WT and mdx muscles; decreased Tr and decreased magnitude of volume recovery (VR), independent of genotype (SOL CON = 19.9±7%, SOL bumetanide = 9.65±22%) and (EDL CON = 25.9±5%, EDL bumetanide = 15.6±14%). Combined Na^+/K^+ ATPase and NKCC inhibition (1.79mM ouabain) decreased Tr (CON=1192±44s, ouabain = 844±62s) and reduced RVI compared to CON (SOL CON = 19.9±7%, SOL ouabain = 9.28±2%) and (EDL CON = 25.9±5%, EDL ouabain = 12.8±13%). With ouabain, Tr and VR decreased in EDLmdx compared to EDLWT. Compared to WT mouse muscle, the ability of the NKCC to regulate volume in mdx mice is impaired during an hypertonic challenge characterized by: a) increased Tr and; b) decreased Tr and VR in EDL following combined inhibition. Both NKCC inhibition and combined inhibition partially inhibited the RVI in mdx and WT muscle. Supported by the Natural Sciences and Engineering Research Council of Canada.

35.10

STRENGTH TRAINING, OVARIECTOMY AND MMP-2 IN SKELETAL MUSCLE

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Matrix metallopeptidases (MMPs) are crucial to the maintenance of healthy tissue. The aim of this study was to investigate MMP-2 activity in soleus and tibialis anterior (TA) muscles after strength training in ovariectomized rats. Wistar adult female rats were grouped into: sedentary (S); ovariectomized sedentary (Sovx); pseudo-ovariectomized sedentary (Pseudo); acute exercise (AE); ovariectomized acute exercise (AEovx); strength trained (T) and ovariectomized strength trained (Tovx) (n= 10 per group). A 12-week strength training that consisted to climb a 1.1-m vertical ladder with weights secured to rats¡¯ tail was used. The sessions were performed once every 3 days with 4-9 climbs and 8-12 dynamic movements per climb. The MMP-2 activity was analyzed by zymography. There was a higher MMP-2 activity in T and Tovx groups and a lower activity in AEovx compared with the S in soleus (p¡Ü0.02). Sovx and Toxv groups presented lower MMP-2 activity compared with the S group in TA. There was a higher MMP-2 activity in AE and AEovx compared with S and Sovx in TA, respectively (p¡Ü0.05). In TA training increased MMP-2 activity compared with S group. Strength training increases MMP-2 activity in soleous and TA muscles, which may be important for muscle remodeling. Ovariectomy downregulates MMP-2 in TA, which may compromise muscle function. Key words: strength training; MMP-2; skeletal muscle; ovariectomy.

35.11

EFFECTS OF HIGH-INTENSITY CYCLING TRAINING ON PHOSPHOCREATINE RECOVERY KINETICS

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Previous studies have shown that the rate of phosphocreatine (PCr) recovery can be used as an in vivo measure of functional oxidative capacity in skeletal muscle. The purpose of this study was to examine the effect of short-term high-intensity interval training on the time constant (tau) of PCr recovery following moderate-intensity exercise. Seven healthy active subjects [21 ± 1 (SE) yrs; 69 ± 4 kg] performed six sessions of 4-6 maximal effort 30-s cycling intervals within a two week period, and seven subjects (24 ± 2 yrs; 80 ± 6 kg) served as controls. Prior to and following training, 31P-MRS (GE 3T Horizon System) was used to measure relative changes in

high-energy phosphates and intracellular pH of the quadriceps muscle during gated dynamic leg-extension exercise (3 cycles of 90-s exercise and 5-min rest). A mono-exponential model was used to estimate the rate of PCr recovery. During the pre and post training leg-extension exercise, intracellular pH at end-exercise was not different than rest. The time constant (tau) of PCr recovery after leg-extension exercise was reduced by 14% with training (pre-training 43 ± 5 s vs. post-training 37 ± 6 s, $p<0.05$) with no change in the control group (44 ± 5 s vs. 43 ± 4 s, respectively, NS). These findings demonstrate that short-term high-intensity interval training is an effective means of increasing functional oxidative capacity in muscle fibers recruited during moderate-intensity exercise.

35.12

AUTOPHAGIC PROTEIN EXPRESSION IN DENERVATED SKELETAL MUSCLE

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Apoptosis and autophagy are two highly conserved cell death processes that may contribute to disuse-induce muscle atrophy. The purpose of our study was to observe the possible role that autophagy may have in denervation-induced muscle atrophy, and to assess its relationship to apoptotic signaling. Denervation of CD-1 mice for 3, 7, or 14 days produced decreases in muscle mass of 5, 18, and 32%. These decreases were accompanied by 9, 11, and 16 % reductions in mitochondrial content. Pro-autophagy proteins LC3 and Beclin-1 were increased by 3.2-and 1.7-fold as a result of 7 days of denervation, while the pro-apoptotic Bax protein was elevated by 1.6-fold. To investigate whether autophagy was affected by reductions in apoptosis, we denervated Bax/Bak knockout mice (DKO) for 7 days. Denervation led to a 12% reduction in muscle mass, less than that observed in normal animals. Denervation also reduced SS and IMF mitochondrial respiration, and resulted in an elevation in the production of reactive oxygen species. The expression of both LC3 and Beclin-1 was increased by 2.5-and 1.5-fold in the DKO mice, which was similar to that found in normal animals. Thus, the induction of autophagy in response to denervation is not dependent Bax/Bak-mediated apoptosis. This study demonstrates that muscle disuse via denervation induces the activation of autophagy, and that this may have a role complementary to apoptosis in the atrophy of skeletal muscle.

