2012 American Physiological Society Meetings

Program and Abstracts Issue

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

2012 Intersociety Meeting:
The Integrative Biology of Exercise VI
October 2012 • Westminster, Colorado

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

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

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

\[1\] From a quote from Pele (b.1940, Minas Gerais, Brazil), probably the most famous ever Brazilian footballer (also an actor and politician). The full quote is “Enthusiasm is everything. It must be taut and vibrating like a guitar string.”
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Kim Barrett, Bene Machado, and Sue Barman outside of the Department of Physiology at USP-RB.

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

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

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

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

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

Andras Garami

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

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

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

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

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

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

Fifty-three of the attendees arrived a day early on Sept. 2 to participate in a day-long workshop sponsored by APS and IUPS: Trends and Challenges in Physiology Education: Africa and the World. The day started with a provocative talk by Olusoga Sofola who spoke on teaching practical physiology with limited equipment. The morning continued with brief talks on how to use stories and narratives to enhance teaching and learning, followed by participants working in small groups to create stories to use in their own teaching. After lunch, each person selected a topic to
discuss in a small group facilitated by an expert in the area. These included such diverse topics as using the internet to promote active learning, creating learning objectives, and active learning in large lectures. Summaries of the small group discussions from morning and afternoon were recorded on posters for all to view and discuss over lunch and at the closing plenary session.

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

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

Chapter News

Indiana Physiological Society
2nd Annual Meeting

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

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

During the poster session there was an education breakout session led by Dr. Patricia Clark of the Department of Biology at IUPUI. There were three discussion items: pedagogy in physiology classes at the university level; INPhys outreach to K-12 classrooms, including promotion and active participation in PhUn week; and other opportunities for the promotion of physiology and sciences in general.
Following the poster and breakout session, the group reconvened for the second keynote speaker R. Dustan Sarazan, the vice president and chief scientific officer for Data Sciences International. The title of his talk was “In vivo cardiovascular research using chronically instrumented animal models.” In his talk he began by enthusiastically discussing his adventures working with whole animal models in research. He mentioned how he traveled and adjusted procedures to different animals, such as giraffes in Africa or bears in Alaska. He then discussed the historical development of devices to study whole animal models from externally mounted equipment to the current status of implanted devices.

After the keynote speaker, the meeting continued with four more student speakers. The day concluded with presentations of awards and the closing statements that included the introduction of the new President-elect, Allan Albig, from Indiana State Univ. and a new councilor, Randall Roper, from Indiana Univ., Purdue Univ. Indianapolis. Guest attendees, Professors Peter Lauf and Norma Adragna from Wright State Univ., generously donated money for a travel award to be used for attendance at an APS meeting. Julia Hum won the travel award for her research entitled, “Live imaging of Src activation in osteocyes in response to mechanotransduction.” Other awards were presented to both undergraduate and graduate students for their research. At this point all
the attendees where thanked for being part of such a successful meeting and reminded of how much hard work went into the planning and organizing of the meeting from the officers, council, and the 2012 organizing committee.

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

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

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

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

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

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

**Fifteenth Annual Meeting of the Nebraska Physiological Society**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Fourth Annual Meeting of the Tennessee Physiological Society

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

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

The three student oral presentations included: “Stabilizing rescued αf508 CFTR at the plasma membrane by potentiation of its interaction with Na+/H+ exchanger regulatory factor 1,” presented by Kavisha Arora, Univ. of Tennessee Health Sciences Center; “Dysfunction in mTORC2/Akt signaling disrupts brain D2R signaling and DA homeostasis,” presented by Olga Dadalko, Vanderbilt Univ.; and “Restoration of function to CXT-damaged mouse ovary using NPBC,” presented by Letitia Lyons, Meharry Medical College.

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

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

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

Dr. Anthony E. Archibong (Associate Professor, Meharry Medical College) presents his research.
reduced following weight-loss associated with roux-en-y gastric bypass surgery. Finally, the Best Undergraduate/High School Student Presentation Award went to Cole Pickney. His poster was entitled: Assessing the role of the MC3R in fat deposition post ovariectomy.

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

Publications

New Editorial Board of Physiology

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

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

Guichun Han
Texas A&M Univ.

Samantha Paige Harris
Univ. of California, Davis

Jeffrey Robb Holt
Boston Children’s Hosp., MA

Pamela J. Hornby
Janssen Pharmaceutical J&J, PA

Devin Horton
Univ. of Utah, Salt Lake City

Xin Huang
Univ. of Wisconsin, Madison

Nicholas Michael Hurren
Univ. of Texas Med. Branch, Galveston

Robert Hyldahl*
Brigham Young Univ., UT

Joseph Michael Hyser
Baylor College of Med., TX

Patrick Y. Jay
Washington Univ., St. Louis, MO

Quan Jiang
Univ. of Hong Kong

David Eric Kling
Boston College, MA

Mary Kotlarczyk
Univ. of Pittsburgh, PA

Gabriel Kreiman
Boston Children’s Hosp., MA

Renee Labiris
McMaster Univ., Canada

Genevieve Nguyen
Center for Interdisciplinary Res. in Bio., Paris, France

Syotaro Obi
Univ. of Tokyo, Japan

Jeb Orr
Vanderbilt Univ., TN

Alejandro Ortiz-Acevedo
Univ. of Puerto Rico, Mayaguez

Christina Pabellick
Mayo Clinic, Rochester, MN

Dinesh Pal
Univ. of Michigan

Frank Palermo
Univ. of Colorado, Boulder

Melissa Pangelinan
Rotman Res. Inst., Toronto, Canada

Anthony M. Payne
Quinnipiac Univ., Hamden, CT

Claire M. Peppiatt-Wildman
Univ. of Kent, UK

Brenda J. Peters
St. Ambrose Univ., Davenport, IA

Paolo Pianosi
Mayo Clinic, Rochester, MN

David Anthony Power
Austin Health, Heidelberg, Australia

Chris Royer
Lovelace Respiratory Res. Inst., NM

Byungkyu Ryu
Korea Univ., Gyeonggi-Do, Republic of Korea

Grazyna Barbara Sadowska
Woman & Infants’ Hospital, RI

Adeel Safdar
Harvard Med. School, Boston, MA

Enrico Schulz
TU München, München, Germany

Stephanie Schulz
Stanford Univ., CA

Jessica Scott
NASA Johnson Space Center, TX

Madhulika Sharma
Univ. of Kansas

Brian J. Siroky
Cincinnati Children’s Hosp., OH

David Anthony Stoltz
Univ. of Iowa

Sun-Sang Joseph Sung
Univ. of Virginia

Masakazu Suzuki
Shizuoka Univ., Japan

Xiaoyue Tan
Nankai Univ., China

Jennifer A. Teske
Univ. of Arizona

Binu Tharakan
Texas A&M Univ., HSC
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<tr>
<td>March</td>
<td>Networking at a Scientific Meeting 7-Day Online Course</td>
</tr>
<tr>
<td>April</td>
<td>Experimental Biology</td>
</tr>
<tr>
<td>May</td>
<td>Interviewing for an Academic Position 10-Day Online Course</td>
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<tr>
<td>June</td>
<td>Writing and Reviewing for Scientific Journals 6-Week Online Course</td>
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<tr>
<td>July</td>
<td>Writing and Reviewing for Scientific Journals 6-Week Online Course</td>
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<tr>
<td>September</td>
<td>Interviewing for an Industry Position 10-Day Online Course</td>
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<tr>
<td>October</td>
<td>Abstract Writing for Scientific Meetings 7-Day Online Course</td>
</tr>
<tr>
<td>November</td>
<td>Creating a Poster for a Scientific Meeting 7-Day Online Course</td>
</tr>
<tr>
<td>December</td>
<td>Find PST on Facebook: facebook.com/APS.PST Watch for the 2014 Calendar</td>
</tr>
</tbody>
</table>

Course availability dependent on enrollment.

Visit our Website for More Information and Deadlines: http://www.the-aps.org/PST
Join APS at Experimental Biology 2013!

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

www.experimentalbiology.org

EB2013
Experimental Biology BOSTON

April 20-24, 2013
Boston Convention & Exposition Center

Sponsors:
American Association of Anatomists (AAA)
The American Physiological Society (APS)
American Society for Biochemistry and Molecular Biology (ASBMB)
American Society for Investigative Pathology (ASIP)
American Society for Nutrition (ASN)
American Society for Pharmacology and Experimental Therapeutics (ASPET)
New Graduate Student Members

Al-Shaimaa Ahmed  
Univ. of Calgary, Canada

Puneet Arora  
New York Chiropractic College

Brittni Baynes  
Louisiana State Univ., HSC

Austin Basil Bigley  
Univ. of Houston, TX

Lance Bollinger  
East Carolina Univ., NC

Sarika Chaudhari  
Univ. of North Texas, HSC

Jennifer Marie Colon  
Univ. of Puerto Rico School of Med.

Elisabeth Cook  
California State Univ., San Bernardino

Emily J. Cox  
Washington State Univ.

Jennifer Dolan  
State Univ. of New York, Buffalo

Andrea Michelle Du Bois  
California State Univ., Fullerton

Anthony Adam Duplanty  
Univ. of North Texas

Lucien Daniel Durosier  
Ctr. De Research Hospital Sainte, Justine, Canada

Rui Feng  
Univ. of Cincinnati, OH

Justin Fletcher  
Univ. of Missouri

Daniel Gamu  
Univ. of Waterloo, Canada

Zachary Aaron Graham  
Univ. of Kansas

Jonathan Gumucio  
Univ. of Michigan

Jamie Hibbert  
East Carolina Univ., NC

Brenna Renee Hill  
Penn State Univ.

Miara Akiel Jeffress  
Howard Univ., Washington, DC

Lawrence Cody Johnson  
Univ. of Colorado, Boulder

Danielle Jin-Kwang Kim  
Penn State Univ.

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Columbia Univ., NY

Alessandro Da Costa Machado  
Univ. Federal Fluminense, Brazil

Neysha Martinez-Orengo  
Ponce Sch. of Med. & Health Scis., Puerto Rico

David Maurer  
Penn State Univ.

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Johns Hopkins Univ., MD

Pia O’Neill  
Columbia Univ., NY

Girija Regmi  
Oklahoma State Univ.

Chance William Reinhart  
Univ. of Alberta, Canada

Megan Kathleen Rhoads  
Univ. of Kentucky

Ruben Rodriguez  
Univ. of California, Merced

Michael Schumacher  
Univ. of Cincinnati, OH

Muhammad Asadullah Siddiqui  
Queen Margaret Univ., UK

Alexander C. Sutton  
Albany Medical College, NY

Lykke Sylow  
Univ. of Copenhagen, Denmark

Marc Tuazon  
Rutgers Univ., NJ

Benjamin Yaden  
Eli Lilly and Company, IN

Johnny Yang  
California State Univ., San Bernardino

Thomas Yarbrough  
Univ. of South Alabama

New Undergraduate Student Members

Carissa Chamney  
Drake Univ., IA

Vinh Dang  
Michigan State Univ.

Rachel Marie Firkins  
Des Moines Univ., IA

New Affiliate Members

Christopher Matthew Trimby  
New Jersey Inst. of Tech.

Recently Deceased Members

Leon Cudkowicz  
Highland, OH

Joe M. Dabney  
Gaithersburg, MD

George D. Davis  
New Orleans, LA

Bjorn Folkow  
Goteborg, Sweden

Arthur B. French  
Ann Arbor, MI

Robert W. Hamilton  
Tarrytown, NY

Francis M. Knapp  
Rancho Santa Fe, CA

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

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

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

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

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

<table>
<thead>
<tr>
<th>Registration Type</th>
<th>Number of Attendees (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS Member</td>
<td>31 (28%)</td>
</tr>
<tr>
<td>Nonmember</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>Postdoctoral</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Student</td>
<td>22 (20%)</td>
</tr>
<tr>
<td>Invited Chairs/</td>
<td>30 (27%)</td>
</tr>
<tr>
<td>Speakers</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>111 (100%)</td>
</tr>
</tbody>
</table>
Travel awardees Tamra Llewelyn (left) and Amy Abbott (second from right) pose with the NIDDK award winners Ronee Harvey (center) and Vanitra Richardson (right) and Conference Organizer, Irving Zucker at the Joslyn Art Museum.

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

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

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

The 2012 APS Intersociety Meeting, The Integrative Biology of Exercise-VI, was held in the vibrant town of Westminster, CO. Intersociety Meetings are held every four years and offer concurrent symposia and exhibits. This meeting was organized by P. Darrell Neufier (Chair), East Carolina Univ.; Keith Baar, Univ. of California, Davis; Frank Booth, Univ. of Missouri, Columbia; David Brown, East Carolina Univ.; Paige Geiger, Kansas Univ. Medical Center; Mark Hargreaves, Univ. of Melbourne, Australia; Judy Muller-Delp, Univ. of Florida; Michael Joyner, The Mayo Clinic; William Kraus, Duke Univ.; Deborah Muoio, Duke Univ.; Henriette Pilegaard, Univ. of Copenhagen, Denmark; Espen Spangenburg, Univ. of Maryland; and Scott Trappe, Ball State Univ. The program for this meeting covered recent advancements in the exercise research area, as well as emerging topics.

This exciting meeting attracted 350 total registrants, including a good presence of young investigators and students. The young investigators and students accounted for 45% of the total registrants. APS members made up 21% of the attendees, closely followed by non-members (14%) and sponsoring societies (5%) attendees respectively. Invited speakers and chairs represented the remaining 15% of attendees. This meeting also had a large international presence with some participants coming for the first time to the United States and their first meeting. Out of the 350 registrants, 9% of registrants came from Canada, 10% of registrants represented countries from Europe and 14% from countries such as Australia, Brazil, Japan, India, South Korea, and Thailand. Table 1 shows the breakdown of the different registration types.

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

The three day meeting also included three separate poster sessions. During these sessions, established scientists and student attendees presented their abstract work to their colleagues and peers. There were a total of 216 programmed abstracts for the meeting. Out of the abstracts that were submitted, 25% had a female first author; 14% of the submitted abstracts came from countries in Europe, closely followed by Canada with 10% and Japan with 9%. Furthermore, 8% of abstracts also came from Richard Holland and generous educational grants from the Univ. of Nebraska Medical Center, Medtronic Cardiae and Vascular Group, the American Autonomic Society, ADInstruments, Quartzy, NIH, National Institutes of Diabetes and Digestive and Kidney Diseases, Data Science International, and Biocontrol Medical.

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Table 1. Registration Statistics

<table>
<thead>
<tr>
<th>Registration Type</th>
<th>Number of Attendees (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS Member</td>
<td>74 (21%)</td>
</tr>
<tr>
<td>Nonmember</td>
<td>49 (14%)</td>
</tr>
<tr>
<td>Postdoctoral</td>
<td>33 (10%)</td>
</tr>
<tr>
<td>Student</td>
<td>123 (35%)</td>
</tr>
<tr>
<td>Invited Speaker</td>
<td>52 (15%)</td>
</tr>
<tr>
<td>Sponsoring Societies</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>350 (100%)</td>
</tr>
</tbody>
</table>
from institutions in Australia, Brazil, and Thailand.

The meeting closed with a Banquet and Awards Presentation, where the Meeting Organizer, P. Darrell Neufer presented the winners of the Research Recognition Award for Outstanding Abstract Presentation by a Graduate Student or Postdoctoral Fellow a certificate and cash prize. The Postdoctoral winners of the award were: Katsuhiko Funai, Washington Univ. School of Medicine, and Erin Giles, Univ. of Colorado, Denver. The student award winners were: Kelsey Fisher-Wellman, East Carolina Univ., Robert Jacobs, Univ. of Zurich, Switzerland, Dara Slopack, York Univ., Canada, and Michael Stec, Univ. of Alabama, Birmingham.

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

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

Meeting attendees during one of the poster sessions.