35.13

ELEVATIONS IN ENDOGENOUS ANABOLIC HORMONES DO NOT ENHANCE MUSCLE HYPERTROPHY OR STRENGTH OF THE ELBOW FLEXORS FOLLOWING RESISTANCE TRAINING IN YOUNG MEN

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The importance of the transient increase in systemic anabolic hormones with resistance exercise to muscle hypertrophy is unclear. Our aim was to determine whether resistance exercise-induced elevations in endogenous hormones enhance muscle strength and hypertrophy during training. Twelve men (19-29 yrs) trained each arm on separate days for 15 weeks. One arm performed only arm curl exercises (A) while the other performed arm curls immediately prior to a high volume of leg resistance exercise (A+L) to elicit a large increase in circulating growth hormone (GH) and testosterone (T). There was no elevation in serum GH or T with A, but significant ($p < 0.001$) elevations, in both early and late training, in GH and T immediately and at 15 and 30min after A+L. Training resulted in increased elbow flexor strength and hypertrophy with no differences between conditions. Muscle cross-sectional area (by MRI) increased significantly ($p < 0.001$): A=12.0±5.7, A+L=9.9±5.7 ($p=0.52$). Elbow flexor strength measures also increased ($p < 0.001$): isometric maximal voluntary contraction (A=19%, A+L=17%; $p=0.80$) and one (A=23%, A+L=25%; $p=0.91$) and ten repetition isotonic maximum (A=46%, A+L=47%; $p=0.63$). We conclude that periodic elevations in endogenous anabolic hormones do not enhance muscle hypertrophy or strength of the elbow flexors following 15 weeks of training. Alternatively, our data demonstrate that local mechanisms are of primary importance in hypertrophy. Supported by NSERC.

35.14

INFLUENCE OF RESISTANCE TRAINING ALONE OR COMBINED WITH CYCLOOXYGENASE INHIBITOR CONSUMPTION ON SKELETAL MUSCLE PROTEOLYSIS IN OLDER HUMANS

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We have previously shown that resting skeletal muscle proteolysis is elevated in older individuals, which may contribute to sarcopenia, and hypothesized that strength training would reverse this age effect. A secondary objective was to determine if consumption of over-the-counter cyclooxygenase inhibitors during resistance training would influence resting muscle proteolysis. We utilized microdialysis to directly sample the m. vastus lateralis interstitial fluid for 3-methylhistidine, a natural tracer of myosin and actin proteolysis. Resting muscle proteolysis was evaluated before and after 12-weeks of knee extensor resistance training (3d/wk, 70% 1RM) in groups consuming Placebo (n=9, 65±2y), Ibuprofen (n=10, 65±2y; 1200 mg/d), or Acetaminophen (n=7, 64±1y; 4000 mg/d). Resting muscle proteolysis was not altered ($p>0.05$) with resistance training alone (Placebo) (pre: 4.64±0.34, post: 4.73±0.48 nmol/mL). Although both drugs enhanced muscle hypertrophy when compared to Placebo ($p<0.05$), neither Ibuprofen (pre: 5.25±0.71, post: 4.74±0.91 nmol/mL) nor Acetaminophen (pre: 4.03±0.30, post: 4.58±0.56 nmol/mL) altered resting muscle proteolysis. These data suggest that in older individuals the hypertrophy associated with resistance training alone or when combined with over-the-counter cyclooxygenase inhibitor consumption is not mediated by changes in resting skeletal muscle proteolysis. NIH R01 AG20532 (TT).

35.15

SHORT TERM, PROGRESSIVE-RESISTANCE WHEEL RUNNING BY C57BL/10 MICE IS NOT SUFFICIENT TO MIMIC A RESISTANCE EXERCISE

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The purpose of this study was to determine if 4 weeks of progressive, resistance wheel running was sufficient to induce skeletal muscle hypertrophy in C57BLl/10 mice. At age 25-d, 15 male mice were separated into three groups: Sedentary (SED, n=5), Non-resistance wheel running (NR, n=7), and Resistance wheel running (R, n=3). NR and R mice were initiated to running on a non-resistance wheel (<1 g) for Wk 1, after which R running wheels were loaded to 4 g (Wk 2), 7 g (Wk 3), and 8 g (Wk 4) of resistance. NR mice ran 7.29 ± 0.26 km/24-h during Wk 2-4, while R mice ran significantly less each week ($P\leq0.0001$) by ~70%. However, R mice demonstrated increased external Work during Wk 2 and 3 (8087 and 7376 N•m/kg body mass, respectively) compared to NR mice (1474 and 1813 N•m/kg body mass, respectively; $P\leq0.006$). Despite the increased Work, R mice displayed no signs of hypertrophy (wet mass and dry:wet mass ratio) of forelimb or hindlimb muscles compared with NR or SED mice ($P\geq0.0656$). Additionally, EDL muscle in vitro contractility was not different between groups. These results indicate that a 4-wk training duration is insufficient to induce skeletal muscle hypertrophy. A longer training period and a more gradual resistance progression may be necessarily to adequately stress skeletal muscle by voluntary wheel running to a point that it better mimics a resistance type of exercise. Supported by MDA 4143.

35.16

CHRONIC HYPOXIA INCREASES GLUCOSE UPTAKE IN SKELETAL MUSCLE AFTER INSULIN STIMULATION

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Acute hypoxia increases basal glucose transport in skeletal muscle. However, we do not know whether chronic hypoxia has a similar effect on skeletal muscle glucose uptake. In this study, we hypothesized that glucose transport would be higher in skeletal muscle after chronic normobaric hypoxia. For this purpose, 8-week old male C57BL mice were kept in normobaric hypoxia (FIO2=10%) for four weeks. Then, mice were anesthetized and killed and the soleus muscles were removed for in vitro study. Glucose transport into the soleus muscles was measured by uptake of deoxy-D[1,2-3H]glucose. Measurements were made under basal conditions and after insulin stimulation (1nM). Four weeks of chronic hypoxia did not increase basal glucose transport (1.60 +/- 0.58 vs 1.71 +/- 0.36 umol glucose/g of muscle/hr, control vs. normobaric hypoxia, n= 6 per group). However, insulin stimulation resulted in a greater increase in skeletal muscle glucose uptake in the hypoxic mice (4.87 +/- 0.83 vs 6.24 +/- 0.53 umol glucose/g/h; $p=0.018$, control vs. normobaric hypoxia respectively, n=6 per group). Based on these results, we conclude that chronic normobaric hypoxia does not alter basal glucose uptake in limb muscles, but it increases insulin-dependent glucose uptake. Further study is required to elucidate the mechanism of the enhanced insulin response after chronic hypoxia.