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

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

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<th>Journal/Editorial Title</th>
<th>Call for Papers Details</th>
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<tr>
<td><strong>Physiological Genomics</strong></td>
<td>Mitochondrial Metabolism</td>
</tr>
<tr>
<td>NextGen Sequencing Technology-Based Dissection of Physiological Systems</td>
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<tr>
<td>Technology Development for Physiological Genomics</td>
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<tr>
<td><strong>Journal of Applied Physiology</strong></td>
<td>The Role of Inflammation in Skeletal Muscle, Connective Tissue, and Exertional Injuries: To Block or Not to Block? (January 1, 2013)</td>
</tr>
<tr>
<td><strong>Advances in Physiology Education</strong></td>
<td>Teaching and Learning of Professional Ethics</td>
</tr>
<tr>
<td><strong>AJP-Cell Physiology</strong></td>
<td>Cellular Circadian Rhythms (December 31, 2012)</td>
</tr>
<tr>
<td>Stem Cell Physiology and Pathophysiology (December 31, 2012)</td>
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<tr>
<td>Proteomic and Metabolomic Approaches to Cell Physiology and Pathophysiology (December 31, 2012)</td>
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<tr>
<td><strong>AJP-Gastrointestinal and Liver Physiology</strong></td>
<td>Physiology and GI Cancer</td>
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<tr>
<td>Intestinal Stem Cells in GI Physiology and Disease</td>
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<tr>
<td>Innovative and Emerging Technologies in GI Physiology and Disease</td>
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<tr>
<td><strong>AJP-Heart and Circulatory Physiology</strong></td>
<td>Mitochondria in Cardiovascular Physiology and Disease (December 31, 2012)</td>
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<tr>
<td>Pathophysiology of Hypertension (March 31, 2013)</td>
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<tr>
<td><strong>AJP-Lung Cellular and Molecular Physiology</strong></td>
<td>Bioengineering the Lung: Molecules, Materials, Matrix, Morphology, and Mechanics</td>
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<tr>
<td>Translational Research in Acute Lung Injury and Pulmonary Fibrosis (July 1, 2013)</td>
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<tr>
<td><strong>AJP-Regulatory, Integrative, and Comparative Physiology</strong></td>
<td>Fetal and Neonatal Programming: Epigenetic Modification of Phenotype (June 30, 2013)</td>
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<tr>
<td>Integrative and Translational Physiology: Inflammation and Immunity in Organ System Physiology (June 30, 2013)</td>
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<tr>
<td>Integrative and Translational Physiology: Integrative Aspects of Energy Homeostasis and Metabolic Diseases (June 30, 2013)</td>
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<tr>
<td><strong>AJP-Renal Physiology</strong></td>
<td>Renal Solute Co-Transporters and Exchangers (July 1, 2013)</td>
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<td>Chronic Kidney Disease and Fibrosis (July 1, 2013)</td>
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<tr>
<td>Renal Acid-Base Physiology (July 1, 2013)</td>
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<tr>
<td>Pathophysiology of Acute Kidney Injury (July 1, 2013)</td>
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<tr>
<td><strong>American Journal of Physiology—Endocrinology and Metabolism</strong></td>
<td>Islet Biology (June 30, 2013)</td>
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<tr>
<td>Novel Aspects of Adipocyte Biology (June 30, 2013)</td>
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<tr>
<td>CNS Control of Metabolism (June 30, 2013)</td>
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</tbody>
</table>

For a complete list of current Calls for Papers, visit The Physiologist website.
PHYSIOLOGY IN PERSPECTIVE:
THE WALTER B. CANNON
AWARD LECTURE (SUPPORTED
BY THE GRASS FOUNDATION)

Michael J. Joyner
Mayo Clinic

“Is Physiology Redundant?”
SATURDAY, APRIL 20, 5:30 PM

HENRY PICKERING BOWDITCH
AWARD LECTURE

Johnathan Tune
Indiana Univ. Sch. of Med.

“Translational Insights Into
the Regulation of Coronary
Blood Flow”
SUNDAY, APRIL 21, 5:45 PM

CLAUDÉ BERNARD
DISTINGUISHED LECTURESHIP
OF THE APS TEACHING OF
PHYSIOLOGY SECTION

Eric Mazur
Harvard School of
Engineering and Applied Sci.

“Confessions of a Converted
Lecturer”
SUNDAY, APRIL 21, 10:30 AM

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

Amira Klip
The Hospital for Sick
Children

“Insulin Signal Transduction
Meets Vesicle Traffic via Rab
GTPases and Unconventional
Myosins”
SUNDAY, APRIL 21, 2:00 PM

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

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

“Collecting Duct
Endothelium: The Last Word
in Sodium and Water
Excretion and Blood Pressure
Regulation”
SUNDAY, APRIL 21, 3:15 PM

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

Roger A. Dampney
Univ. of Sydney

“Central Mechanisms
Regulating Co-ordinated
Cardiovascular and
Respiratory Function in
Stress and Arousal”
MONDAY, APRIL 22, 8:00 AM

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

Ellis R. Levin
Univ. of California, Irvine

“Extra-nuclear Estrogen
Receptors: Functions for
Physiology and Patho-
Physiology”
MONDAY, APRIL 22, 10:30 AM

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

Douglas R. Seals
Univ. of Colorado

“The Remarkable Anti-aging
Effects of Aerobic Exercise on
Arteries”
MONDAY, APRIL 22, 2:00 PM
The Physiologist
Vol. 55, No. 6, 2012

ROBERT M. BERNE
DISTINGUISHED LECTURESHIP
OF THE APS CARDIOVASCULAR
SECTION
David J. Lefer
Emory Univ. Sch. of Med.
“A Long and Winding Road:
The Story of Nitric Oxide in
the Heart”
TUESDAY, APRIL 23, 2:00 PM

JULIUS H. COMROE, JR.
DISTINGUISHED LECTURESHIP
OF THE APS RESPIRATION
SECTION
Aron Fisher
Univ. of Pennsylvania Sch. of Med.
“The Serpentine Path to a Novel Mechanism Based Inhibitor of Acute Inflammatory Lung Injury”
TUESDAY, APRIL 23, 10:30 AM

HORACE W. DAVENPORT
DISTINGUISHED LECTURESHIP
OF THE APS GASTROINTESTINAL & LIVER SECTION
Ole H. Petersen
Cardiff Univ.
“Calcium Signal Mechanisms in Epithelial Cells: Roles in Physiology and Pathology”
TUESDAY, APRIL 23, 3:15 PM

APS PRESIDENT’S SYMPOSIA
NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE LECTURE

Linda Buck
Fred Hutchinson Cancer Res. Ctr.
“Unraveling Smell”
WEDNESDAY, APRIL 24, 4:45 PM
APS/NIDDK Minority Travel Fellows Attend the 2012 APS Conferences

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

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

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

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

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

<table>
<thead>
<tr>
<th>Travel Fellow</th>
<th>Meeting Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronee Harvey</td>
<td>Thomas Lohmeier</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Univ. of Mississippi Med. Ctr.</td>
</tr>
<tr>
<td>Vanitra Richardson</td>
<td>John Horn</td>
</tr>
<tr>
<td>Univ. of Arizona</td>
<td>Univ. of Pittsburgh</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Fellow</th>
<th>Meeting Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicholas Aguirre</td>
<td>Troy Hornberger</td>
</tr>
<tr>
<td>Univ. of California, Davis</td>
<td>Univ. of Wisconsin, Madison</td>
</tr>
<tr>
<td>Olubusayo Awe</td>
<td>Greg Cartee</td>
</tr>
<tr>
<td>Morehouse College</td>
<td>Univ. of Michigan</td>
</tr>
<tr>
<td>Zachary Graham</td>
<td>Keith Baar</td>
</tr>
<tr>
<td>Univ. of Kansas</td>
<td>Univ. of California, Davis</td>
</tr>
<tr>
<td>Ana Valencia</td>
<td>Bill Schrage</td>
</tr>
<tr>
<td>Univ. of Maryland</td>
<td>Univ. of Wisconsin</td>
</tr>
</tbody>
</table>

Vanitra Richardson, Travel Fellow, and Irving Zucker at the AUTO Conference.
Below is a listing of undergraduate summer research fellowships offered by the American Physiological Society. Note that fellowships that specifically target underrepresented students are marked with an asterisk (*). All APS fellowships encourage applications from women and minority trainees.

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

**Undergraduate Summer Research Fellowships**
*Available to: Undergraduate students*
These fellowships support full-time 1st- through 3rd-year undergraduate students with minimal research experience to work 10 weeks in the laboratory of an established APS investigator and to attend the following year's Experimental Biology meeting. The program is open to any undergraduate worldwide. Fellows receive $4,000 stipend and up to $1,300 in reimbursement for EB travel; hosts receive $300 unrestricted grant.
*Application deadline: February 2*
the-aps.org/ugsr

**NEW! Undergraduate Research Excellence Fellowships**
*Available to: Undergraduate students*
These fellowships support full-time 2nd- through 4th-year undergraduate students with significant research experience to work for 10 weeks in the laboratory of an established APS investigator and to attend the following year's Experimental Biology meeting. The program is open to any undergraduate worldwide. Fellows receive $4,000 stipend and up to $1,300 in reimbursement for EB travel; hosts receive $300 unrestricted grant.
*Application deadline: February 2*
the-aps.org/ugref

**APS STEP-UP Fellowships for Underrepresented Undergraduate Students***
*Available to: Undergraduate students*
These fellowships support full-time undergraduate U.S. students from groups traditionally underrepresented in biomedicine (e.g., from disadvantaged backgrounds and certain racial and ethnic groups and individuals with disabilities) to work for 8-12 weeks in the laboratory of an established APS investigator working in an National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) related area. Students will also attend a STEP-UP symposium at the end of the summer with other STEP-UP fellows from across the U.S. Fellows receive $3,500 stipend and reimbursement for travel to the STEP-UP meeting.
*Application deadline: February 22*
the-aps.org/stepup

**NEW! APS STRIDE Fellowships for Underrepresented Undergraduate Students***
*Available to: Undergraduate students*
The APS STRIDE fellowship provides hands-on summer research experience for underrepresented undergraduate students interested in exploring biomedical research careers. The program provides exposure to the core National Heart, Lung, and Blood Institute (NHLBI) mission areas of cardiovascular, pulmonary, hematologic, and sleep disorders research. Fellows receive $4,000 stipend and up to $1,200 in reimbursement for EB travel; hosts receive $500 unrestricted grant. Accommodations are available for students with disabilities.
*Application deadline: February 2*
the-aps.org/stride

**NEW! APS IOSP Fellowships for Underrepresented Undergraduate Students***
*Available to: Undergraduate students*
The APS Integrative Organismal Systems Physiology (IOSP) fellowship provides hands-on summer research experience for undergraduate underrepresented students interested in exploring comparative and evolutionary biology research careers. The program provides exposure to IOS mission areas of comparative and evolutionary research. Fellows receive $4,000 stipend, $1,050 subsistence, and up to $750 in reimbursement for EB travel; hosts receive $500 unrestricted grant. Accommodations are available for students with disabilities.
*Application deadline: February 2*
the-aps.org/iosp
How to Believe in Others (and Other Musings on Mentoring)

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

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

As for most people, my approach to and passion for mentoring have been immensely shaped by my own positive experiences with a series of talented mentors. I was a very shy child and teenager, but my teachers—and especially Valerie Tickner, Elsa Cameron, Ann Parkin and Gill Ellis—had great confidence in me and supported my development as a fledgling scientist. They provided me with the confidence to consider university, which was a path for only a small minority in 1970’s England and an unknown world to my parents, neither of whom even finished high school in wartime London. In particular, my high school chemistry teachers, Ann and Gill, alerted me to opportunities to explore different colleges such as a two day introductory course at the one I finally selected, Univ. College London. It was at this event that I met my next influential mentor, Fred Pearce, at that time a young faculty member in the Department of Chemistry. My group was assigned to work with him on a lab exercise and I was very impressed (and a little star-struck) by his ability to ask the sorts of questions about our results that allowed us to build our own understanding. I was horrified, therefore, at the last social gathering of the course, to spill an entire cup of steaming tea down his front. I was truly mortified, and even more so when I arrived for an interview for a place at UCL about a year later and realized to my utmost dismay that Fred would be my interviewer. However, he betrayed no evidence that he remembered the tea debacle, and set about putting me at ease and recruiting me to the school. He later became my PhD supervisor, and remains to this day a trusted advisor, all-round supporter, and friend.

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

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Dr. Kim Barrett, a native of the United Kingdom, obtained her B.Sc. and Ph.D. degrees from the Department of Chemistry at University College London. Following a post-doctoral fellowship at the National Institutes of Health, she joined the faculty of UCSD School of Medicine in 1985, and rose to her current rank of Professor of Medicine in 1996. Her research interests center on the normal and abnormal biology of the intestinal epithelium and their relevance to a variety of digestive diseases including inflammatory bowel diseases, infectious diarrheal diseases, and peptic ulcer disease. She has received a number of honors for her research, including the Bouditch and Davenport Lectureships of the American Physiological Society, the McKenna Lectureship of the Canadian Association of Gastroenterology, and the degree of Doctor of Medical Science, honoris causa, from Queens University Belfast. She is the author or editor of several books and monographs, including Gastrointestinal Physiology (McGraw-Hill, 2006) and more than 200 peer-reviewed journal articles, book chapters and reviews. She has also been highly active in professional societies and in scholarly editing. She is President-Elect of the American Physiological Society and will begin a one-year term as President in 2013. She was Chair of the APS Publications Committee for six years, which involved oversight of the Society’s 14 journals and adjudication of all ethical issues arising in the journals. She is also the past Editor-in-Chief of American Journal of Physiology-Cell Physiology and the current Deputy Editor-in-Chief for the Americas of Journal of Physiology, among other editorial assignments.
chosen field. However, it is important to remember that your mentor does not need necessarily to have shared your life experiences to be effective—they just have to display a willingness to understand them. I have also received great sustenance from a group of women peers—we all supported each other as we navigated the early hurdles of grants, tenure, papers and the inevitable rejections together.

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

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

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

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

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

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

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

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

Science Policy

Stand Up for Animal Research with the Science Action Network

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

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

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

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

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

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

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

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

APS Members Elected to the Institute of Medicine

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

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

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

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

Positions Available

**Physiologist Position**

**Vertebrate Physiologist:** Georgia Southern University’s Department of Biology Vertebrate Physiology Position Search #67064 invites applications for a vertebrate physiologist position. The full text advertisement, including information about the department, faculty, and the complete position announcement with all qualifications and application instructions, is available at www.bio.georgiasouthern.edu. The position requires teaching, service, and research responsibilities as well as a terminal degree. We seek a vertebrate physiologist with broad training in physiology and anatomy. The successful candidate’s research will address questions in organismal physiology using approaches that integrate multiple levels of organization. The successful applicant will teach undergraduate and graduate courses, including Comparative Animal Physiology. Ability to teach Comparative Vertebrate Anatomy is preferred. Required qualifications: PhD by December 31, 2012; demonstrated excellence in research; potential to attract extramural funding; expertise to teach Comparative Animal Physiology. Preferred Qualifications: postdoctoral experience; expertise to teach Comparative Vertebrate Anatomy. Screening of applications begins November 5, 2012 and continues until the position is filled. The preferred position starting date is August 1, 2013. A complete application consists of a cover letter addressing the qualifications cited above; a curriculum vitae; statements of research interests and teaching interests/philosophy; three letters of reference. Applications must be sent electronically as a single PDF attachment (include applicant name in file name); letters of recommendation in PDF format may be sent separately via email. Other documentation may be requested. Only complete and electronically submitted applications will be considered. Finalists will be required to submit to a background investigation. Georgia is an open records state. Georgia Southern is an AA/EO institution. Individuals who need reasonable accommodations under the ADA to participate in the search process should
and/or MD degree, a strong record of academic achievement, a solid level of extramural research funding and experience in both graduate student and medical student education. Interested candidates should submit a cover letter, curriculum vitae and a description of their leadership vision to http://jobs.slu.edu (Req. ID# 20120062). Letters of nomination may be sent by email to Enrico Di Cera, Chair of the Search Committee (enrico@slu.edu). Saint Louis University is an Affirmative Action, Equal Opportunity Employer, and encourages nominations and applications of women and minorities.

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

Michigan Technological University is an Equal Opportunity Educational Institution/Equal Opportunity Employer.

Positions Available

Faculty Positions

Department Chair, Pharmacological and Physiological Science: Saint Louis University, a Catholic Jesuit institution dedicated to education, research, service and health care, has started a national search for the next William Beaumont Professor and Chair of the Department of Pharmacological and Physiological Science (http://medschool.slu.edu/pharmphys). The department encompasses multidisciplinary research in the cardiovascular, endocrine and neuroscience areas and has an outstanding record in graduate education supported in part by an NIH-T32 training grant currently in its 22nd year. The department seeks an individual with the vision and leadership to build and maintain robust basic and translational research programs, and continue the strong commitment to graduate and medical education. The successful applicant will have a PhD in our laboratories. Many of these individuals have made major contributions to their fields. It was a most gratifying important thing that a faculty member can do. We recently had a reunion at Asilomar, CA attended by 60 neuroscientists, most of whom received training in our laboratories. Many of these individuals have made major contributions to their fields. It was a most gratifying experience for me as it was also a celebration of my 80th birthday.”

Letters to Terry Dwyer

Craig Hassler writes: “Sorry for the tremendous delay in my response. "As with most young people, I headed off for college without any idea what I was going to do with my working life. I started off to be an engineer as was the tradition in my family. However this was not to be and I ended up as a physiologist. "Following a marvelous stay in the laboratories of Walter Randall (at Loyola-Chicago), for my doctoral work, it was time to find a job. I was recruited by the Battelle Memorial Institute (a large non-profit contract research laboratory. Battelle had won several large government projects relevant the development of an artificial heart. They needed a cardiovascular physiologist and I needed a job which has now extended for 42 years. "Cardiovascular physiology has been the common thread throughout my career. And physiologic measures have become more integral part of the drug discovery and safety evaluation processes, an area in which Battelle is extensively involved. In addition, I have enjoyed being involved in a wide range of projects not directly related to cardiovascular physiology. "I have had the pleasure to see cardiovascular physiology grow from smoke kymographs with manual calculation of parameters to the common usage of sophisticated instrumentation such as implantable telemetric devices, automated data collection systems and imaging."

David A. Prince writes: “Thank for your letter of August 13th inquiring about my current activities. I am still an active investigator with support from the NIH. There are four postdoctoral fellows in my lab at the moment and we have continued to do work related to the pathophysiology of epilepsy in animal models. My lab and office are at Stanford Medical Center and we have had a number of interesting recent publications related to mechanisms of cortical synaptic and other activities following traumatic brain injury in a rat model. “All in all, my academic career in neuroscience has been a gratifying one, particularly in relation to the outstanding group of trainees who have come to the laboratory. This is, after all, the most important thing that a faculty member can do. We recently had a reunion at Asilomar, CA attended by 60 neuroscientists, most of whom received training in our laboratories. Many of these individuals have made major contributions to their fields. It was a most gratifying experience for me as it was also a celebration of my 80th birthday.”
Hi all:
Between travel and work, opportunities for tasting have become less and less, so I cannot offer you a report of the usual quality you have come to expect. For this I apologize. While I expect to compensate in November when Harrieth and I will be taking a couple of weeks “off” in Barossa and McLaren Vale (South Australia), I am not sure I can provide a useful column in November since the wines we will see in Oz are likely not available in the USA, plus with the equality between USA and AUS dollars, they will have outgrown my budget anyway. But I will try. Just don’t hold your breath. Not worth it.

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

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

Red wines
2010 Seghesio Zinfandel, Sonoma county, CA $19. While their “lowest tier” zin, it is just as good this year as in past years, and a bit better than the 2009 which I recommended October 2011. It has a young, fresh and forward grapey/raspberry nose, with a touch of oak char. It has excellent red cherry and raspberry fruit, with soft tannin and good acidity. There is no sweetness, but a nice touch of dry herbs. It is very clean, balanced and has good length. It is not extracted, tannic, overdone or sweet. Just nice and tasty.

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

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

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

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

2009 Point Concepcion Pinot Noir, “Salsipuedes,” Santa Barbara, CA $16. This is a big wine, 14.7% alcohol, with a nose of cherry, vanilla and anise. The palate is very forward and rich with dark cherry and plum, spice, modest oak, good acid, light tannin, and a bit of heat at the finish. Enjoy! It may all you get from me until December.
2013

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

Information: Shirley Dinenson, Conference Secretary, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland. Tel.: +41 22 5330 948; Fax: +41 22 5802 953; Email: sdinenson@paragon-conventions.com; Internet: http://www.ocularinfections.com/.

March 10-13

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

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

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

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

June 30 to July 3, 2013

July 15-19

July 21-26

September 6-9

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CALL FOR NOMINATIONS

For the Arthur C. Guyton Educator of the Year Award

The Arthur C. Guyton Educator of the Year Award supported by Elsevier ($1,000 cash prize, plus reimbursement of the advanced registration fee, a framed, inscribed certificate, up to $750 in travel reimbursement to the Experimental Biology meeting and a complimentary ticket to the Section Dinner) recognizes a full-time faculty member of an accredited college or university and member of the APS who has independent evidence of: (1) excellence in classroom teaching over a number of years at the undergraduate, graduate, or professional levels; (2) commitment to the improvement of physiology teaching within the candidate’s own institution; and (3) contributions to physiology education at the local community, national or international levels. The awardee is requested to write an essay on his/her philosophy of education for publication in The Physiologist.

The typical nominee will have shown excellence in teaching and have made significant contributions in student advisement, graduate education, and/or curriculum design and reform at their institution. The activities that distinguish a candidate in the rankings include outreach activities at the state, national, or international level; contributions to education through APS activities; peer-reviewed educational journal articles; and widely disseminated publications such as commercially produced textbooks, lab manuals, or software. The award winner is announced at the APS Business Meeting during Experimental Biology.

Nominations Process: Each nominee must be nominated by a member of APS. All candidate materials must be uploaded no later than January 8, 2013. To upload documents, please visit the APS Award Module at the-aps.org/awardapps/login/index.cfm. Finalists will be contacted and asked to provide further information.
2012 American Physiological Society Conference

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

MEETING PROGRAM AND ABSTRACTS

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

APS Council

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Univ. of Nebraska Med. Ctr.   Univ. of Nebraska Med. Ctr.
Michael J. Joyner   Harold D. Schultz
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Acknowledgements

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

Richard Holland
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C-2
## 2012 APS Conference:
**Autonomic Regulation of Cardiovascular Function in Health and Disease**
**July 7—10, 2012**
**Omaha, Nebraska**

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<tr>
<td>3:00 PM Registration Opens</td>
<td>7:00—9:00 AM Breakfast</td>
<td>7:00—9:00 AM Breakfast</td>
<td>7:00—9:00 AM Breakfast</td>
</tr>
<tr>
<td>7:00—10:00 PM Opening and Welcome Reception</td>
<td>9:00—10:00 AM Plenary Lecture I: Advances in the Central Renin-angiotensin System C. Sigmund, Univ. of Iowa</td>
<td>9:00—10:00 AM Plenary Lecture II: Neuromodulatory Pathways and Central Control of Sympathetic Activity in Hypertension and Heart Failure F. Leenen, Univ. of Ottawa, Canada</td>
<td>9:00—10:00 AM Plenary Lecture III: Muscle Sympathetic Reflexes in Humans L. Sinoway, Pennsylvania State Univ.</td>
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<tr>
<td>10:00 AM—12:00 Noon Symposium I: Angiotensin Converting Enzyme 2 and ANG (1-7): Roles in Central Hypertension Participants: I. Zucker, (Chair), Univ. of Nebraska Med. Ctr. L. Gao, (Chair), Univ. of Nebraska Med. Ctr. D. Diz, Wake Forest Univ. E. Lazartigues, Louisiana State Univ. Hlth. Sci. Ctr.</td>
<td>10:00 AM—12:00 Noon Symposium IV: Sympatho-excitatory Mechanisms in Cardiovascular Disease Participants: N. Sharma (Chair), Univ. of Nebraska Med. Ctr. H. Zheng, (Chair), Univ. of Nebraska Med. Ctr. M. Esler, Univ. of Melbourne, Australia J. Francis, Louisiana State Univ. Coll. of Vet. Med.</td>
<td>12:00 Noon—2:30 PM Lunch and Poster Presentations</td>
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<tr>
<td>4:00—4:15 PM Coffee Break</td>
<td>4:15—6:00 PM Symposium III: Mechanisms of Baro and Chemoreceptor Sensory Transduction: A Link to Sympatho-excitation in Disease Participants: R. Del Rio, (Chair), Univ. of Nebraska Med. Ctr. N. Marcus, (Chair), Univ. of Nebraska Med. Ctr. F. Abboud, Univ. of Iowa N. Prabhakar, Univ. of Chicago</td>
<td>4:30—4:45 PM Coffee Break</td>
<td>4:45—5:45 PM Career Session: The Ins and Outs of Authorship Presented by: I. Zucker, Univ. of Nebraska Med. Ctr. M. Frank, American Physiological Society</td>
</tr>
<tr>
<td>4:15—6:00 PM Mechanisms of Baro and Chemoreceptor Sensory Transduction: A Link to Sympatho-excitation in Disease Participants: R. Del Rio, (Chair), Univ. of Nebraska Med. Ctr. N. Marcus, (Chair), Univ. of Nebraska Med. Ctr. F. Abboud, Univ. of Iowa N. Prabhakar, Univ. of Chicago</td>
<td>Symposium VI: The Gladiator Session Participants: I. Zucker, (Chair), M. Chapleau, (Chair), Univ. of Iowa Coll. of Med.</td>
<td>7:00—10:00 PM Dinner and Awards Presentation</td>
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Location:
The 2012 APS Conference: Autonomic Regulation of Cardiovascular Function in Health and Disease will be held July 7—10, 2012 at the Hilton Omaha hotel located at: 1001 Cass Street, Omaha, NE 68102, telephone (402) 998-3400, FAX: (402) 998-4242.

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

On-Site Registration Fees:
APs Member………………………………………… $600
Retired Member……………………………………… $400
Nonmember………………………………………….. $700
Postdoctoral……………………………………… $450
Student…………………………………………………… $400

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

Payment Information:
Registrants may pay by institutional or personal check, traveler’s check, MasterCard, VISA or American Express. Checks must be payable to “The American Physiological Society” and drawn on a United States bank payable in US dollars.

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

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

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

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

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

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

Target Audience:
The intended audience for this conference includes all levels of researchers working in the field of autonomic regulation.
Plenary Lecture

1.0  **PLENARY LECTURE I**
Sun., 9:00 - 10:00 AM, Blackstone B.
Chair:  **Irving Zucker, Univ. of Nebraska Med. Ctr.**

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

Symposia I

2.0  **ANGIOTENSIN CONVERTING ENZYME 2 AND ANG (1-7): ROLES IN CENTRAL HYPERTENSION**
Sun., 10:00 AM - 12:00 Noon, Blackstone B.
Chairs:  **Irving Zucker, Univ. of Nebraska Med. Ctr.**  **Lie Gao, Univ. of Nebraska Med. Ctr.**

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

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

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

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

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

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

Poster Session

3.0  **POSTER SESSION I**
Sun., 12:00 Noon - 2:00 PM, Blackstone A.

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

2  3.2 Caudal Ventrolateral Medulla Activation by Acute Hypoxia is Independent of Changes in Arterial Blood Pressure.  **L. Gao, J. Chao, J. Gao, and K-J. Parbhlu, Univ. of Nebraska Med. Ctr.**

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

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

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

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

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


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

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

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

12  3.12 Activation of Nuclear Factor-kappa B Lowers Protein Expression of Voltage-gated Sodium Channels in Nodose Neurons from Heart Failure Rats.  **H. Tu, J.
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<th>Board #</th>
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<tr>
<td>14</td>
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<td>L. Xiao, and I. Zucker. Univ. of Nebraska Med. Ctr.</td>
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<td>19</td>
<td>Severe Hypertension is Unmasked in Methionine Sulfoxide Reductase-A Deficient Mice by Controlling for Differences in Locomotor Activity.</td>
<td>R. Sabharwal, F. M. Abboud, and M. W. Chapleau. Univ. of Iowa.</td>
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<td>20</td>
<td>Expression of ROS Catabolic Enzymes in the Medial Nucleus Tractus Solitarii of Rats and Up-regulation During Acute Hypoxia.</td>
<td>T. Ostrowski, S. Barr, H. Dantzler, E. Hasser, D. Kline, and C. Hesech. Univ. of Missouri.</td>
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<td>21</td>
<td>Withdrawn.</td>
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**Symposia II**

**4.0 OXIDATIVE STRESS AND SYMPATHETIC REGULATION**

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

- **2:30 PM 4.2** Nanoformulated Antioxidants: Delivery to Central Neurons and Modulation of Angiotensin II Intra-neuronal Signaling. Matthew Zimmerman. Univ. of Nebraska Med. Ctr.
- **3:00 PM 4.3** ER Stress in RVLM Mediates Neurogenic Hypertension through Activation of PI3K/Akt Pathway. Yung-Mei Chao. Natl. Cheng Kung Univ., Tainan, Taiwan. (3.18).
- **3:15 PM 4.4** Severe Hypertension is Unmasked in Methionine Sulfoxide Reductase-A Deficient Mice by Controlling for Differences in Locomotor Activity. Rasna Sabharwal. Univ. of Iowa. (3.19).
- **3:30 PM 4.5** Expression of ROS Catabolic Enzymes in the Medial Nucleus Tractus Solitarii of Rats and Up-regulation During Acute Hypoxia. Tim Ostrowski. Univ. of Missouri. (3.20).

**Symposia III**

**5.0 MECHANISMS OF BARO AND CHEMORECEPTORS**

**SENSORY TRANSDUCTION: A**
**DAILY SCHEDULE**

**LINK TO SYMPATHO-EXCITATION IN DISEASE**
Sun., 4:15 - 6:15 PM, Blackstone B.

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

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

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

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

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

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

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

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**MONDAY, JULY 9, 2012**

**Plenary Lecture**

**6.0**

**PLENARY LECTURE II**
Mon., 9:00 - 10:00 AM, Blackstone B.

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

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

**Symposia IV**

**7.0**

**SYMPATHO-EXCITATORY MECHANISMS IN CARDIOVASCULAR DISEASE**
Mon., 10:00 AM - 12:00 Noon, Blackstone B.

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

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

10:30 AM  **7.2** Role of Inflammatory Cells in the Progression of Cardiovascular Disease.
<table>
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<th>Institution</th>
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<tr>
<td>34</td>
<td>8.9 Rho Kinase Inhibition Lowers Sympathetic Nerve Activity and Restores Baroreflex in Conscious Rats with Chronic Heart Failure.</td>
<td>K. Haack, L. Gao, P. Curry, and I. Zucker.</td>
<td>Univ. of Nebraska Med. Ctr.</td>
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<td>8.11 Withdrawn.</td>
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<td>40</td>
<td>8.15 Baroreflex Control of Leg Vascular Conductance During Simulated Carotid Hypertension in Young and Older Women.</td>
<td>D. Credeur, L. Vianna, and P. Fadel.</td>
<td>Univ. of Missouri.</td>
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<td>42</td>
<td>8.17 Nocturnal Hypoxemia Induced by Obstructive Sleep Apnea Determines</td>
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<td>44</td>
<td>8.19 Withdrawn.</td>
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**Symposia V**

**SYMPATHETIC MECHANISMS IN HUMAN HYPERTENSION**

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

**2:30 PM**

9.1 Impaired Autonomic Regulation of Blood Pressure and Hypertension. Italo Biaggioni, Vanderbilt Univ.

**3:00 PM**


**3:30 PM**

9.3 Paradoxical Elevations in Angiotensin II, Independent of Plasma Renin, Contribute to the Supine Hypertension of Primary Autonomic Failure. Amy Arnold, Vanderbilt Univ. (8.5).

**3:45 PM**

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

**4:00 PM**


THE GLADIATOR SESSION
Mon., 4:45 - 6:00 PM, Blackstone B.
Chairs: Mark Chapleau, Univ. of Iowa Coll. of Med. Irving Zucker, Univ. of Nebraska Med. Ctr.

NITRIC OXIDE AND SYMPATHOVAGAL REGULATION
Tues., 10:00 AM - 12:00 Noon., Blackstone B.
Chair: Yu-Long Li, Univ. of Nebraska Med. Ctr.

DAILY SCHEDULE

Board #


Symposia VIII
14.0 DEVICE THERAPY FOR HYPERTENSION AND HEART FAILURE
Tues., 2:30 - 4:30 PM, Blackstone B.

Chairs:
Italo Biaggioni, Vanderbilt Univ.

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

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


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


Career Session
15.0 THE INS AND OUTS OF AUTHORSHIP
Tues., 4:45 - 5:45 PM, Blackstone B.

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

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

Richard Holland
University of Nebraska Medical Center
Medtronic Cardiac & Vascular Group
American Autonomic Society
AD Instruments
Quartzy
NIH, National Institutes of Diabetes And Digestive Kidney Diseases
Data Science International
Biocontrol Medical
Abstracts of Invited and Contributed Presentations

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2.0 Angiotensin Converting Enzyme 2 and ANG (1-7): Roles in Central Hypertension..C-12
3.0 Poster Session I........................................................................................................C-12
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9.0 Sympathetic Mechanisms in Human Hypertension........................................................C-21
11.0 Plenary Lecture III......................................................................................................C-21
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13.0 Poster Session III.......................................................................................................C-22
14.0 Device Therapy for Hypertension and Heart Failure....................................................C-24

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1.0: PLENARY LECTURE I

1.1 ADVANCES IN THE CENTRAL RENIN-ANGIOTENSIN SYSTEM

Curt Sigmund*

Pharmacology, Univ. of Iowa, 2-434 BSB, Iowa City, IA, 52242.

The renin-angiotensin system (RAS) in the brain is well recognized as an important controller of cardiovascular (CV) function through its effects on blood pressure (BP), fluid intake, and sympathetic outflow, and has been implicated in hypertension. Growing evidence advancing the concept that the RAS, both in the brain and periphery, is also a controller of energy expenditure. We have obtained compelling data indicating that activation of the brain RAS, while simultaneously decreasing circulating RAS, results in increased energy expenditure. These data advance the novel concept that the central and peripheral RAS may differentially control energy balance. Moreover, our most recent data suggest a novel role for adipose AT1R as a modulator of the actions of the brain RAS on adipose tissue and its resulting effect on energy expenditure. Activation of adipose AT1R blunts energy expenditure induced in response to elevated brain RAS activity. Activation of the brain RAS also increases BP and fluid intake through effector mechanisms distinct from those controlling energy expenditure. This plenary lecture will review the central pathways regulating ANGIlll synthesis, the role of renin in the brain, the contrasting mechanisms regulating cardiovascular and metabolic output of the brain RAS, and the interaction between the RAS in the brain and adipose tissue and its effects on energy balance. This work was funded by grants from the NIH, AHA, and the Roy J Carver Trust.