35.17

DIFFERENTIAL STIMULATION OF MYOFIBRILLAR AND SARCOPLASMIC PROTEIN SYNTHESIS WITH PROTEIN INGESTION AT REST AND AFTER RESISTANCE EXERCISE

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Feeding and resistance exercise both stimulate the synthesis of mixed muscle proteins. It is unclear whether there is a differential stimulation of the contractile myofibrillar (MYO) and the cellular sarcoplasmic (SARC) proteins after ingestion of protein and how this is affected by resistance exercise. Fasted (FAST) muscle fractional synthetic rate (FSR) was measured in five healthy young men with a primed constant infusion of ring-[13C6]phenylalanine. Participants then performed an intense bout of unilateral resistance exercise followed by the consumption of a drink containing 25 g of whey protein to maximally stimulate protein synthesis in the rested (FED) and exercised (FED-EX) legs. In FED there was an elevated ($P<0.01$) MYO FSR above FAST at 3 h (~200%) but not at 1 and 5 h (~67 and 65%, respectively; $P>0.05$). In contrast, FED-EX stimulated MYO FSR above FAST at 1, 3, and 5 h (~160, 330, and 280%, respectively; $P<0.01$) with the increase at 5 h being greater than FED ($P<0.01$). Thus, the synthesis of muscle contractile proteins is stimulated by both feeding and resistance exercise early (3 h) but is sustained longer and to a greater extent (5 h) with resistance exercise. In contrast, SARC FSR was similarly elevated ($P<0.01$) by ~207% at 3 h in both FED and FED-EX suggesting non-myofibrillar protein synthesis is stimulated by feeding but that this response is not augmented by resistance exercise. These data highlight the importance of measuring the synthetic response of specific muscle protein fractions when examining the acute effects of exercise and nutrition. Supported by NSERC.

35.18

GROWTH RESPONSE TO RESISTANCE EXERCISE: INFLUENCE OF EXERCISE DEVICE

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The aim of this study was to compare the response of selected skeletal muscle genes following an acute bout of resistance exercise (RE) in the fasted state or following amino acid infusion (RE+AA). Muscle biopsies were obtained from the vastus lateralis of 14 recreationally active subjects (25 ± 5 y, 76 ± 20 kg) before and 4-h following an acute bout of leg extension exercise. In the RE group (n=8), subjects were fasted for the duration of the exercise trial while the (RE+AA) group (n=6) received an amino acid infusion following the conclusion of RE. RE+AA attenuated ($P < 0.05$) proteolytic gene induction for MuRF-1 (1.1 vs. 2.0 fold) and myostatin (1.4 vs. 3.3 fold) compared to RE. Myogenin expression was higher ($P < 0.08$) in RE+AA (3.6 fold) vs. RE (1.8 fold). Conversely, MRF4 was lower ($P < 0.05$) in RE+AA (0.9 fold) compared to RE (4.5 fold). The results of this study suggest that RE in combination with amino acid feeding leads to a suppression of the proteolytic response and an increase in the expression of selected myogenic genes versus RE alone. This data provides novel insight into the effect of amino acids on genetic markers of muscle adaptation in response to resistance exercise. Supported by NASA grant NNJ06HF59G.

35.19

EFFECT OF AMINO ACID SUPPLEMENTATION ON MYOGENIC AND PROTEOLYTIC GENE EXPRESSION FOLLOWING RESISTANCE EXERCISE

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The aim of this study was to compare the response of selected skeletal muscle genes following an acute bout of resistance exercise (RE) in the fasted state or following amino acid infusion (RE+AA). Muscle biopsies were obtained from the vastus lateralis of 14 recreationally active subjects (25 ± 5 y, 76 ± 20 kg) before and 4-h following an acute bout of leg extension exercise. In the RE group (n=8), subjects were fasted for the duration of the exercise trial while the

(RE+AA) group (n=6) received an amino acid infusion following the conclusion of RE. RE+AA attenuated ($P < 0.05$) proteolytic gene induction for MuRF-1 (1.1 vs. 2.0 fold) and myostatin (1.4 vs. 3.3 fold) compared to RE. Myogenin expression was higher ($P < 0.08$) in RE+AA (3.6 fold) vs. RE (1.8 fold). Conversely, MRF4 was lower ($P < 0.05$) in RE+AA (0.9 fold) compared to RE (4.5 fold). The results of this study suggest that RE in combination with amino acid feeding leads to a suppression of the proteolytic response and an increase in the expression of selected myogenic genes versus RE alone. This data provides novel insight into the effect of amino acids on genetic markers of muscle adaptation in response to resistance exercise. Supported by NASA grant NNJ06HF59G.

35.20

MITOCHONDRIAL ADAPTATIONS FOLLOWING EXERCISE TRAINING IN DYSTROPHIC MOUSE SKELETAL MUSCLE

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Duchenne's Muscular Dystrophy (DMD) patients lack the structural protein dystrophin which leads to muscle weakness and loss of mobility. Exercise may be a good intervention to offset these pathologies. The mdx mouse, an animal model of DMD, engages in voluntary wheel running, but to a lesser extent than wild-type. The purpose of this study was to determine if hindlimb muscles of mdx mice undergo the well-defined adaptations of improved skeletal muscle oxidative capacity following 8 weeks of voluntary wheel running. Wild-type and mdx mice were divided into sedentary and exercise treatment groups. Tibialis anterior muscles were analyzed for β-hydroxyacyl-CoA dehydrogenase (β-HAD) and citrate synthase (CS) activities as markers of mitochondrial function. β-HAD and CS activities were 36% and 25% greater, respectively, in wild-type mice following training compared to sedentary mice. However, both β-HAD (36.2 ± 2.9 vs. 40.2 ± 1.9 U/min/mg) and CS activities (38.1 ± 1.3 vs. 34.4 ± 1.9 U/min/mg) were not different between sedentary and trained mdx mouse muscle. Despite non-adaptive mitochondrial enzyme activities, beneficial adaptations that occurred in mdx mice included changes in muscle mass, fiber size, and fiber type based on myosin heavy chain isoform expression. These data suggest that while some beneficial adaptations can occur, the mitochondria from dystrophic muscle may not respond to exercise the same as healthy muscle. Supported by MDA grant 4143.