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

Debra Dju†


Altered angiotensinogen (ANG) II and Ang-(1-7) in dorsal medullary nuclei favor activation of the sympathetic vs. parasympathetic systems, respectively, reveals divergent actions of the peptides on resting mean arterial pressure (MAP), baroreflex sensitivity for control of heart rate (BRS) and indices of metabolic function. Our studies further identify different anatomical, neurotransmitter and signaling pathways involved as potential mechanisms for the distinct actions of the peptides. Examples illustrating these concepts will be drawn from models of aging, as well as acute and chronic elevations of MAP in stress, fetal-programming and genetic conditions.

2.1 BRAIN ANGIOTENSIN PEPTIDES AND CONTROL OF BLOOD PRESSURE

Eric Lazartigues


ACE2 appears to be the main pivotal enzyme that can stimulate the ACE2/Ang-(1-7)/mas receptor axis. Although several enzymes are involved in these modulatory effects, changes in different levels of local transmitters known to be involved in BRS, will be highlighted using data from transgenic animals. The functional interactions between angiotensin II and Ang-(1-7) in dorsal medullary nuclei favor activation of the sympathetic vs. parasympathetic systems, respectively, reveals divergent actions of the peptides on resting mean arterial pressure (MAP), baroreflex sensitivity for control of heart rate (BRS) and indices of metabolic function. Our studies further identify different anatomical, neurotransmitter and signaling pathways involved as potential mechanisms for the distinct actions of the peptides. Examples illustrating these concepts will be drawn from models of aging, as well as acute and chronic elevations of MAP in stress, fetal-programming and genetic conditions.

2.2 ACE2 REGULATION IN HYPERTENSION

Luis A. Alikunju†, Matthew Zimmerman‡

Veterinary Biomedical Sci., Uni. of Missouri, 134 Research Park Dr., Rm 352 Dalton Cardiovascular Res. Ctr., Columbia, MO, 65211.

We performed experiments using transgenic and wild-type rats with known ACE2 expression to evaluate the function of the AT2R in the intermediolateral cell column (IML) of the thoracic spinal cord in normal rats. We hypothesized that AT2R in the IML would exert a sympatho-inhibitory effect. We found that: (1) AT1R and AT2R are expressed in the spinal cord, with higher levels in grey matter compared with white matter. (2) Microinjection of Ang II into the IML dose-dependently increased blood pressure (MAP) and sympathetic nerve activity (RSA), which was completely abolished by Losartan, and attenuated by TEMPOL and apocynin; (3) activation of AT2R in the IML with CGP42112 evoked hypotension (MAP: -21 ± 4 mmHg) and sympatho-inhibition (RSA: 73 ± 3 % of baseline), which were completely abolished by PD123319 and L-NNAME (4 blockade of AT2R in the IML with PD123319 significantly increased MAP (11 ± 1 mmHg) and sympathetic nerve activity (RSA: 133 ± 13 % of baseline). Moreover, PD123319 significantly enhanced the AngII induced pressor response. (4) Employing whole-cell patch clamp, we further found that CGP42112 treatment augmented potassium current and decreased resting membrane potential in isolated IML neurons. In conclusion, these results suggest that, in the normal condition, AT2R in the IML tonically inhibits sympathetic activity by an NO/NO2-dependent pathway inducing activation of potassium channel.

2.3 CAUDAL VENTROLATERAL MEDulla (CVM) ACTIVATION BY ACUTE HYPOXIA (AH) IS INDEPENDENT OF CHANGES IN ARTERIAL BLOOD PRESSURE (ABP)

Urmil Basu*, Saleena Alikunju†, Matthew Zimmerman‡

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We hypothesized that activation of CVM cells was similar in both AH and NOAH conditions (AH: 59+11 vs AH+PE: 59+13). Data suggest that decreased ABP during hypoxia do not contribute substantially to CVM neuronal activation due to chemoreflex stimulation.

3.0: POSTER SESSION I

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

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We previously demonstrated that AT2R in the brainstem participated in the regulation of sympathetic outflow and cardiovascular function. In the present study, we evaluated the function of the AT2R in the intermediolateral cell column (IML) of the thoracic spinal cord in normotensives. We hypothesized that AT2R in the IML would exert a sympatho-inhibitory effect. We found that: (1) AT1R and AT2R are expressed in the spinal cord, with higher levels in grey matter compared with white matter. (2) Microinjection of Ang II into the IML dose-dependently increased blood pressure (MAP) and sympathetic nerve activity (RSA), which was completely abolished by Losartan, and attenuated by TEMPOL and apocynin; (3) activation of AT2R in the IML with CGP42112 evoked hypotension (MAP: -21 ± 4 mmHg) and sympatho-inhibition (RSA: 73 ± 3 % of baseline), which were completely abolished by PD123319 and L-NNAME (4 blockade of AT2R in the IML with PD123319 significantly increased MAP (11 ± 1 mmHg) and sympathetic nerve activity (RSA: 133 ± 13 % of baseline). Moreover, PD123319 significantly enhanced the AngII induced pressor response. (4) Employing whole-cell patch clamp, we further found that CGP42112 treatment augmented potassium current and decreased resting membrane potential in isolated IML neurons. In conclusion, these results suggest that, in the normal condition, AT2R in the IML tonically inhibits sympathetic activity by an NO/NO2-dependent pathway inducing activation of potassium channel.

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

C. Hasser

Dalton Cardiovascular Res. Ctr., Columbia, MO, 65211.

We tested the hypothesis that AngII stimulation of central neurons influences the levels of potassium channel, and that potassium channel activity in central neurons remains unclear. Here, we tested the hypothesis that AngII stimulation of central neurons influences the levels of potassium channel.

have weaknesses. Therefore, new schemes are necessary that would ideally prevent both reduction of ACE2 expression and activity. Here, we will: 1) review the current state of knowledge regarding ACE2 dysregulation in hypertension, 2) highlight the advantages and inconveniences of the various strategies to restore ACE2 compensatory effects and 3) present some new data on novel approaches to restore a functioning compensatory ACE2/Ang-(1-7)/mas receptor axis (NIH R01 HL093178, P20 GM103514 & AHA EIA0300004).Xu, P., Srimanula, M., Lazartigues E. 2011. Am J PhysiolRegulIntegr Comp Physiol. 300(4):R804-17.
and activity of redox-sensitive proteins including calcium/calmodulin kinase II (CaMKII) and protein phosphatase 2A (PP2A). Mouse CATH. aneurysms were treated with AngII(100nM; 5 min - 24 hr) and activity of CaMKII was assayed by detecting its phosphorylated levels; while PP2A activity was determined using a specific phosphatase activity assay. AngII significantly increased phosphorylated CaMKII levels from 2 to 24 hr (3.17 and 3.19-fold increase vs. vehicle, P<0.05) of stimulation. In contrast, AngII modestly decreased PP2A protein levels from 30 min to 24 hr of stimulation. PP2A activity decreased within 5 min of AngII stimulation to 1 hr (148 pM phosphate released after 5 min and 134 pM at 1 hr vs 486 pM in vehicle-treated neurons). These data indicate that in neurons AngII inhibits PP2A activity while activating CaMKII. Future studies will investigate the role of ROS in mediating these AngII-induced changes in PP2A and CaMKII activity.

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

Xuming Sun,1 Ellen Tomassi2, Remu Sahi3, Debra Digs4, Snezana Petrovic5

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The proton receptor GPR4, a G protein-coupled receptor that accepts protons as ligands, is activated in physiological pH range. We hypothesized that pH sensitivity of GPR4 could play a profound role in cardiorespiratory reflexes. Support: RO1 HL098602.

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

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Since hypoxia is an important stimulus for human pulmonary artery smooth muscle cell (HPASMC) proliferation and PAH, we performed mRNA microarray assays in HPASMC. We found that hypoxia is a potent inducer of miRNA-210 in HPASMC. Induction of miR-210 was also observed in whole lungs of mice with chronic hypoxia-induced PAH. We found that transcriptional induction of miR-210 in HPASMC is HIF-1α-dependent. Inhibition of miR-210 in HPASMC caused a significant decrease in cell proliferation due to increased apoptosis. We found that miR-210 appears to mediate its anti-apoptotic effects via the regulation of transcription factor E2F3, a direct target of miR-210. Our results have identified miR-210 as a hypoxia-inducible miRNA both in vitro and in vivo, which inhibits pulmonary vascular smooth muscle cell apoptosis in hypoxia by specifically repressing E2F3 expression.

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

Rodrigo Del Rio, Noah Marcus, Harold Schultz,1

1Coll. of Life Sciences, Shenzhen Univ., Nanhai Rd. 3688, Shenzhen, 518060, China, People's Rep. of.
low-frequency HRV and BPV concomitant with a significant increase in the high-frequency HRV (32.7±2.3 vs. 51.2±13.1 au). Moreover, the reduced BPGin CHF rats was partially reversed after CBD (P<0.05). Our results show that CBD significantly improves breathing stability and autonomic function in CHF-rats. Supported by NIH PO1-HL62222.

3.10 NONCLASSICAL G PROTEIN COUPLED RECEPTOR KINASE 5 REGULATION OF ANGIOTENSIN II TYPE 1 RECEPTOR IN CATHA NEURONS
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Cellular and Integrative Physiology, Univ. of Nebraska Med. Ctr., 985850 Nebraska Med. Ctr., Omaha, NE, 68198.

The Angiotensin II type 1 Receptor (AT1R) plays a pivotal role in the development of heart failure, and as such is upregulated in a number of tissues. AT1R and other G Protein Coupled Receptors are marked for internalization and recycling via G Protein Coupled Receptor Kinase (GRK) phosphorylation. GRK5, a regulator of AT1R, has been shown to be a potential therapeutic target. The aim of this study was to examine the effects of overexpression of GRK5 on the expression and localization of AT1R in cardiac neurons.

Overexpression of GRK5 led to a significant upregulation of AT1R and increased AT1R expression of a GRK5 nuclear export signal mutant increased AT1R expression. NFκB do not associate. Examination of nuclear and cytosolic fractions of these immunoprecipitation studies indicated that GRK5 and IκBα are co-immunoprecipitated; conversely, GRK5 overexpression of GRK5 nuclear export signal mutant increased AT1R expression. Taken together, these data suggest a nontraditional role of GRK5 as a regulator of AT1R.

3.11 GANGLIONIC DOUBLING OF SYMPATHETIC BAROREFLEX GAIN
John Horn1, Paul Kullmann2, Mitchell Springer3
1Dept. of Neurobiology, Univ. of Pittsburgh, E1440 Biomedical Science Tower, 3500 Terrace St., Pittsburgh, PA, 15261.

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

3.12 ACTIVATION OF NUCLEAR FACTOR-KAPPA B LOWERS PROTEIN EXPRESSION OF VOLTAGE-GATED SODIUM CHANNELS IN NODOSE NEURONS FROM HEART FAILURE RATS
Huyvin Lin1, Jinwu Lin1, Yinglong Li1

Our previous study has shown that chronic heart failure (CHF) reduces protein expression of voltage-gated sodium (NaV.1.7) channels in rat nodose neurons. In the present study, we investigated the involvements of nuclear factor-kappa B (NFkB) in CHF-decreased NaV channel expression in rat nodose neurons. CHF was induced by left coronary arterial ligation. CHF reduced the protein expression of NaV.1.7 in the nodose neurons, and protein expression of NFkB p65 and phosphorylated p65 in the nodose neurons was higher in CHF rats than that in sham rats. Chromatin immunoprecipitation (ChIP) assays found that p65 NFkB could interact with the promoter of NaV.1.7, and CHF increased p65 binding to the promoter of NaV.1.7. Treatment with an NFkB inhibitor (caffeic acid phenethyl ester, 10 µM, 24 h) significantly increased NaV channel density in CHF nodose neurons, and partially reversed the reduced protein expression of NaV.1.7 channels in the heart failure nodose neurons. These results indicate that activating NFkB decreases the protein expression of NaV.1.7 channels in CHF nodose neurons.

3.13 INTEGRATED CIRCULATION AND RESPIRATION IN PHYSIOLOGY AND MEDICINE I: WHY WE CHANGED OUR CIRCULATORY STRUCTURE AND FUNCTION AFTER BIRTH
Xing-Guo Sun1
1State Key Lab. of Cardiovascular Disease, Fudan Hosp., Natl. Ctr. for Cardiovascular Diseases, Chinese Academy of Med. Sci., 167 Beilishi Rd., Xicheng District, Beijing, 100037, People’s Rep. of China.

INTRODUCTION: Since APS/EB2011&2012, ACCP2011 and APSR2011, we introduced theory system of integrated control and regulation of respiration-circulation, it appears to be clear for understanding many questions in physiology and medicine. First, we try to explain mechanism of circulatory structural and functional changes after birth. QUESTION: Before birth, pulmonary blood flow is only ~9%, and ~90% blood goes through foramen oval (FO) from right directly go to left atrium. After birth FO was closed normally. However, the mechanism of this closure is unclear.

HYPOTHESIS: We try to use the sudden/abrupt change in alveolar PO2 (dominant) and PCO2 and blood pressure difference between the right and left sides resulted closure of FO.

3.14 REGULATION OF THERMOCPERGIC CAPACITY BY THE BRAIN RENIN-ANGIOTENSIN SYSTEM: ROLE OF ADIPOSE AT2 RECEPTORS
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1Pharmacology, Univ. of Iowa, 3181 MERF, 375 Newton Rd., Iowa City, IA, 52242.

Manipulation of the renin-angiotensin system (RAS) has robust effects upon metabolism, and increasing evidence supports opposing roles for the local tissue versus the systemic RAS with brain versus adipose tissue. Previously we developed a mouse model of brain-specific RAS hyperactivity (the sRA model), with transgenic expression of human renin in neurons via the synapxin promoter, and human angiotensinogen via its own promoter. sRA mice are small and lean due to a robust elevation in resting metabolic rate, mediated through both increased adipose sympathetic drive and a suppression of the circulating RAS. Uncoupling protein-1 (UCP1) was specifically induced within inguinal adipose of sRA mice (25-fold, P<0.02). Treating differentiating 3T3L1 cells with 10 µM Ispartan had no effect on UCP1 mRNA, however 10 µM PD-123,319 specifically induced (2.4-fold, and) and CGP-4211a dose-dependently suppressed UCP1 both at baseline and with norepinephrine induction (P<0.05). Chronic infusion of CGP-4211a (50 ng/kg/min s.c., 8 weeks) into sRA mice resulted in normalization of metabolic rate of 70% of sRA+CGP 3.10±0.2 mL O2/100g/min) and had similar PO2 to room air, i.e. ~140-150mmHg. Hyper-oxygen pulmonary vascular relaxation resulted that right heart had decreased afterward resistance due to over contracted pulmonary vascular structures and easily pumped all blood into pulmonary artery. Then its decreased blood volume in right atrium backward resulted in right atrium pressure lower than that in left atrium. Almost blood through lung came into left heart and increased its blood volume and cardiac output. The pressure difference between the right and left sides resulted closure of FO.

3.15 ANGIOTENSIN II ENHANCES SYNAPTIC AMPLIFICATION IN SYMPATHETIC GANGLIA IMPLICATIONS FOR BAROREFLEX GAIN AND BLOOD PRESSURE CONTROL
Mitchell Springer1, John Horn1
1Dept. of Neurobiology, Univ. of Pittsburgh, E1440 Biomedical Science Tower, 3500 Terrace St., Pittsburgh, PA, 15261.

Angiotensin II (ATII) increases ganglionic gain and the refore baroreflex gain by 50%. We tested that ATII increases synaptic amplification that occurs when nicotinic EPSPs summate to drive postganglionic action potentials. To test this idea, dissociated rat sympathetic neurons (P13–P15) from the superior cervical ganglion were stimulated with bursts of virtual EPSPs (dynamic clamp) to mimic barosensitive synaptic inputs. These results show that ATII can double preganglionic synaptic activity, periodic entrainment raises ganglionic gain, microelectrode damage masks gain in vivo, and they shed light on human microencrophygometry.
that AT1 receptor antagonists used clinically to control blood pressure act in part by decreasing synaptic gain in sympathetic ganglia.

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

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1Dept. of Cellular and Integrative Physiology, Univ. of Nebraska Med. Ctr., 985850 Nebraska Med. Ctr., Omaha, NE, 68198.