35.21

WHEY PROTEIN STIMULATES A GREATER INCREASE IN MIXED MUSCLE PROTEIN SYNTHESIS THAN CASEIN OR SOY AT REST AND AFTER RESISTANCE EXERCISE IN YOUNG MEN

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Postprandial muscle anabolism is affected by the rate (i.e., fast or slow) of protein digestion. However, direct measurements of muscle protein synthesis have not been made following ingestion of 'fast' and 'slow' proteins. This study was designed to compare the acute response of mixed muscle protein synthesis to whey, casein, or soy protein ingestion at rest and after resistance exercise. Ten healthy young men (22±2.7 y, 1.82±0.048 m, 86.6±14.6 kg) performed a bout of unilateral resistance exercise followed by the consumption of a drink containing 10 g of essential amino acids as whey, casein, or soy protein. Mixed muscle protein fractional synthetic rate (FSR) was determined by a primed constant infusion of ring-[$^{13}C_6$]phenylalanine. Ingestion of whey protein resulted in a larger increase in blood amino acid concentration than either casein or soy ($p<0.05$). At rest, FSR was ~83 and 59% greater after whey protein consumption compared to casein and soy, respectively ($p<0.01$). FSR following whey consumption was ~94% greater than casein and 65% greater than soy after exercise ($p<0.05$). There was no difference in FSR between individuals consuming casein or soy at rest or following resistance exercise. We conclude that whey protein stimulates mixed muscle protein synthesis to a greater degree than casein or soy in young men, both at rest and after resistance exercise, likely due to increased amino acid availability. Supported by the US National Dairy Council.

35.22

EARLY CHANGES IN MYOSIN HEAVY CHAIN ISOFORM EXPRESSION AFTER SPINAL CORD TRANSECTION IN ADULT RATS

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The short-term changes in expression of the adult myosin heavy chain (MyHC) isoforms in the rat soleus following spinal cord transection (ST) were evaluated. MyHC mRNA isoforms were quantified 3 and 7 days after ST via RT-PCR. Pre-mRNA and natural antisense RNAs (NATs) were quantified at 7 days via one-step RT-PCR. Activation levels of the NFAT signaling pathway were determined by measuring MCIP1.4 mRNA and via an NFAT-dependent promoter. The control soleus expressed primarily MyHC mRNAs I (slow) and IIa (fast), but little of the fast IIx and IIb isoforms. MyHC isoforms I & IIa were reduced 7 days post-ST, whereas, MyHCs IIx and IIb were elevated by 3 days. MyHC I pre-mRNA was decreased and there was a tendency for a decrease in IIa pre-mRNA ($p = 0.08$). Pre-mRNAs for both IIx and IIb were increased after ST. The NATs for all of the fast MyHC isoforms were elevated after ST and did not show the expected inverse relationship to the corresponding pre-mRNAs. For instance, the NATs were elevated for isoforms IIx and IIb, as were the IIx and IIb pre-mRNAs. Since after ST, the rat soleus expresses high amounts of IIx mRNA and protein, these data suggest that elevated expression of a particular NAT does not always result in down regulation of that particular isoform. MCIP1.4 mRNA and NFAT-dependent promoter activity were decreased after ST, suggesting that the calcineurin-NFAT pathway could potentially play a role in ST-induced fiber type transformation. Supported by NIH GM53933.

35.23

AEROBIC ENDURANCE RUNNING PHENOTYPE INFLUENCES ADIPOSE FATTY ACID TRANSPORT PROTEIN IN RESPONSE TO HIGH FAT DIET

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Background: We have previously demonstrated that when rats phenotypically selected for inherent endurance running capacity were subjected to high fat feeding (HFF), low capacity running (LCR) animals demonstrated significant increases in adipose tissue mass and decreased insulin sensitivity, while the high capacity running (HCR) animals did not, despite similar intake patterns. Purpose: Test the hypothesis that differences in weight gain in response to high fat feeding could be explained by the level of fatty acid transporters in adipose tissue. Methods: Following 12 weeks of HFF (50% calories from fat), animals were euthanized, and abdominal adipose was obtained to determine the level of the fatty acid transporters (CD36, FATP4; western blot). Results: No significant differences in FATP4 content were seen between groups on chow or HFD. There were no differences between chow fed HCR and LCR rats CD36 (208758 ± 50881 AU vs. 265627 ± 95290 AU), but HCR rats increased CD36 content when compared to their chow counterparts (444348 ± 140649, $p < 0.005$), while LCRs did not. Conclusion: Resistance to adiposity in HCR animals occurred despite an increase in adipose fatty acid uptake, suggesting that increased adipose lipolysis must also be up-regulated in this strain. Conversely, the inability to increase transporter proteins in LCRs is consistent with relatively elevated serum levels, and decreased insulin sensitivity in response to HFF. Supported in part by NIH RR-17718.