Elevated central angiotensin (Ang) II signaling contributes to the sustained increase in sympathetic outflow during chronic heart failure (CHF), which is associated with downregulation of ACE2 in the brain. We have previously shown that sympathetic outflow was attenuated in mice with neuron-selective ACE2 overexpression (SA) during CHF. However, it is not clear whether this putative sympathetic-inhibitory effect is due to Ang-(1-7) and mas receptor signaling in the pre-sympathetic neurons in these mice. When administered intraventricularly, the RVLM increases cardiac sympathetic drive in SA mice during CHF. Five weeks after coronary artery ligation, baseline mean arterial pressure (MAP) and heart rate (HR) were recorded with telemetry for 3 days. Mas receptors were knocked down using lentiviral vectors encoding MAS1 shRNA (masKD) or scrambled control shRNA (scrB). MasKD mice had a significant decrease in systolic arterial pressure (SAP), alongside suppression of the sympatho-inhibitory effect of ACE2 overexpression in CHF is partially mediated by Ang-(1-7) and mas receptors.

3.17 NUCLEAR FACTOR-KB (NFkB) GENE SILENCING IN THE ROstral VENTROLATERAL MEDULLA (RVLM) ATTENUATES ANGIOTENSIN-INDUCED HYPERTENSION

Amit Mitra1,2,3, Julie Y. H. Chan1,2, Eileen Hassel2,3, David Klip1

1Cellular and Integrative Physiology, Univ. of Nebraska Med. Ctr., 5011 Durham Res. Ctr., UNMC, Omaha, NE, 68198-5850.

AngII intracellular signaling in sympathetic-excitatory centers in the brain such as the RVLM, causing upregulation of the Angiotensin-Type1-receptor (AT1R). We have shown that NFkB gene expression in the RVLM, measured by the neuron-specific nuclear factor of activated T cells (NFATc) immunofluorescent staining, was increased during AngII infusion. Moreover, NFkB inhibition by a chemical inhibitor, Bay 11-7082, significantly reduced AT1R mRNA expression. In preliminary experiments, NFkB gene silencing by lentivirus delivery of NFkB siRNA significantly reduced AT1R gene expression. In the present study, male rats were infused with NFkB siRNA lentivirus for 1 day and 4 days, followed by AngII infusion for 14 days. NFkB gene silencing prevented AngII-induced upregulation of AT1R via NFkB signaling.

3.18 ER STRESS IN RVLM MEDIATES NEUROGENIC HYPTENSION THROUGH ACTIVATION OF PI3K/akt PATHWAY

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

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

Eun-Ja Sim1, Jun Min Yu2, Eun Ha Cho2, Eun-Jung Kim2, Yue Wu2, Yoonsun Chun3,4


We recently demonstrated that mice deficient in the antioxidant enzyme methionine sulfoxide reductase-A (Msra) exhibit mild hypertension (+10 mmHg; P<0.05) accompanied by decreases in locomotor activity and baroreflex sensitivity (Baroreflex on J Am Heart. J. 50:1504-1512, 2012). Because activity influences blood pressure (BP), we hypothesized that hypotension in Msra−/− mice would be more pronounced if the comparison to control mice is made when activity is similar. BP activity were recorded by telemetry for 1 hour young (11-18 wks) Msra−/− (n=12) and control C57BL6J (n=7) mice. Activity (units), mean BP (mmHg), systolic BP variability (BPV, SD, mmHg) and BRS (sequence technique, ms/mmHg) were measured. At similar low levels of activity, BP and BPV were markedly elevated in Msra−/− vs. control mice. Activity level should be considered when assessing hypertension phenotypes.

3.20 Temperature TROLLING FOR DIFFERENCES IN LOCOMOTOR ACTIVITY; and UP-REGULATION DURING ACUTE HYPOXIA

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Reactive oxygen species (ROS) increase in the nTS following acute hypoxia and likely contribute to hypoxia-induced changes in cardiopulmonary function. H2O2 is a diffusible signaling molecule that is inactivated by catalase (CAT) and glutathione peroxidase (GPx). Immunohistochemistry in untreated rats identified CAT throughout the nTS. In NeuN-identified neurons, CAT was expressed in nTS, and with neither connected. CAT, GPx1, and GPx4 was expressed in tissue punches of the medial nTS of male rats 5-7 days post injection, as compared to the scrambled-shRNA group. Ten days after delivery, the animals were euthanized and the brains removed for RVLM analysis. mRNAs transcripts of p65, Elk-1 and AT1R showed significant reduction in the RVLM, compared to the scrambled-shRNA animals. Our results demonstrate the role of NFkB in activating downstream transcription factors leading to AT1R gene regulation in the RVLM.

3.21 Activity-level should be considered when assessing hypertension phenotypes; and BRS (sequence technique, ms/mmHg) were measured. At similar low levels of activity, BP and BPV were markedly elevated in Msra−/− vs. control mice. Activity level should be considered when assessing hypertension phenotypes.

3.22 CARDIOVASCULAR RESPONSES TO HYPOXIA WITH BOTH, ONE, NEITHER ARTERIAL CHEMO-RECEPTOR(S)

Robert Fitzgerald1,2, Abbas Dehban5, Samara Kabih1


The purpose of this study was to determine the anesthetized, paralyzed, artificially ventilated cat’s cardiovascular responses to hypoxia with both carotid and aortic bodies connected to NTS, with neither carotid bodies or the aortic bodies connected to NTS, and with neither connected. Cats of either sex (2.5-4.0 kg) intravitally were exposed to 8-10% oxygen (O2) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia for 15min (CO) hypoxia

3.23 Withdrawn.
went to NTS. Under COHint only abs, to NTS. Under HbHar only cbs, to NTS. Under COHHar neither cbs nor abs, to NTS. The data suggested that both cbs and abs are needed to maintain peak homeostasis in the face of an hypoxic challenge; e.g., to offset the extensive systemic vasodilatation. In some cases the cbs seem to exercise a greater influence than the abs, e.g., cardiac output, diaphragm, respiratory response, pulmonary vascular resistance. Supported by the NHLBI: HL 0-507-12-15.

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

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The sleep apnea syndrome, characterized by chronic intermittent hypoxia (CIH) is recognized as an independent risk factor for hypertension. A crucial step in the CIH-induced hypertension is the potentiation of carotid body (CB) chemosensory responses to hypoxia, associated with enhanced hypoxic ventilatory and sympathetic responses, attenuation of spontaneous baroreflex efficiency (SBR) and alterations of heart rate variability (HRV). Since the time-course of the chemosensory and cardiorespiratory alterations are not well known, we hypothesized that CB chemosensory potentiation should precede the autonomic alterations and hypertension. Thus, we studied the effects of CIH on CB chemosensory and ventilatory responses to acute hypoxia, blood pressure, HRV. Experiments were performed on male Sprague-Dawley rats exposed to 5%O2, 12 times/hr for 8 hrs, 4 times/hr for 21 days, or sham condition for 21 days. Exposure to 7%CIH enhanced CB chemosensory and ventilatory responses to hypoxia and reduced SBR, effects maintained until 21 days of CIH. After 14 days, CIH shifted the HRV power spectrum toward the low frequency band suggesting a predominance of the sympathetic component. Cardiorespiratory alterations occurred without significant BP elevation until 21 days of CIH. Thus, present results show that the CIH-induced hypertension was preceded by an early potentiation of CB chemosensory and ventilatory responses to hypoxia, reduction of SBR and alterations of HRV. Support by FONDECYT 1100405.

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

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Objective: We tested the hypothesis that chemoreflex sensitivity is heightened in patients with MetS and OSA. Methods: Forty six newly diagnosed MetS patients was deferred as an apnea/hypopnea index >15 events/hour (polysomnography). We evaluated chemoreflex sensitivity in patients with MetS. These findings suggest mechanisms to explain the heightened sympathetic outflow in patients with MetS and comorbid OSA.

3.2.5 CI AND RTN NEURON STIMULATION PRODUCES CORTICAL AROUSAL IN SLEEPING RATS

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1Dept. of Pharmacology, Univ. of Virginia, 1300 Jefferson Park Ave, Charlottesville, VA, 22908

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

4.0: OXIDATIVE STRESS AND SYMPATHETIC REGULATION


Intracerebroventricular administration of angiotensin II (Ang II) induces increased superoxide production and redox-sensitive activation of p38 mitogen-activated protein kinase (p38MAPK) and extracellular signal-regulated protein kinase (ERK)1/2 in the rostral ventrolateral medulla (RVLM). Ang II-dependent neurogenic hypertension is suppressed in RVLM, leading to overexpression of sympathetic vasomotor activity and manifestation of hypertension. Moreover, oxidative stress upregulates transcription of the brain-derived neurotrophic factor (BDNF), this in turn exerts a negative-feedback regulation of superoxide production via upregulation of UCP2. In RVLM, the redox-sensitive transcription of uncoupling protein 2 (UCP2), an endogenous mitochondrial antioxidant, is downregulated. Transcriptional upregulation of UCP2 alleviates oxidative stress and promotes anti-hypertension in SHR. However, peripherally administered angiotensin II (AngII) signaling in the central nervous system (CNS) and neurogenic hypertension are linked to excessive superoxide (O2-) levels. Previously, we and others reported that anginomediated overexpression of the O2- scavenging enzyme, superoxide dismutase 1 (SOD1), in the brain inhibits Ang II-induced hypertension. However, peripherally administered adenosine induces toxicity and does not target the brain. To improve CNS delivery of SOD1, we developed SOD nano, a polyion complex nanotechnology delivery system that efficiently delivers SOD1 to the brain following peripheral administration. These data demonstrate that SOD1 nano delivers functional SOD1 protein to neurons and modulates the AngII-dependent neurogenic hypertension.

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

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Aberrant angiotensin II (AngII) signaling in the central nervous system (CNS) and neurogenic hypertension are linked to excessive superoxide (O2-) levels. Previously, we and others reported that anginomediated overexpression of the O2- scavenging enzyme, superoxide dismutase 1 (SOD1), in the brain inhibits Ang II-induced hypertension. However, peripherally administered adenosine induces toxicity and does not target the brain. To improve CNS delivery of SOD1, we developed SOD nano, a polyion complex nanotechnology delivery system composed of a polyethylene glycol corona and polyethyleneimine core (PEI-PEG) that electrostatically binds SOD1 protein. We hypothesize that SOD nano delivers functional SOD1 protein to neurons and modulates AngII-neuronal signaling and the central AngII-activated pressor response. Using cultured neurons, we have shown that SOD nano delivers functional SOD1 protein intracellularly, via active endocytosis, as evident by a decrease in O2- levels. In vivo studies revealed that the central AngII-induced pressor response is inhibited by the intracerebroventricular injection of SOD nano, but not free SOD1 protein, thus suggesting delivery of SOD nano to the brain following peripheral administration. These data demonstrate that SOD1 nano delivers functional SOD1 protein to neurons and suggest therapeutic potential of SOD nano for AngII-dependent neurogenic hypertension.
5.0: MECHANISMS OF BARO AND CHEMORECEPTORS SENSORY TRANSDUCTION: A LINK TO SYMPATHO-EXCITATION IN DISEASE

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

5.2 GASEOUS MESSENGERS IN OXYGEN SENSING BY THE CAROTID BODY
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This presentation focuses on the role of gas messengers in oxygen sensing by the carotid body. Carbon dioxide (CO) and nitric oxide (NO), generated by heme oxygenase-2 (HO-2) and neuronal nitric oxide synthase (nNOS), respectively, inhibit carotid body activity. Molecular O2 is a required substrate for the enzymatic activities of HO-2 and nNOS. Stimulation of carotid body activity by hypoxia may reflect reduced formation of CO and NO. Glomus cells, the site of O2 sensing in the carotid body, express cystathionine γ-lyase (CSE), an H2S generating enzyme. C6 H12O6 mice, which lack CSE, exhibit severely impaired hypoxia-induced H2S generation, sensory excitation, and stimulation of breathing in response to low O2. Hypoxia-evoked H2S generation in the carotid body requires the interaction of CSE with HO-2, which generates CO. Heightened carotid body activity has been implicated in the pathogenesis of autonomic morbidity associated with sleep-disordered breathing, congestive heart failure, and essential hypertension. NIH-HL-76537, HL-90554, and HL-86493. Prabhakar NR et al. 1993. Hypoxia inhibits NO generation in the carotid body and NO is a required substrate for enzyme activity of H2S. Proc Natl Acad Sci U.S.A 107:10719-10724.

6.0: PLENARY LECTURE II
6.1 NEUROMODULATORY PATHWAYS AND CENTRAL CONTROL OF SYMPATHETIC ACTIVITY IN HYPERTENSION AND HEART FAILURE
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The classical neurotransmitters, glutamate and GABA, mediate fast (insec- tive) synaptic transmission and modulate its effectiveness through slow (sec to min) signaling processes. Activation of angiotensinergic pathways from the lamina terminals to the PVN/SON and RVL by stimuli such as circulating Ang II or CSF[Na+] leads to sympathetic excitation largely by decreasing GABA and increasing glutamate release. The aldosterone “ouabain” pathway is a much slower pathway. Aldosterone enhances “ouabain” release, which then increases chronic activity in angiotensinergic pathways by eg increasing expression of AT1R and NADPH oxidase substrates in the PVN. Blockade of this pathway largely prevents chronic sympathetic excitation and presynaptic responses to CSF[Na+] or Ang II. These 2 neuropeptidomimetic pathways allow the CNS to rapidly cause and sustain sympathoexcytically over hours/days. In models of salt-sensitive hypertension, high salt diet increases CSF[Na+] and hypothalamic aldosterone and “ouabain”. The resulting sympatho-excitation and hypertension can be prevented by specific CNS blockade of any of the steps in the pathway from aldosterone synthesis to AT1R. Whether this pathway also is activated in other hypertension models, depending on central AT1R stimulation, has not yet been studied. Post MI, AT1R stimulation in the PVN plays a critical role. Chronic activation of the hypothalamic aldosterone-“ouabain” pathway, possibly by plasma Ang II, is the main mechanism contributing to this persistent AT1R stimulation and thereby to sympathetic hyperactivity. How eg corticotropins and microglia activation are involved, still needs to be assessed. Integration of rapid, slow and very slow CNS pathways contributing to sympatho-excitation provides a frame-work to understand how different stimuli and mechanisms may interact. Support:CHIR:MOP-74432;13182;119273.

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

7.2 ROLE OF INFLAMMATORY CELLS IN THE PROGRESSION OF CARDIOVASCULAR DISEASE
Joseph Francis
Louisiana State Univ. Coll. of Med.
Neuroendocrine immune interactions play an important role in the pathophysiology of cardiovascular disease. Each of the systems, namely the nervous system, endo- crine system and immune system interact with each other via their mediators to maintain cardiovascular homeostasis. However, in cardiovascular disease this internal milieu is disturbed, resulting in excessive production of mediators and ultimately resulting in cardiovascular disease. In this presentation, we will examine how these neuromodulators contribute to the development of cardiovascular dis- ease. We will examine some of our recent findings using the angiotensin (ANGII) infu-sion model of hypertension to understand the role played by the brain in the development of hypertension. We will use a comprehensive, whole animal, mo- lecular, cellular and genetic approach to explore the possible mechanism by which cytokines and their transcription factor, nuclear factor kappa B (NFkB), in the paraventricular nucleus of the hypothalamus contribute to the development of hypertension. Finally, we will also present data on the effect of direct manipulation of PVN NFkB and renin-angiotensin system modulation in the development of hypertension. Some of
our findings will suggest that cytokine or NFκB-induced changes within the PVN might be an important modulator of hypertension. The central link between cytokines and neurohumoral system activation in hypertension may lead to a better understanding of the progression of the disease processes and ultimately lead to new and effective strategies to treat hypertension.

8.0: POSTER SESSION II

8.1 KLOTHO AND CENTRAL REGULATION OF SYMPATHETIC NERVE DISCHARGE

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Klotho is a recently identified anti-aging gene and genetic mutation of klotho is associated with the presentation of numerous aging phenotypes (e.g., arteriosclerosis, hypoglycemia, hypocoagulability). The working hypothesis is that silencing of brain klotho significantly potentiates SND responses to acute stress. To silence brain klotho in vivo we constructed recombinant adeno-associated virus (AAV) carrying short hairpin interference RNA (AAV-sh-klotho) and AAV carrying a scrambled shRNA (AAV-sc-shRNA). Sprague-Dawley rats (250-350 g) were anesthetized and microinjected i.c.v. with either AAV-sh-klotho or AAV-sc-shRNA (exp. group) or AAV-sc-shRNA (control group) 7.0±0.01 µl and allowed to recover. Rats completed acute cold stress experiments at either 10, 15 or 20 days following injections. Renal SND was recorded in anesthetized rats while core body temperature was decreased from 38° to 30°C. Preliminary results indicate that renal SND was decreased 50-70% in each of rats receiving AAV-sc-shRNA, regardless of the recovery duration. In contrast, renal SND tended to be increased in response to cooling in the AAV-klotho-treated rats. The AAV-klotho-shRNA reduced endogenous klotho expression 50-70% compared to the AAV-sc-shRNA-treated rats. These preliminary data suggest that brain klotho may influence the responsiveness of sympathetic neural circuits to acute stress. Funding provided by NIH grants HL091342 and HL-092392.