35.24

LACTATE STIMULATES THE PGC-1α TRANSCRIPTION BY REDUCING THE NAD^+/NADH REDOX STATE AND REPRESSING SIRT1 HISTONE DEACETYLASE

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During sustained contractile activities, lactate is produced continuously in skeletal muscle serving as a fuel source for metabolism as well as a signaling molecule for muscle adaptation. However, the molecular mechanism of lactate signaling in skeletal muscle remains elusive. Using a luciferase reporter expression system in cultured cells, we show that lactate at physiological pH stimulates the promoter activity of the peroxisome proliferator-activated receptor-γ coactivator (*Pgc*)-1α gene. Direct addition of NADH to the culture medium, or siRNA-mediated silencing of the expression of Nampt or Nmnat-- key enzymes for NAD^+ synthesis, mimics the effects of lactate, which could also be recapitulated by functional inhibition of the NAD^+-dependent SIRT1 histone deacetylase by a specific inhibitor, Sirtinol, or an NAD^+ antagonist, nicotinamide. Finally, lactate-induced *Pgc-1α* transcriptional activity can be blocked by isonicotinamide, a constitutive activator of SIRT1 independent of the redox status. Our findings reveal a functional signaling pathway in which lactate reduces the NAD^+/NADH ratio and stimulates the *Pgc-1α* gene transcription by repressing the SIRT1 activity, and contributes to adaptive changes in skeletal muscle in response to exercise training. *These two authors had equal contribution.

35.25

ANABOLIC STEROIDS WITHDRAWAL IN STRENGTH TRAINED ATHLETES: HOW DOES IT AFFECT SKELETAL MUSCLES?

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It is well known that the use of anabolic steroids has powerful myotrophic effects on skeletal muscles. However, our understanding of the effects of steroids withdrawal on muscles remains very poor partly because of the difficulty to investigate this issue. In this report, we analysed muscle characteristics of seven power athletes who previously had used anabolic steroids for long periods of time but stopped their usage some years ago (PREV group). Muscle characteristics were compared with those from earlier studies performed on two groups of strength-trained power-lifters. One group was designated the P group (Power lifters) and the other the PAS group (Power lifters using anabolic steroids). Muscle fiber distribution, fiber area, subsarcolemmal and internal myonuclear number per fiber, myonuclei expressing androgen receptors, satellite cell number per fiber and proportion of split fibers were analysed in two skeletal muscles: a limb muscle, the vastus lateralis and a neck-shoulder muscle, the trapezius. For both muscles, the mean fiber area was very similar between the PREV and the P groups but both these groups had significantly smaller fiber areas than the PAS group. In vastus the number of nuclei per fiber was of the same magnitude as in the P group but lower than that of the PAS group, whereas in the trapezius the highest number was found in the PREV group. The PREV group had a significantly lower number of nuclei per fiber in the vastus lateralis compared to the trapezius. The PREV group had a lower proportion of fibers with internal nuclei in vastus compared to the P and PAS groups. In trapezius, the PREV group had the same proportion as the PAS group and both these groups had more fibers with internal nuclei than the P group. Interestingly, in the PREV group the number of androgen receptor-containing nuclei was significantly higher in vastus compared to that of the P and PAS groups. In trapezius they were of the same magnitude in both the P and PAS groups. In conclusion, several years after anabolic steroid withdrawal and with no or low intensity strength-training, the muscle fiber area and the number of nuclei per fiber in vastus lateralis is still comparable to that of athletes that are performing high intensity strength training. In trapezius, fiber areas are comparable to high intensity trained athletes and the number of nuclei per fiber is even higher than in the steroid-using group. The high number of nuclei might be beneficial for an athlete that continue or resume strength training because a high number of myonuclei gives the possibility to an increased protein synthesis. These results can be interpreted to indicate that a period of anabolic steroid usage is an advantage for a power lifter in competition several years after secession of drug intake.

36.0: MUSCLE INJURY

36.1

MRI IMAGING OF SKELETAL MUSCLE INJURY IN THE TIBIALIS ANTERIOR MUSCLE OF LIVE RATS

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We have shown that increased repetitions of stretch-shortening cycles (SSCs) results in increased myofiber necrosis and inflammatory infiltrates in the tibialis anterior (TA) muscles of rats. In the present study, 3 month old male Fischer 344 x Brown Norway hybrid rats (N=12) were exposed to either 0, 30, 70, or 150 SSCs in vivo using a custom-designed dynamometer. Rats were anesthetized 72 hours after exposure, infused with Prohance, and then imaged using a 7T rodent MRI imaging system (MR Path, Inc.). Rats were euthanized after imaging and the lower

limbs were removed and placed in formalin. The TA muscles were prepared for histological analyses using standard hematoxylin and eosin staining and quantified using a stereological technique. MRI images were quantified using a damage index consisting of the volume of tissue disruption in the TA and image contrast using a mean area gray value (mArGV). MRI images were processed using Optimas software. Stereological analyses of the tissue sections showed that myofiber necrosis and inflammatory infiltrates significantly increased with exposure to 70 SSCs and 150 SSCs as compared to the 30 SSCs and the control. Analysis of the MRI images shows that the percent of affected area significantly increased with exposure to the 70 SSCs and 150 SSCs. The mArGV also increased significantly with increasing SSC repetitions. The results show that the MRI imaging in live animals produces similar results to stereological analyses.

36.2

EVIDENCE OF MUSCLE DAMAGE IN ELECTRICALLY STIMULATED HUMAN SKELETAL MUSCLE IN AN ISOMETRIC POSITION

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It is unknown whether muscle damage at the level of the sarcomere can be induced without lengthening contractions. To investigate this, 7 young healthy men underwent 30 minutes of repeated electrical stimulated contraction of m. gastrocnemius medialis. This study conformed to the Declaration of Helsinki. Two muscle biopsies were collected 48 hours later, one from the stimulated muscle and one from the contra-lateral leg. Immunohistochemical analysis of the biopsies from the stimulated muscle revealed macrophage infiltration and desmin-negative staining in a small percentage of myofibres. Electron microscopical investigation uncovered Z-line disruption at varying magnitudes in all subjects and displayed a trend towards a positive correlation (r=0.73, P=0.0663) with the force produced by stimulation. Increased muscle soreness in all subjects combined with a significant increase in CK activity ($p<0.05$) are indirectly suggestive of muscle damage, and the novel findings of the present study, i.e. 1) macrophages infiltration, 2) lack of desmin staining, and, 3) z-line disruption, provide direct evidence of damage at the myofibre and sarcomere levels. These data support the hypothesis that muscle damage at the level of the sarcomere can be induced without lengthening muscle contractions. Funded by Lundbeck Foundation and the Danish Medical Research Foundation.

36.3

THE EFFECT OF ELEVATED MUSCLE FLUID VOLUME ON INDICES OF MUSCLE DAMAGE FOLLOWING AN ACUTE BOUT OF ECCENTRIC EXERCISE

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The purpose of this study was to determine if an increase in muscle fluid content could alter the acute muscle damage response following a bout of eccentric exercise. Healthy males (n=8) participated in a randomized cross-over design involving a hydration (HYD; infusion of 0.45% saline) and control trial (CON), separated by four weeks. During each trial, participants completed a bout of single leg isokinetic eccentric exercise using the quadriceps (10 sets of 10 repetitions). Muscle biopsies were taken to estimate muscle fluid content. Blood samples were collected pre- and 0, 3, and 24 hrs post-exercise. Results demonstrated an increased muscle fluid volume in HYD following the infusion compared to CON ($p<0.05$). Creatine kinase levels were significantly greater 24 hrs post exercise for both conditions ($p<0.05$). Lactate dehydrogenase at 24 hours was also higher than pre for both conditions ($p<0.05$). C-reactive protein levels progressively increased at each subsequent time point for both conditions ($p<0.05$). No differences in IL-6 were observed at any of the time points for either conditions. Thus, the HYD condition was a viable method to acutely increase muscle fluid content in human skeletal muscle, but had little influence on indices of muscle damage after eccentric exercise. Supported by NSERC (Canada).

36.4

PROTEASE-ACTIVATED RECEPTOR-MEDIATED CA^{2+} SIGNALING AND CYTOKINE PRODUCTION IN CULTURED C2C12 SKELETAL MUSCLE CELLS

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Protease-activated receptors (PARs) are activated by proteases such as thrombin, via proteolytic cleavage. In non-muscle cells, PAR activation is thought to play a significant role in the inflammatory process by eliciting a rise in intracellular Ca^{2+}, and triggering the release of inflammatory cytokines. In this study, we examined the effect of PAR stimulation on intracellular Ca^{2+} signaling and IL-6 production in cultured skeletal muscle myotubes. C2C12 myotubes were grown under standard culture conditions. PARs were activated with thrombin. Ca^{2+} was measured using the fluorescent Ca^{2+} indicator fura-2. IL-6 levels in the culture supernatant were detected by ELISA. Exposure of the myotubes to thrombin resulted in a marked increase in intracellular Ca^{2+} (mean amplitude; 0.38 ± 0.03 μM, n = 13) that was larger in peak than electrically-induced Ca^{2+} transients elicited in similar cells (mean amplitude; 0.20 ± 0.07 μM, n = 11). Exposure of myotubes to thrombin (5U/ml) for 24 hours increased supernatant IL-6 levels to 140% of control levels (p=0.01). Pre-exposure to thrombin (10U/ml) for one hour, followed by a 24 hour exposure to thrombin (5U/ml) 12 hours later, increased IL-6 levels to 188% of control levels (p=0.01). These results indicate that thrombin exposure results in the release of IL-6 from skeletal muscle cells, possibly via PAR-mediated Ca^{2+} signalling. This system could play a role in the cellular response to muscle injury. Funded by a UWA project grant.

36.5

CHARACTERIZATION OF MMP-3 AND TIMP-1 PROTEIN EXPRESSION IN RESPONSE TO SKELETAL MUSCLE INJURY IN MICE

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Matrix metalloprotease (MMP)-3 directly regulates activation of other MMPs as well as degrades abundant ECM proteins. After insult, the rate and onset of ECM remodeling by MMP-3 is regulated at many levels, one being inhibition via tissue inhibitor of metalloproteases-1 (TIMP-1). We characterize temporal MMP-3 and TIMP-1 protein content in response to skeletal muscle injury as well as post-translational processing of latent MMP-3 into its intermediate active and active forms. Mouse tibialis anterior (TA) muscles were exposed to a -100ºC steel probe for 10s. Muscles from injured and uninjured legs were harvested at 3, 10, 24, 48, and 72h post-injury and protein content was determined by immunoblotting. Latent MMP-3 content was increased by a minimum of 170% (24 and 72h; $P<0.01$) in injured legs with the greatest increase seen at 3h (325%; $P<0.01$). TIMP-1 shows an inverse response to latent MMP-3 response with 50, 120, 70, and 100% reductions (3, 10, 24, and 48h post-injury, respectively; $P<0.01$) and a return to uninjured values at 72h. Intermediate active MMP-3 was consistently reduced by 50% at all times in injured vs. uninjured legs ($P<0.01$). Similarly, active MMP-3 was reduced 30-50% from 3-48h ($P<0.01$), but equal to uninjured at 72h. These results suggest increased latent MMP-3/TIMP-1 ratios with impaired post-translational processing of MMP-3 in response to injury. Additionally, other factors besides TIMP-1 are involved in inhibiting MMP-3 processing. Funding provided by In-House Laboratory Independent Research (ILIR).

36.6

NITRIC OXIDE SYNTHASE INHIBITION EXACERBATES ISOLATED EDL MUSCLE FORCE DEFICITS DURING AND IMMEDIATELY AFTER PERFORMING ECCENTRIC CONTRACTIONS

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The purpose of this study was to determine if nitric oxide synthase (NOS) activity alters the magnitude of immediate force deficits incurred by performing eccentric contractions (ECCs). Male C57/B6 mice were anaesthetized and extensor digitorum longus (EDL) muscles were isolated for in vitro functional testing at 35˚C. EDL muscles performed two isometric force-frequency (10 – 300 Hz) tests separated by 20 min of incubation in Krebs buffer only (control; n=4) or with the addition of a NOS inhibitor (L-NAME, 10mM; n=4). Muscles, in their same respective incubation media, then performed 10 ECCs (0.90 to 1.1 of physiological muscle length at 1.5 muscle lengths/s) followed by a post-injury force-frequency test. Maximal isometric force (P_o) was similar between control and L-NAME muscles both before (23.5 ± 1.0 vs. 24.0 ± 0.6 Ncm^{-2}) and after (23.3±1.1 vs. 21.6±1.2 Ncm^{-2}) the incubation period. Peak force produced during the 1st eccentric contraction was similar between control and L-NAME muscles (40.5± 2.5 vs. 36.4±3.6 Ncm^{-2}), but the decline in eccentric force was greater for L-NAME (~37%) than control (~24%) muscle. Immediately after the ECCs, isometric force was reduced at all stimulation frequencies for control (24-37%) and L-NAME (45-52%) muscles; however, P_o was reduced to a greater extent for L-NAME (11.5±1.2 Ncm^{-2}) than control (17.4±0.9 Ncm^{-2}) muscle. These results suggest that NOS activity preserves muscle function during and immediately after the performance of ECCs.