8.2 A2C-ADRENOCEPTOR STIMULATION RESTORES A1-ADRENOCEPTOR MALFUNCTION IN HYPERTENSIVE RATS

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α2-adrenoceptors α2AR control blood pressure (BP) by limiting central sympathetic output and peripheral noradrenaline (NA) and adrenaline (A) release and by acting on blood vessels. α2AR functions may result in high BP. We studied the effect of α2AR agonists/antagonists, with different subtype profiles and abilities to cross the blood-brain-barrier, on catecholamine release and vascular resistance (TPVR) in spontaneously hypertensive (SHR) and normotensive (WKY) rats. The peripheral α1AR antagonist L-659,066 increased resting NA overflow to plasma when combined with NA-reuptake (NA-uptake inhibitor, particularly in SHR. Tyramine-activated NA release through NET will inhibit reuptake. Effects due to presynaptic release control is therefore superimposed on NET-mediated release. Centrally active α2A-AR-agonist (clonidine), but not fadomidine (peripheral), re-duced renal SND, BP and heart rate, and resting and tyramine-stimulated NA overflow in SHR. L-659,066 increased NA overflow and reduced the TPVR response to tyramine in WKY, but, in SHR, only when combined with peripheral, α2C-AR-stimulating agonist. α2A-AR-modulation of experiment-induced, central activation of A secretion, mostly paralleled that of NA. Conclusions: α2AR failed to produce baseline BP, TPVR and heart rate (HR) measurements and the renal nerve was dissected and clamped with electrodes to RSNA recordings. We also evaluated the cardiovascular effects of GABA AA agonist (muscimol) and antagonist (bicuculline) microinjected in the PVN of conscious controls and hyperadipose rats. The anesthetized MSG rats presented baseline hypertension (CT= 90.00 ± 3.65; MSG=110.4 ± 8.25 mmHg) and increased RSNA compared with control (CT=72.01 ± 6.42; MSG= 94.48 ± 7.75 spikes/s). The conscious MSG rats also presented baseline hypertension (CT= 111.7 ± 1.61; MSG=118.6 ± 1.12 mmHg) and the microinjection of muscimol in the PVN produced a higher decrease in MAP compared with control rats (ΔCT=-8.26 ± 1.67; MSG=-24.40 ± 1.82 mmHg), with no difference in pressure and tachycardic responses to bicuculline. (CT= 41.27 ± 6.90; MSG=43.51 ± 2.53 mmHg). Our results suggest the involvement of the renal sympathetic nervous system in the pathophysiology of the MSG obesity and a possible involvement of α2AR-neurons.

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

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A characteristic feature of chronic heart failure (HF) is that the risk of mortality is elevated sympathetically. The subfornical organ (SFO) is involved in neural control of sympathetic drive and may be influenced by circulating peptides such as angiotensin (Ang) II and endothelin (ET)-1 due to a weak blood-brain barrier. We hypothesized that an activated SFO, by Ang II/ET-I, contributes to enhanced sympathetic activity in HF. Sprague-Dawley rats were subjected to coronary artery ligation to induce HF. HF was confirmed by echocardiography and orthosympathomimetic drug challenge. The anesthetized of the SFO was measured by immunohistochemistry. Rats with HF had an increase FoB-positive cells in the SFO compared to sham rats (101 vs. 29 FoB-positive cells). In urethane-anesthetized rats, microinjection of Ang II (50-200 pmol) into the SFO increased renal sympathetic nerve activity (RSNA), blood pressure, and heart rate to a greater extent in HF than in sham rats (ARNSA:31±15% of basal value;100pmol). Rats also exhibited an enhanced protein expression of AT (67%), ETα(69%), ETα(40%) re-ceptors, while they had reduced level of GABAα, receptor (42%) in the SFO. The enhanced activation of the SFO by circulating peptides such as Ang II and ET-I that are known to be elevated during HF, may contribute to the sympathoexcitation exhibited in HF. Supported by the UNMC Skala Fellowship and NIH grant HL62222.

8.5 PARADOXIC ELEVATIONS IN ANGIOTENSIN II, INDEPENDENT OF CHLOROTHALIDONE, CONTRIBUTE TO SUPINE HYPER- TENSION OF PRIMARY AUTONOMIC FAILURE

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Despite profound impairments in sympathetic activity, at least 50% of primary autonomic failure (PAF) patients exhibit supine hypertension. While the mechanisms are unknown, plasma renin activity is often undetectable suggesting renin mechan-isms are not involved. However, the preservation of aldosterone enabled us to examine the status and contribution of the renin-angiotensin (Ang) system in AF. Supplemental plasma Ang peptides were measured in hypertensive patients [AF-HT, n=18], normotensive patients [AF-NT, n=11] and matched healthy subjects [n=10]. Ang II levels were paradoxically elevated in AF [AF-HT vs AF-NT vs healthy: 42.6±7.4 pg/mL healthy; p<0.05], despite suppressed renin. In contrast, Ang I (7-17) was reduced in AF patients [7.1±1 AF-HT vs 4.1±1 AF-NT vs 2.2±1 pg/mL healthy; p<0.05]. Plasma aldosterone was preserved in AF and did not correlate to Ang II levels to determine the function of Ang II administration. We found that short-time losartan (50mg, PO) to 9 AF-HT patients and measured supine systolic blood pressure q2 hours for 12 hours. Losartan significantly reduced blood pressure [25±15 mm Hg at 6 hours after administration]. These findings suggest an imbalance in Ang II and Ang-(1-7) in AF that is independent of sympathetic status. The elevation in Ang II appears to contribute to hypertension in AF patients. Overall, these patients offer a unique model to study blood pressure regulation and the production of Ang II in the absence of both autonomic and renin influences.

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8.6 NOREPINEPHRINE INCREASES NADPH OXIDASE-DERIVED SUPEROXIDE PRODUCTION IN PERIPHERAL BLOOD MONOCYTE CELL LINE FROM HEALTHY HUMANS

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Many diseases associated with sympathetic overactivity also exhibit elevated active oxygen species (ROS). Although animal studies suggest that exogenous admin-istration of the sympathetic neurotransmitter norepinephrine (NE) increases systemic ROS, the ability of NE to increase ROS in humans is unknown. Thus, we sought to examine the potential contribution of NE via the NADPH oxidase pathway in increasing superoxide production in peripheral blood mononuclear cells (PBMCs) from healthy humans. PBMCs were isolated from blood samples in 7 healthy males. NADPH oxidase (gp91 phox and p22 phox) mRNA expression was assayed using real-time RT-PCR at 1, 6, 12 and 24 hours following NE (50ng/ml...
and 50pg/ml) or vehicle treatment. In addition, intracellular superoxide production was measured at 1, 6, 12, 24 and 36 hours using dihydroethidium following NE only, NE + diphenyle ionidion (DPI; selective NADPH oxidase blocker) and vehicle. At physiological concentrations of NE (50ng/ml and 50pg/ml), expressions of gp91phox and p47phox were increased at 12 and 24 hours (e.g., gp91phox 12/14and 4/3 fold; NE (50ng/ml) vs. vehicle; P<0.05). This was followed by an increase in superoxide production at 36 hours (1.4±0.3 fold; NE (50ng/ml) vs. vehicle; P<0.05). Importantly, NE-increased induces in superoxide production were attenuated by DPI. These findings suggest that NE increases the expression of NADPH oxidase subunit genes and NADPH oxidase-derived superoxide production in human PBMCs.

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

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Potential mechanisms underlying the sex-dependent blood pressure (BP) responses to mental stress (MS) remain unclear, but previous evidence suggests that it is unlikely related to endogenous levels of sex steroids, sympathetic outflow or differences in stress-induced forearm vasodilatation. Importantly, exercise has been proposed as a coping resource for stress management. Given this, the purpose of the present study was to determine the role of cardiac output (CO; ModelFlow) and forearm vascular responses (plethysmography) in mediating the pressor response (Finometer) to MS (3 min, stroop word-colour test) before and 60 min after a maximal exercise (1846±373watts) in young healthy men (n=15) and women (n=19). Before exercise, BP response was significantly (P<0.05) attenuated in men (Δ16±2 mmHg) compared to women (Δ11±1 mmHg). This heightened response to MS was also accompanied by greater increases in CO in men (Δ31±7 %; P<0.05) compared to women (Δ15±5 %) and similar forearm vasodilatation between sexes (Δ70±20 mmHg vs. Δ78±16 %women). After exercise, the BP, CO responses to MS were attenuated only in men and, consequently, no sex differences were observed during this period. Vascular responses to MS were not affected by exercise. In summary, these findings highlight for the first time a potential role for CO in mediating the exaggerated BP response in men as well as how exercise could benefit male subjects in regards to the cardiovascular reactivity during a mental stress.

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

Alexandra Pintil MD, Tamás Horváth MD, Adrienn Sárközi, Domonkos Cseh, Mark Kollai MD, PhD


Background: Sudden cardiac death (SCD) is a common late complication in patients with tetralogy of Fallot (ToF). Reduced cardiovascular baroreflex sensitivity (BRS) was found to be an independent predictor of SCD. Reduced BRS was reported in ToF patients, but the underlying mechanism is not clear. Our laboratory has shown earlier that BRS is related to carotid artery distensibility (DC) in healthy subjects and that DC is reduced in ToF. Considering the above, we aimed to test the hypothesis that reduced BRS is related to impaired carotid artery elastic function. Methods and results: We studied 36 ToF patients (21±11 yrs and 50 age- and gender-matched healthy control subjects. Carotid artery diastolic diameter and pulse wave attenuation was determined by wall tracking and carotid blood pressure was measured by tonometry. DC was calculated subsequently. Spon- taneous blood pressure fluctuations coupled with adequate heart rate responses were used to calculate spontaneous BRS (sBRS). Intravenous phenylephrine-induced blood pressure elevation followed by heart rate reduction was used to determine BRSphe.. Results: (mean±SD) BRS indices were markedly reduced in patients compared with controls (sBRS 9.3±1.2 vs. 17.5±5.6 mmHg/L; BRSphe 16.8±10.2 vs. 32.6±11.4 mmHg/L). DC also showed significant difference between groups (5.1±1.8 vs. 6.8±2.6×10-3/mmHg). DC correlated significantly and positively with BRS across patients and control subjects as well (sBRS r=-0.49; P< r=0.42; BRSphe r=0.31 vs. r=-0.73*). Multiple regression analysis indicated that DC is an independent determinant of BRS indices in ToF patients. (P<0.05; P<0.01). Discussion: Our data demonstrate that reduced DC can contribute to impaired BRS in ToF patients. Lifestyle modifications, such as moderate aerobic exercise, sodium restriction and omega-3-fatty acid intake, appear to be efficient interventions in preventing and treating carotid artery stiffness and --indirectly-- impaired baroreflex function.

8.9 RHODOPHIA INHIBITION LOWERS SYMPATHETIC NERVE ACTIVITY AND RESTORES BAROREFLEX IN CONSCIOUS RABBITS WITH CHRONIC HEART FAILURE

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Rho-Associated protein kinase (RhoK) is a serine/threonine kinase involved in calcium sensitization and vascular smooth muscle cell contraction. RhoK over-activation is implicated in chronic heart failure (CHF) and a potential contributor to the heightened sympathetic nerve activity (SNA) seen in CHF. Thus, we investigated the effect of the novel RhoK blocker on renal SNA (RSNA) in a pacing rabbit model of CHF. We induced CHF by placement of left ventricular pacing leads and characterized CHF by an ejection fraction of ~45%. Renal nerve recordings and an ictus cannula and osmotic minipump (rate: 1 µL/h) containing saline or furosemide was administered. Statistical analysis was performed using repeated measures two-way ANOVA. Mean arterial pressure (MAP) was significantly lower in the CHF group compared to the control group (P<0.05). This was followed by a significant increase in sympathetic nerve activity (SNA) (P<0.05). After 4 weeks, the CHF group showed a significant decrease in MAP (P<0.05) and SNA (P<0.05) compared to the control group. This was accompanied by a significant decrease in SNA (P<0.05) after RhoK inhibition. These findings suggest that RhoK inhibition may be a potential target for the treatment of CHF.

8.10 BLOUNTED ADRENERGIC VASOCONSTRICITION IMPAIRS BLOOD PRESSURE RECOVERY FOLLOWING SEVERE HEMORRHAGE IN OBESE ZUCKER RATS

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Obesity has impaired baroreflex activity and elevated sympathetic tone which may impair the buffer capacity in response to hemorrhage. We hypothesize that blood pressure compensation following severe hemorrhage is impaired in obesity due to a blunted baroreflex and altered sympathetic mediated vasconstriction. A loss of 35% of total blood volume was induced in conscious lean (LZ) and obese Zucker (OZ) rats (OZ-11-12 weeks). Blood pressure (BP) and heart rate (HR) were monitored during the hemorrhage and a 1 hour recovery. The baseline BP, HR, and total peripheral resistance (TPR) were not different between groups. During hemorrhage, BP in LZ did not decrease until 15% loss of total blood volume. This was associated with a transient increase in HR. In OZ, BP dropped below basal levels after a 5% loss associated with an absence of tachycardia. After a 1 hour recovery, BP was partially compensated through an increased TPR in LZ and OZ, with the intestines in BP and TPR blunted in OZ. Prazosin selective (Α1 antagonist) treatment caused a larger decrease in basal BP in OZ as compared with LZ. Prazosin treatment blocked the BP compensation and increase in TPR in both in LZ and OZ. Our results suggest that the compensatory mechanisms mediated by baroreflex and sympathetic vasconstriction following severe hemorrhage are blunted in OZ.

8.11 Withdrawn.

8.12 C-TYPE NATRIURETIC PEPTIDE IN THE PVM MEDIATES RENAL SYMPATHETIC INHIBITION

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Volume expansion produces a reflex decrease in renal sympathetic nerve activity (RSNA) that is mediated by the paraventricular nucleus (PVN). However, the mechanisms for the sympathoinhibitory role of the PVN and the neurochemical factors involved remain to be identified. C-type natriuretic peptide (CNP) has been shown to attributes to be a potential candidate as a mediator of this sympathoinhibition in the PVN. First, microinjection of CNP into the PVN significantly decreased heart rate (HR) (-23.6±3.5 vs. -0.3±0.9 beats/min), renal sympathetic nerve activity (RSNA) (-25.8±1.8 vs. -3.6±1.5%) and mean arterial pressure (MAP) (-15.0±1.9 vs. -1.0±0.9 mmHg) compared with microinjection of artificial cerebrospinal fluid. Second, 19 spontaneously active neurons were recorded in the PVN in normal rats with extracellular single-unit recording in vivo, and 6 units were antidromically activated from the rostral ventrolateral medulla (RVLM). Picrocinnin of CNP significantly decreased the basal discharge in 5/6 PVN-RVLM neurons, and in 6/13 neurons that were not antidromically activated from the rostral ventrolateral medulla. Third, CNP significantly decreased the basal discharge in 5/6 PVN-RVLM neurons, and in 6/13 neurons that were not antidromically activated from the RVLM. There were no significant changes after picoinjection of artificial cerebrospinal fluid. Third, we determined whether natriuretic peptide receptor type C (NPR-C) was present on PVN neurons that projected to the RVLM. The retrogradely transported fluorescent tracers LatexGreen was injected into the RVLM. The NPR-C was present on PVN neurons that projected to the RVLM as detected by immunohistochemistry. Double-labeled neurons were present only in the parvocellular part of the PVN. These results suggest a potential role for CNP in the regulation of renal sympathetic nerve activity.

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

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Neuroinflammation, which increases sympathetic drive, contributes to cardiovascular diseases including hypertension. Rostral ventrolateral medulla (RVLVM), which regulates central sympathoexcitatory outflow, is involved in neural mechanisms of hypertension. Kv4.3, one of voltage-gated K+ channels, in RVLVM has been demonstrated to regulate sympathoexcitatory outflow. We investigated whether neuroinflammation causes downregulation of Kv4.3 ion channel in RVLVM to mediate neurogenic hypertension under chronic systemic inflammation (CSI). CSI was induced via a continuous intraperitoneal infusion of E coli lipopolysaccharide to normotensive Sprague-Dawley rats. Activation of microglia, microglial activation is mediated by p38 mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NFκB). In anesthetized rats, injection of ethanol increased aortic blood pressure. Following the administration of ethanol, RVLVM responded with increases in sympathetic nerve activity. The results suggest that CSI activates microglia to evoke a COX-dependent neuroinflammation, oxidative stress and Kv4.3 downregulation in RVLVM, leading to neurogenic hypertension. This study was supported by research grants NSC-99-2811-B-075-001 and NSC-99-2321-B-075-001 from the National Science Council, Taiwan, Republic of China.

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

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Evidence indicates that central mechanisms contribute to the increased sympathoexcitatory response to ethanol intake. One of the key areas that link ethanol-induced sympathoexcitation is the central nucleus of the amygdala (CeA). However, the underlying neural mechanisms have not been determined. We tested the hypothesis that the sympathoexcitatory response to CeA injection of ethanol requires activation of local ionotropic excitatory amino acid (EAA) receptors. In anesthetized rats, CeA injection of ethanol increased aortic blood pressure (SSNA), spinal baroreflex and intercellular adhesion molecule-1 expression, and decrease in endothelial nitric oxide synthase expression were observed in RVLVM under CSI. A long-term pressor response was accompanied by an increase in tissue level of superoxide and a downregulation of Kv4.3 expression was also detected in the RVLVM. Pressor response and cellular events were significantly prevented by inhibition of microglia activation, COX-2 inhibition, cytokine suppression, and superoxide scavenger. Together, these results suggest that CSI activates microglia to evoke a COX-2-dependent neuroinflammation, oxidative stress and Kv4.3 downregulation in RVLVM, leading to neurogenic hypertension. (This study was supported by research grants NSC-99-2811-B-075-001 and NSC-99-2321-B-075-001 from the National Science Council, Taiwan, Republic of China).

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

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Recent data indicate that β-adrenergic stimulation offsets α-adrenergic vasoconstriction in young women and this effect is lost in post-menopausal women. These findings suggest that sympathoexcitatory control of vascular conductance differs in women. However, the impact of these age-related vascular changes on baroreflex control of blood pressure remains unknown. Thus, the purpose of this study was to examine the effect of baroreflex stimulation on leg vascular conductance (LVC) and mean arterial pressure (MAP) in 7 young (YW, 25±5 yrs) and 5 older women (OW; 60±5 yrs), femoral arterial blood velocity and diameter (duplex Doppler ultrasound), MAP (Finometer) and head heart rate (HR; ECG) were continuously measured during 10 sec of neck suction (10 Torr) to simulate carotid hyperemia. Resting LVC, MAP and HR were similar between groups. In response to neck suction, increases in LVC were significantly less in YW compared to OW (YW, +7.3 vs. OW, +12±1% m/min/mmHg; P<0.05), whereas, YW exhibited greater decreases in HR (YW, -14±2 vs. OW, -8±2 bpm; P<0.05). Inter-estingly, carotid baroreflex-mediated decreases in (YW, +12±1 vs. OW, +11±3 mmHg; P>0.05) were similar between groups. These preliminary findings suggest that older women have a greater reliance on changes in vascular conductance to mediate blood pressure during simulated carotid hyperemia, whereas younger women rely more on cardiac responsivity. Supported by R01HL093167.
control subjects had an 11.1% increase (P<0.05). DBP was significantly in-creased in male patients, male control subjects and female control subjects. The 6-MWT test is a safe and simple instrument for demonstrating cardiovascular responses to sub maximal exercise in patients with heart disease.

8.19 Withdrawn.

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

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INTRODUCTION: The new theory system of respiration-circulation integrated control and regulation appears to be clear for understanding of many questions in physiology and medicine. Second, we try to explain mechanism of the variability of heart rate (HR), systolic blood pressure (SBP) and anatomic tone depending upon breath rhythms. QUESTION: There is variability of HR, SBP and anatomic tone normally following the breath rhythms. However, the mechanism is unclear. HYPOTHESIS: We try to use the continuous dynamic change in the Trinity of PaO2 (dominant), PaCO2 and [H+] in blood, which originally results from lung inspiratory and expiratory ventilation, to explain the mechanism for variability of HR, SBP and anatomic tone. EXPLANATIONS: As we described while introduced the new theory, alveolar gases pressures continuously go up/down during lung inspiratory and expiratory period. The signals of these changes of lung/alveolar PO2 and PCO2, go to arterial side following blood flow, then arterial oscillatory changes of respiratory mode, which stimulate the peripheral chemical sensors via the nerve system, to result variability of HR and anatomic tone. Based upon the hyper-oxygen pulmonary vascular relaxation and hypo-o2-construction, alveolar PO2 and PCO2 oscillation results similar patterns of pulmonary blood flow and resistance. As Starling's principle, afterward preloading of left ventricle makes variability in stroke volume and SBP.

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

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INTRODUCTION: Since APS/EIR2011&2012, ACCP2011 and APSR2011, new theory system of respiration-circulation integrated control and regulation appears to be clear for understanding of many questions in cardiovascular physiology and medicine. Third, we try to explain mechanism of oscillatory breathing (O.B) in heart failure (HF) patients. QUESTION: Is there O.B during sleep and exercise in HF. However, mechanism is unclear. HYPOTHESIS: Poor left ventricle function (lower EF, SV and CO) de-creased magnitude of oscillatory information in arterial blood, which can be explained by decreased oscillatory information in PaO2 etc. QUESTION: Is there O.B during sleep and exercise in HF. However, mechanism is unclear. HYPOTHESIS: Poor left ventricle function (lower EF, SV and CO) de-creased magnitude of oscillatory information in arterial blood, which can be explained by decreased oscillatory information in PaO2 etc. QUESTION: Is there O.B during sleep and exercise in HF. However, mechanism is unclear. HYPOTHESIS: Poor left ventricle function (lower EF, SV and CO) de-creased magnitude of oscillatory information in arterial blood, which can be explained by decreased oscillatory information in PaO2 etc. QUESTION: Is there O.B during sleep and exercise in HF. However, mechanism is unclear. HYPOTHESIS: Poor left ventricle function (lower EF, SV and CO) de-creased magnitude of oscillatory information in arterial blood, which can be explained by decreased oscillatory information in PaO2 etc. QUESTION: Is there O.B during sleep and exercise in HF.

9.0: SYMPATHETIC MECHANISMS IN HUMAN HYPERTENSION

9.1 IMPAIRED AUTONOMIC REGULATION OF BLOOD PRESSURE AND HYPERTENSION

Italo Biaggioni*1


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

9.2 ACUTE AND CHRONIC ORTHOSTATIC INTOLERANCE, MALADAPTIVE AUTONOMIC REGULATION

Julian Stewart*2


Vagal withdrawal and sympathetic circulatory control are key to the rapid cardiovascular adjustments that occur within seconds of standing upright (orthostasis) and which are required for bipedal stance. Indeed, patients with ineffective sympathetic adrenergic vasoconstriction rapidly develop "orthostatic hypotension" prohibiting all effective upright activities. One speaks of "orthostatic intolerance" (OI) when signs (e.g. decreased BP) and symptoms of cerebral hypoperfusion (e.g. lightheadedness) and sympathetic activation (e.g. jitteriness) occur when upright and are relieved by recumbence. The experience of transient mild OI is part of daily life. However, many people experience episodic acute OI, in the form of postural faint or chronic OI, in the form of orthostatic tachycardia syndrome and postural hypotension which significantly reduces quality of life. Potential mechanisms for OI include forms of sympathetic hyperfunction, forms of sympathetic hyperfunction ("hyperadrenergic"), orthostatic intolerance that results from regional blood volume redistribution due to selective orthostatic vascular bed inadequacy, and orthostatic intolerance that results from postural hypopnea with consequent tachycardia, hypertension and cerebral hypoperfusion. Reference: Stewart J. Impaired SNS function in human cardiovascular control. 1993. Oxford University Press, Inc. New York.
1.2 THE BLOOD BRAIN BARRIER AND CONTROL OF ARTERIAL PRESSURE
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The mechanisms for long term regulation of arterial pressure in conditions of hypertension remain an enigma. Our goal is to understand the origin of sympathetic over activity and to parallel the development of hypertension. Our research has focussed on the roles of the endothelium within the brainstem and delivery of blood to this portion of the brain via the verteobasilar circulation as major determinants of the set-point of arterial pressure. I will review the importance of brainstem endothelial cell derived nitric oxide and its importance in modulating neuronal function via ‘vascular-neuronal signalling’ for the long term regulation of arterial pressure. I will provide evidence that the microcirculation within the brainstem is inflamed in conditions of hypertension and provide evidence for upregulation of adhesion molecules in the trapping of leukocytes. Putative downstream actions of chemokines and cytokines on neuronal circuitry regulating arterial pressure will be demonstrated in a pre-clinical rodent model of hypertension. Finally, I will demonstrate that the brainstem of the spontaneously hypertensive rat is hyperperfused and that this reflects the situation in hypertensive humans. Our recent evidence supports the provocative hypothesis that brainstem hyperperfusion is causative to the development and maintenance of hypertension. In conclusion, the microcirculation plays a major role in determining the set point of arterial pressure and this includes signalling across the blood brain barrier as well as the role of blood perfusion. Bristol Heart Foundation funded research.

13.0: POSTER SESSION III

13.1 INVOLVEMENT OF PIN IN ANGIOTENSIN II DEPENDENT REGULATION OF NEURONAL NITRIC OXIDE SYNTHASE IN THE PVN OF RATS WITH CHRONIC HEART FAILURE
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Expression of neuronal nitric oxide synthase (nNOS) decreased in the paraventricular nucleus (PVN) of rats with chronic heart failure (CHF), however the molecular mechanism remains unclear. In the present study protein levels of PIN (a protein inhibitor of nNOS, known to dissociate nNOS dimers into monomers) increased (1.120.09 vs. Sham 0.756.010) with approximately 60% decrease in dimer/monomer ratio in the PVN of rats with CHF (6-8 wks. after coronary artery ligation). In vitro studies using neuronal cell line, NG108 showed that PIN protein expression is 2.3-fold higher in response to angiotensin II (Ang II). Silencing of PIN in NG108 cells leads to 2-fold accumulation of nNOS suggesting a regulatory role of PIN in NO synthesis. Moreover, dimer/monomer ratio of nNOS also increased by 80% with PIN knockdown in NG108 cells. Furthermore, Ang II treatment in NG108 cells in the presence of proteasome inhibitor, lactacystin, suggested that post-translational processes such as protein degradation/stabilization are involved in Ang II dependent up-regulation of PIN. We conclude that post-translational accumulation of PIN, mediated by Ang II, leads to a decrease in the dimeric form of nNOS as well as protein levels of nNOS which may lead to reduced nitric oxide mediated inhibition of sympathetic tone during CHF. Supported by NIH grant HL62222

13.2 AUTONOMIC/HYPOXEMIA-INDUCED VENTRICULAR FIBRILLATION IN EPILEPTIC RATS
Isaac Naggaa1, Harson Kamraga1, Jason Lazar1, Mark Stewart1
The effects of seizures on the autonomic activity can be severe and cardiac damage and arrhythmias may be the result of seizures. Rats that undergo status epilepticus (SE) show cardiac myofilament damage. They are more susceptible to ventricular fibrillation (VF) with an arrhythmogenic drug, but these changes do not appear if rats are pre-administered a beta blocker. In normal rats, we have characterized the conditions necessary for extreme autonomic changes to cause VF, and we studied these conditions in epileptic rats. Rats were made epileptic with a single period of kainic acid-induced SE. When rats peaked in seizure frequency, they were anesthetized with urethane. Echocardiography was used to measure left ventricular (LV) mass, the ejection fraction (EFGK) and LV volumes. EFGK was recorded, and vagotomy and in- fusions of isoproterenol were performed. Trials of hypoxemia used fixed dead space volumes (1-8 ml) placed over an endotracheal tube. LV mass was greater in epileptic rats (1.06 ± 0.07 g vs. 0.79 ± 0.05, p = 0.004; 22 epileptic, 20 control). During long-term EKG, 4/13 of epileptic rats had ventricular tachyarrhythmias compared to 6/6 of controls. However, VF was induced in only one epileptic rat (1/7 rats, 26 attempts) compared to 100% (4/4) of controls (8/18 attempts). Epileptic rats have altered susceptibility to autonomic/hypoxemia-induced VF. Seizure-induced cardiac damage may be compensated for by cardiac hypertrophy. This hypertrophy may be related to VF susceptibility.

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

13.4 CAROTID BODY DENERVATION ATTENUATES INCREASED SYMPATHETIC NERVE ACTIVITY IN CONGESTIVE HEART FAILURE
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In congestive heart failure (CHF) the carotid body chemoreflex (CBC) is enhanced and contributes to increased sympathetic nerve activity (SNA) that exacerbates progression of the disease. We hypothesized that SNA is increased in a rabbit model of pacing-induced CHF, and that denervation of the CB (CBD) would ameliorate these changes. Phlebography was used to measure ventilatory responses to hypoxia (Hx). SNA was measured directly from the renal nerves of conscious animals. Autonomic control of cardiovascular function was assessed indirectly by spectral analysis of blood pressure variability (BPV) using telemetry. We found that RSNA and ventilatory responses to Hx were augmented in CHF, and that CBD nearly abolished the responses to Hx. Spontaneous baroreflex sensitivity was attenuated in CHF, (α-0.96±0.03 pre-pac vs. 0.70±0.11 CHF) and was improved by CBD (α-1.03±0.03). The low frequency component of systolic BPV (reflecting sympathetic tone) increased in CHF (82%±38 above pre-pac) and this was attenuated after CBD (24%±23 above pre-pac). RSNA was greater in CHF (21±1% sham vs. 54±4% CHF), and this increase was not apparent after denervation (23±1% CHF-CBD). Our findings support previous findings that enhanced CBC contributes to increased SNA in CHF, and suggest that CB denervation may be an effective treatment to reduce SNA and improve baroreflex sensitivity in CHF. This work was funded by NIH PO1 HL62222 and Coridea NC1, Inc.
that BNA consistently exhibited significant improvement in the signal amplitude (77.09 µV ± 7.35 vs. 32.11 µV ± 6.34 for the MH electrode; *P < 0.001) and SNR (35.71 dB ± 2.44 vs. 25.08 dB ± 2.31 for the MH electrode; *P < 0.001) of the measured SNA. Moreover, the BNA was capable of recording electrical events lost in the noise floor of the measurements using MH electrodes. We conclude that BNA technology improves the SNR of SNA recordings and significantly advances techniques to investigate the pathophysiological role of SNA.

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

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2Clinical studies have shown that the arterial baroreflex was blunted in patients with type-2 diabetes mellitus (T2DM). As a final pathway for the arterial baroreflex control of the cardiac function, intracardiac ganglion (ICG) neurons are excited by acetylcholine acting on the nicotinic acetylcholine receptors (nAChRs). Our recent study has demonstrated that ICG neuron excitability was lowered by the decreased N-type Ca2+ currents in high-fat diet-low-dose streptozotocin-induced T2DM rats. In the present study, we examined whether the sensitivity of ICG neurons to nicotine (a nAChR agonist) is impaired in T2DM rats. Immunofluorescence data showed that there was no significant difference on the protein expression of nicotinic receptors in ICG neurons from sham and T2DM rats. Using whole-cell patch clamp technique, we found that nicotine concentration-dependent changes in ICG neuron excitation (action potential frequency) and the sensitivity of ICG neurons to nicotine in diabetic rats was lower than that in sham rats (EC50 value is 2.96 µM for T2DM rats vs. 0.49 µM in sham rats). Diabetes also decreased the response of Ca2+ channels to nicotine in ICG neurons compared to sham rats. Additionally, nicotinic receptor antagonist (100 µM hexamethonium) and N-type Ca2+ channel blocker (1 µM omega-conotoxin GVIA) completely blocked the effect of nicotine on ICG neuron excitability and Ca2+ currents in sham and T2DM rats. Our results indicate that T2DM decreases the sensitivity of ICG neurons to nicotine.

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

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2Glutamate release by contraction-activated skeletal muscle afferents into the dorsal horn of the spinal cord initiates the central component of the exercise pressor reflex (EPR). However, the role of glutamate as well as glutamatergic receptors in mediating the exaggerated EPR might modulate sympathetic neural function. We used no change in sympathetic neural function. These data indicate renal DNx enhances the autonomic components of BR function. These data indicate renal DNx enhances the autonomic components of BR function. However, DNx rats had lower systolic blood pressure than CHF rats.