36.7

NF-κB FUNCTIONS AS AN INHIBITOR OF MYOGENESIS DURING POST-NATAL DEVELOPMENT

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Previous studies indicate that NF-κB is constitutively active in proliferating myoblasts and functions to inhibit muscle differentiation in vitro and in vivo during acute and chronic muscle injury. The goal of this study was to determine whether this regulation of myogenesis by NF-κB is physiologically relevant during muscle development. By a series of analysis involving DNA binding assays, luciferase assay, and Western blots, we show that NF-κB activity is highly elevated in muscles from neonatal mice (P5), but dramatically reduced in muscles approaching adolescence (P15). The decrease in NF-κB in these maturing muscles is similar to that observed from differentiating cultured myoblasts. In order to address the potential role of NF-κB during this time in development, limb muscles were analyzed in $p65^{+/+}$ and $p65^{-/-}$ mice. We find that at P8, $p65^{-/-}$ muscles contained approximately 30% more fibers than $p65^{+/+}$ littermate controls. Furthermore, myonuclei number per fiber was reduced in $p65^{-/-}$ mice compared to wild types, suggestive of an accelerated myogenic program. To address whether this regulation occurred at an earlier time during development, we examined the expression of myogenic markers in limbs from E10.5 to E13.5 mice. By both immunofluoresence and quantitative real-time PCR, we were unable to detect significant differences in the markers or the phenotype of the muscle fibers, suggesting that regulation of muscle differentiation by NF-κB is restricted to post-natal development. To test this notion we expressed the transdominant inhibitor of NF-κB, called the I□B□super-repressor (SR), in neonatal mice. Repression of NF-□B activity again resulted in both an approximate 20% increase in soleus muscle fibers and an enhancement of myogenic markers. Collectively, these results support that NF-□B functions as a negative regulator of post-natal muscle development.

37.0: ROLE OF INFLAMMATION IN HEALTHY, DISEASED AND AGED MUSCLES

37.2

IMPACT OF EXERCISE ON INFLAMMATION IN ACUTELY- AND CHRONICALLY-INJURED SKELETAL MUSCLE

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There is no disputing that an inflammatory response is required for skeletal muscle to recover from an acute injury. However, the same cannot be said for inflammation of long duration such as that occurring in chronically-injured muscle. This has led to debate as to whether modulation of the inflammatory response, either down or up, should be attempted and if so, when in the injury process it should be attempted. Complicating the debate is the observation that the inflammatory response and subsequent repair/regeneration process is dependent on the means by which the muscle is injured. In equally-injured muscles, one injured by an acute bout of exercise exhibits a qualitatively different inflammatory response than that observed in a traumatically-injured muscle. These different inflammatory responses are coupled with the observation that in comparison to traumatically-injured muscle, muscle injured by exercise is better able to repair its injured muscle fibers and relies to a lesser extent on replacement of such fibers. It is not clear if and how exercise can modulate the inflammatory response and subsequent repair/regeneration process following any kind of acute muscle injury. The two extremes, inactivity and high levels of physical activity, following an acute injury worsen the recovery as does virtually any level of exercise done by chronically-injured muscle. One can only speculate as to a possible

exacerbation of the inflammatory response by exercise in these situations. REFERENCE: Warren GL, et al. Mechanisms of skeletal muscle injury and repair revealed by gene expression studies in mouse models. J Physiol 582(2): 825-841, 2007.

37.3

IMPACT OF EXERCISE ON INFLAMMATION IN DISEASED MUSCLE

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Although exercise could benefit Duchenne muscular dystrophy (DMD) patients by increasing muscle strength and endurance, increased muscle use can also cause additional muscle damage by inflammatory cells. Modified use or acute injury in healthy muscle causes a coordinated inflammatory response that results in complete repair and adaptation. First, muscle is infiltrated by Th1-type inflammatory cells, including classically-activated macrophages that target and remove debris. Next, Th2-type inflammatory cells, including alternatively-activated macrophages, infiltrate and promote muscle repair and regeneration. However, dystrophin-deficient muscle undergoes repeated cycles of degeneration and incomplete regeneration and is characterized by chronic inflammation. Moreover, the inflammatory response in dystrophic muscle is uncoordinated with Th1 and Th2-type inflammatory cell populations present in the muscle concomitantly and inducing muscle fiber damage and pathological fibrosis. Th1-type inflammatory cells, including classically-activated macrophages and cytotoxic T-cells, lyse dystrophic muscle fibers. However, eosinophils that typically represent a Th2 inflammatory response also increase dystrophic muscle damage by fiber lysis in vivo. The Th2 response in dystrophic muscle is dominated by alternatively-activated macrophages that exhibit pro-fibrotic characteristics including increased arginase expression. Pathological fibrosis is also promoted by major basic protein released by eosinophils. Thus, exercise could result in functional gains for DMD patients, but may also induce inflammation that promotes muscle pathology. (NIH R01 AR47855, R01 AR047721 to JGT; Muscular Dystrophy Association 4006 to MW-H and 3898 to JGT).

37.4

REGULATION OF NF-KB BY EXERCISE AND LESSONS LEARNED FROM MYOGENESIS AND MUSCLE WASTING

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Accumulating evidence indicates that exercise regulates NF-kB activity, but exactly how this signaling occurs and to what extent this regulation results in downstream physiological events remains poorly understood. Given that exercise stimulates ROS production and ROS is an activator of NF-kB, the prevailing hypothesis has been that exercise activates NF-kB. In most instances this hypothesis has been upheld, as both in vivo and in vitro models of exercise have been shown to increase NF-kB nuclear translocation. Differences in these results may be due to specie and skeletal muscle type specificity. However, in several examples of treadmill exercise, transient activation of IKK and the NF-kB classical p50/p65 heterodimer was observed, which may or may not be mediated through the degradation and re-synthesis of the IkBa protein. In our own studies examining NF-kB/IKK signaling in skeletal myogenesis, we find that similar to acute exercise, classical NF-kB is also transiently regulated during muscle maturation. This activity correlates with Ser536 phosphorylation of p65 and NF-kB dependent gene expression. We also find in hindlimb muscles from mdx mice that chronic activation of NF-kB/IKK signaling occurs with sustained Ser536 phosphorylation. Therefore, p65 post-translation modification may be a common step in activating NF-kB in a number of skeletal muscle stimuli. How studies in myogenesis and muscle wasting may be used to further understand NF-kB signaling and function during exercise will be further discussed.

37.5

IMPACT OF EXERCISE ON INFLAMMATION IN SARCOPENIA

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Muscles of old mice demonstrate muscle atrophy, an impaired ability to adapt following contractions and a poor recovery following severe contraction-induced damage. We hypothesise that altered immune cell sequestration may play a major role in these age-related muscle deficits. Data demonstrated that aberrant signalling, particularly to redox-sensitive transcription factors (TFs) such as NFkB and AP-1 occurs in muscles of old mice such that quiescent muscles demonstrate a chronic increase in TF DNA binding activity and a modified activation post-contractions compared with muscles of old mice. This inability to acutely activate TFs resulted in the lack of production of cytoprotective proteins such as stress or heat shock proteins (HSPs) and antioxidant defence proteins and was associated with a modification in immune cell infiltration and cytokine content of muscles. The functional effects of such changes have been demonstrated in muscles of old mice, where lifelong or acute production of cytoprotective stress proteins such as HSPs by transgenic or pharmacological approaches provided protection against age-related loss of muscle function. Further evidence for a role for aberrant redox signalling and TF activation in this process is demonstrated in mice lacking superoxide dismutase 1 (SOD1) whereby these mice demonstrate an accelerated age-related loss of muscle mass and function. In summary, data support the proposal that altered immune cell sequestration and cytokine production may play a major role in the development of age-related muscle deficits and correction of such alterations will improve muscle function in older individuals. The authors thank the MRC, BBSRC, National Institute of Aging and the University of Liverpool for financial support.

38.0: SARCOLEMMAL, T-TUBULE AND INTRACELLULAR DETERMINANTS OF CONTRACTILE FUNCTION IN SKELETAL MUSCLE

38.2

DETERMINANTS OF EXCITABILITY OF THE SARCOLEMMA AND T-TUBULE SYSTEM

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Excitability of a muscle fiber can be defined as the proneness to be activated in an all-or-nothing manner by an electrical stimulus. In a muscle fiber, it is important for an efficient contraction, that the excitation is evenly spread across the cell membrane. This is a major task performed by the sarcolemma, from which the excitation wave spreads into the depth of the fibers via the network of the T-tubular system (TTS) to reach all sarcomeres. The excitability of the sarcolemma might be coupled to the metabolic state of the subcortical compartment by ATP-sensitive K^+ channels. The TTS in turn is specialised to ensure an efficient excitation-contraction coupling. It is a system of narrow tubes, traversing the fibers and getting in close proximity to the sarcoplasmic reticulum at the triads. Due to the big surface area to volume ratio of the TTS, the inner electrolyte homeostasis is exposed to an incessant challenge. With every action potential intracellular K^+ is lost into the T-tubular space during the repolarisation phase and hence progressively depolarises the TTS and decreases its excitability. Thus K^+ must rapidly be transported back into the cytoplasm to avoid early fatigue. Despite the Na^+/K^+-ATPase other transport mechanisms are important, especially for the short-term maintenance of excitability. Of particular importance is the interplay between the high tubular Cl^- and the strong inwardly rectifying K^+ conductance. The efficiency of this mechanism is increased at lower pH levels. Additionally $Na^+/K^+/2\ Cl^-$-cotransporters support the restoring inward flux of K^+.

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CONTRACTILE PROTEIN – CYTOSKELETAL MECHANICAL LINK

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The function of contractile proteins is to generate force and this can be deterred by age, injury, or disease. In turn, interventions such as exercise can be implemented to offset the detriments. These alterations in force generation can be a direct result of modulating contractile proteins or secondary to changes in other proteins that are necessary for optimal muscle function. The focus of this presentation will be on the most elementary force-producing molecule, myosin. Two paradigms in which myosin structure-function is altered to different extents and by differing mechanisms are presented. First, muscular dystrophy which is caused by the lack dystrophin results in force loss. A perturbation in myosin structure:function accounts for only a third of this force deficit and is a secondary consequence. Forcing dystrophic mice to exercise exacerbates disease pathology but voluntary exercise causes beneficial muscle adaptations. In contrast to muscular dystrophy, an alteration in myosin structure:function fully explains contractile deficits due to estrogen deprivation in female mice. Estradiol replacement reverses deficits in force and myosin and may be mediated by estradiol's genomic mechanism via regulation of oxidative stress-related genes. Exercise enhances muscle function in estrogen-deficient mice, in this case not by improving myosin function but rather by hypertrophy. Support: NIH AG25861, MDA 4143. References: Moran AL, Nelson SA, Landisch RM, Warren GL, and Lowe DL. Estradiol replacement reverses ovariectomy-induced muscle contractile and myosin dysfunction in mature female mice. J Appl Physiol 102:1387, 2007.

NOTES

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