Sham CHF

Before After Before After

KYN 17.5±2.2 32.3±2.6 8.5±0.8* †
0 9.3±1.1* †
CNQX 16.1±1.2 28.3±3.0 11.8±1.8
0 7.5±1.0* *
AP-5 20.0±2.1 14.3±1.8 34.5±3.0 17.6±2.0
6 4 *

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

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

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

13.9 UNILATERAL RENAL DERENNERATION ENHANCES THE BAROREFLEX FUNCTION IN CONSCIOUS RABBITS WITH CHRONIC HEART FAILURE

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Renal nerve denervation (DxN) is currently being assessed as a therapy for resistant hypertension and other disorders characterized by sympatho-excitation, such as chronic heart failure (CHF). We hypothesized that renal DNx enhances arterial baroreflex (BR) control of heart rate (HR) in normal and CHF rabbits. All animals were instrumented with ventricular pacing leads and an arterial pressure (AP) radiotransmitter (APRT). After recovery the left kidney was denervated by stripping the renal artery of all visible fibers. Intact animals were subjected to a sham operation. Two weeks later, CHF animals were subjected to ventricular pacing. HR changes in HR in CHF were indistinguishable between CHF and normal rabbits. APRT and phenylephrine bolus injection and after injection of atrope and metoprolol. BR function was determined by fitting mean AP and HR data to a 4-parameter logistic equation. Renal DNx increased the BP by 34% (HR: 298±3.9 bpm, p <0.02). HR range was also enhanced in CHF DNx animals (CHF, intact: 110±16 bpm; CHF, DNx: 294±15 bpm, p <0.002). Preliminary data suggest renal DNx enhances HR range after atropine or metoprolol blockade, potentially improving both vagal and sympathetic components of BR function. These data indicate renal DNx enhances the autonomic components of BR control of HR in the normal and CHF states. Supported by: P01-HL62222.

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

Xue-Guo Sun1,2
2INTRODUCTION: During maximal exercise, muscles blood flow increased 20-40 folds, which comes from 3-5 folds increase in cardiac output (CO) and 6-10 folds from blood redistribution. New theory appears to be clear in physiology. Fourth, we try to explain mechanism of muscle blood flow increase due to blood flow redistribution. QUESTION: The mechanism of muscle blood flow increase during exercise is unclear. HYPOTHESIS: We try to use exercise tissues, changes P02 (dominant) ↑Trinity↑ to explain blood flow redistribution. EXPLANATIONS: At rest, opened capillary, more higher P02 arterial blood (low PCO2 and low [H+]↑) and then resulted in this capillary closed. After time passed, mitochondria uptake O2, lower P02 to the capillary, i.e. O2 supply tissues are alternatively opened and more closed. During exercise, mitochondria materials oxygenate rate increased to match energy demand, resulted in fast P02 decrease (PCO2 and [H+] increases). They progressively increase capillary opened rate and time, and relax more arterial vascular structures. At peak exercise, all arterial vascular structures maximally opened and all capillaries continues opened. But O2 supply still less than demanded, body via nerve and blood systems to increase blood vascular tone and contraction, then decrease blood flow into other exercise tissues. Finally, at peak exercise, blood flow relative percentage of total CO increased from ~10% to up 85-90% of CO while the CHF increased 3-5 folds.

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

Xue-Guo Sun1,2
2INTRODUCTION: In physiology, ventilation control and regulation, cardiovascular and metabolic regulation was discussed separately but none of combining discussion. New theory appears to be clear in physiology. Fourth, we try to explain mechanism of muscle blood flow increase due to blood flow redistribution. QUESTION: The mechanism of muscle blood flow increase during exercise is unclear. HYPOTHESIS: We try to use exercise tissues, changes P02 (dominant) ↑Trinity↑ to explain blood flow redistribution. EXPLANATIONS: At rest, opened capillary, more higher P02 arterial blood (low PCO2 and low [H+]↑) and then resulted in this capillary closed. After time passed, mitochondria uptake O2, lower P02 to the capillary, i.e. O2 supply tissues are alternatively opened and more closed. During exercise, mitochondria materials oxygenate rate increased to match energy demand, resulted in fast P02 decrease (PCO2 and [H+] increases). They progressively increase capillary opened rate and time, and relax more arterial vascular structures. At peak exercise, all arterial vascular structures maximally opened and all capillaries continues opened. But O2 supply still less than demanded, body via nerve and blood systems to increase blood vascular tone and contraction, then decrease blood flow into other exercise tissues. Finally, at peak exercise, blood flow relative percentage of total CO increased from ~10% to up 85-90% of CO while the CHF increased 3-5 folds.
namically matching mitochondria oxygenation rate with energy demand, so return blood has relatively normal (i.e. high) PvO2. During exercise, progressively increased capillary opened rate and time, relax arterial vassals increase venous return. However, O2 supply is still less than demand, higher metabolic [H+] (above anaerobic thresholds) helps to unload more O2 at and higher percentage of blood passed muscles results in lower PvO2. Lower PvO2 arrive at lung, larger PA-VO2 and faster loading O2 in blood, then larger magnitude of PaO2 up-down wave inspiratory-expiratory period. It, via fast peripheral sensors, increases both ventilation and blood flow in dynamically matching. During this period, relatively higher averaged/mean PaCO2 and [H+], via central chemical sensors, increase gain too. All together, CO increases 3-5 folds for optimal matching with ventilation for optimal O2 exchange.

13.12 AUTONOMIC MODULATION: EMERGING PARADIGM FOR CARDIOVASCULAR TREATMENT?
Kenneth J. Dormer1, Sunny. S. Po2,3, Benjamin J. Scherlag3

Objective: Consider physiological interventions of the autonomic nervous system (ANS) as they relate to treatments for cardiovascular diseases and note a developing theme for autonomic modulation. Summary: Increasingly, experimental and clinical data on ANS denervation or stimulation are reporting therapeutic effects: a) Regional radiofrequency catheter ablation of atrial ganglionated plexus (GP) restored sinus rhythm in 71% of patients with atrial fibrillation (AF); b) Low level electrical stimulation of the vago-sympathetic trunks significantly suppresses AF inducibility in the canine; c) Likewise, we demonstrated that polymeric microparticles (110 nm) delivering a neurosuppressant payload and targeted by an external magnetic field to GP, suppressed/prevented AF inducibility; d) Vaso-vagal syncope (inntricad cardiac ANS dysreflexia) had no recurrence in patients with partial GP ablation. Drug resistant hypertension was significantly reduced out to 22% months, with increased insulin sensitivity in hypertensive patients receiving renal nerve catheter ablation. Additionally, probably slowing of chronic kidney disease progression occurred following renal nerve ablation. Conclusion: Together these observations suggest that targeted ANS denervation or suppression, by devices or nanomaterials, may present as future therapeutic cardiovascular interventions.

13.13 CARDIOVASCULAR AUTONOMIC CONTROL IN THE FIRST YEAR AFTER SPINAL CORD INJURY
Jessica Inskip1,2, Maureen McGrath1, Brian Kwan1,3, Victoria Claydon1, Simon Fraser Univ., Burnaby, BC, Canada.

Autonomic pathways that travel in the spinal cord are susceptible to spinal cord injury (SCI) and their disruption can result in a range of cardiovascular dysfunctions. The development and evolution of these complications remains poorly understood. Here we sought to evaluate cardiovascular function in the first year after traumatic SCI using spectral analyses. Resting supine beat-to-beat blood pressure and 3-lead electrocardiography were recorded during supine rest for 15 minutes at several time points in the first year post-injury. Here we present results from recordings performed in the first two weeks after injury, and again at one-year, on the same eight subjects: four with cervical SCI and four with low thoracic injuries. Also, we demonstrated that polymeric microparticles (110 nm) delivering a neurosuppressant payload and targeted by an external magnetic field to GP, suppressed/prevented AF inducibility; d) Vaso-vagal syncope (inntricad cardiac ANS dysreflexia) had no recurrence in patients with partial GP ablation. Drug resistant hypertension was significantly reduced out to 22% months, with increased insulin sensitivity in hypertensive patients receiving renal nerve catheter ablation. Additionally, probably slowing of chronic kidney disease progression occurred following renal nerve ablation. Conclusion: Together these observations suggest that targeted ANS denervation or suppression, by devices or nanomaterials, may present as future therapeutic cardiovascular interventions.

13.14 HEART RATE VARIABILITY RESPONSES TO EXERCISE IN THAI BRUGADA SYNDROME SURVIVORS
Raoyin Channavirut1, Pattarapong Makarakwat2, Naruemon Leelayuwat2

Brugada syndrome is one of major causes of sudden death in male Southeast Asian population. Previous studies suggested that an abnormality of autonomic modulation may be related to the syndrome. Therefore, the objective of this study was to assess and compare responses of autonomic nervous system to exercise testing between Thai Brugada Syndrome survivors and age-matched healthy subjects. Fifteen males per group performed an incremental exercise testing on electromagnetic cycle ergometer. Electrocardiogram was recorded throughout the process and was analyzed for Heart rate variability (HRV) to identify autonomic function. The protocol was conformed to the Declaration of Helsinki and was approved by the local ethics committee. There was no difference in autonomic activity between the groups during resting. However, Brugada survivor group showed a significantly higher parasympathetic activity (p<0.05) during a final stage of testing, 1 min of HRV testing. These findings may provide useful information for early detection and intervention of this abnormality in Brugada syndrome survivors.

14.0: DEVICE THERAPY FOR HYPERTENSION AND HEART FAILURE

14.1 INSIGHT INTO LONG-TERM NEURAL CONTROL OF ARTERIAL PRESSURE BY CHRONIC BAROREFLEX ACTIVATION
Thomas Lohmeier1, Radu Iliescu2
1Physiology, Univ. of Mississippi Med. Ctr., 2500 N. State St., Jackson, MS, 39216-4505.

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


14.2 WHEN THE LEVEE BREAKS: SYMPATHETIC CONTROL OF SPLENIC VESSELS LEADING TO ACUTE HEART FAILURE
Mark E. Dunlap
Heart & Vascular Ctr., MetroHealth Campus of Case Western Res. Univ., Cleveland, OH.

A growing body of evidence reveals that most patients do not experience net weight gain prior to an acute heart failure event. Support: NIH HL-51971.

When the levee breaks: Sympathetic control of splanchic vessels leading to acute heart failure. Support: NIH HL-51971.
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*Indicates Invited Speaker
2012 APS Intersociety Meeting

The Integrative Biology of Exercise VI

Meeting Program

Westin Westminster Hotel
Westminster, Colorado
October 10-13, 2012

2012 APS Intersociety Meeting
The Integrative Biology of Exercise VI

APS Council

President  Past President  President-Elect
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John C. Chatham  Hannah V. Carey  Martin Frank
Ronald M. Lynch  Thomas A. Pressley  Hershel Raff
Jeff M. Sands  

Conference Organizers

P. Darrell Neufer (Chair)
East Carolina Univ.

Keith Baar  Frank W. Booth  David A. Brown  Paige C. Geiger
Univ. of California, Davis  Univ. of Missouri, Columbia  East Carolina Univ.  Kansas Univ. Med. Ctr.

Mark Hargreaves  Judy Muller-Delp  Michael J. Joyner  William J. Kraus
Univ. of Melbourne, Australia  Univ. of Florida  Mayo Clinic  Duke Univ.

Deborah M. Muoio  Henriette Pilegaard  Espen Spangenburg  Scott W. Trappe
Duke Univ.  Univ. of Copenhagen, Denmark  Univ. of Maryland  Ball State Univ.

Acknowledgements

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

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

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

Location:
The 2012 APS Intersociety Meeting: The Integrative Biology of Exercise VI will be held October 10—13, 2012 at the Westin Westminster Hotel, 10600 Westminster Blvd., Westminster, CO 80202, telephone (303) 410-5000, FAX:(303) 410-5005.

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

On-Site Registration Fees:
APS Member……………………..$600
ACSM Member……………………$600
CSEP Member……………………$600
APS Retired Member……………$400
Nonmember………………………$700
Postdoctoral……………………..$450
Student…………………………$400

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

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

Payment Information:
Registrants may pay by institutional or personal check, traveler’s check, MasterCard, VISA or American Express. Checks must be payable to “The American Physiological Society” and drawn on a United States bank payable in US dollars.

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

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

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

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

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

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

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

Target Audience:
The intended audience for this meeting includes all professionals involved in teaching, research, and clinical fields related to exercise biology.
### DAILY SCHEDULE

**THURSDAY, OCTOBER 11, 2012**

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<th>Wells, F. Booth, and J. S. Rector. Univ. of Missouri, Columbia.</th>
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#### Symposium I

**1.0** INTEGRATING HUMAN "OMICS" TO THE MOLECULAR PHYSIOLOGY OF EXERCISE  
**Thurs., 8:30 - 10:45 AM, Standley Ballroom.**

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

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<td>9:35 AM</td>
<td>1.4 Modulation of the Proteome by Exercise. Dustin Hittel. Univ. of Calgary, Canada.</td>
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#### Symposium II

**2.0** MECHANISMS BEHIND ADAPTATIONS TO PHYSICAL ACTIVITY/INACTIVITY  
**Thurs., 8:30 - 10:45 AM, WB III/IV.**

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

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<td>8:35 AM</td>
<td>2.2 Role of PGC-1α in Exercise-Induced Adaptations in Skeletal Muscle. Christophe Handschin. Univ. of Basel.</td>
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<td>9:05 AM</td>
<td>2.3 Exercise-Induced Autophagy in Skeletal Muscle Adaptations. Zhen Yan. Univ. of Virginia.</td>
</tr>
<tr>
<td>9:35 AM</td>
<td>2.4 Role of DNA Methylation in Exercise-Induced Adaptations. Romain Barres. Univ. of Copenhagen, Denmark.</td>
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<td>10:05 AM</td>
<td>2.5 Molecular Mechanisms Regulating Insulin Sensitivity in Skeletal Muscle with Activity/Inactivity. Jorgen Wojtaszewski. Univ. of Copenhagen, Denmark.</td>
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#### Plenary Lecture

**P1** PLENARY LECTURE  
**Thurs., 11:00 AM - 12:00 Noon, WB III/IV.**


#### Poster Session

**3.0** GENOMICS/PROTEOMICS  
**Thurs., 1:15 - 3:15 PM, WB I/II.**

**Board #**


2. **Molecular Signatures of Adipose Tissue in an Ossabaw Swine Model of Childhood Obesity Using Transcriptome Analysis. R. Toedebusch, K.**
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<td>EXERCISE AND DRUG INTERACTIONS</td>
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<td>17</td>
<td>6.1 Rat Metabolic Responses During Treadmill Running Following Doxorubicin Injections in Sedentary and Exercise Trained Rats. K. Keneffieck, J. Smith, E. Bredahl, and D. Hydock.</td>
<td>Univ. of Northern Colorado.</td>
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<td>20</td>
<td>6.4 Tissue Specific Effects of Acetaminophen and Treadmill Exercise on Collagen Content in Male Wistar Rats. C. Carroll, A. Peterson, and T. Broderick.</td>
<td>Midwestern Univ.</td>
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<td>6.7 MAC25 Promotes Muscle Hypertrophy by Coordinating both IGFII and Tgf beta Pathways. B. Yaden, A. Ryan, G. Dai, and V. Krishnan.</td>
<td>Indiana Univ, Purdue Univ, Indianapolis, and Eli Lilly and Co.</td>
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<td>24</td>
<td>6.8 Influence of Nrf2 Activator Supplementation on Physiological Responses to Short Term Sprint Exercise.</td>
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<td>6.9 Effects of the Phosphodiesterase-5 Inhibitor Tadalafil on Physiological Responses During Sub-maximal Exercise in Normoxia. C. Buzzacchera, L. Guidetti, L. Di Luigi, M. G. Gallotta, P. Sgrò, G. P. Emerenzian, E. Franciosi, and C. Baldari.</td>
<td>Univ. of Rome Foro Italico, Italy, and North Univ. of Parana, Brazil.</td>
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<td>7.0 Nitrous Oxide Narcosis and Hyperthermia Enhance the Pattern of Breathing During Light Exercise. K. Henderson, S. Ghaflari, P. L. L. McDonald, M. L. Walsh, and M. D. White.</td>
<td>Simon Fraser Univ, Burnaby, Canada.</td>
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<td>7.5 A 28 Day Sojourn to 3454m Diminishes Skeletal Muscle Respiratory Capacity but Enhances Efficiency in Humans. R. Jacobs, A-K. Meinally, and C. Lundbye.</td>
<td>Univ. of Zurich, Switzerland.</td>
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<td>35</td>
<td>7.9 Glycolytic Skeletal Myofibers Display Higher P/O Ratios than Cardiac Myofibers Due to Adenylate Kinase: Preliminary Findings Using a Novel</td>
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Specific Effects on Protein Synthesis. Fdn., Oklahoma City, and Univ. of Oklahoma Hlth. and E. Anderson.

NFATc3 Regulates Muscle Fiber-Type Transition Independently From the Activation of Calcineurin During Long-Term Endurance Training in Rats. A. Aguilar, I. Vechetti-Júnior, F. Almeida, and M. Dal-Pai-Silva.

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


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


MOLECULAR REGULATORY MECHANISMS

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


AGING

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

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<th>Personalized Medicine Track</th>
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<td>RAGE and STAT3 Signaling in Chronic AICAR-Treated Young Adult and Old Skeletal Muscle. M. Jacobs, S. Hardman, T. Moore, J. Lew, P. Reynolds, and D. Thomson. Brigham Young Univ.</td>
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### 10.0 PERSONALIZED EXERCISE PRESCRIPTION BASED UPON INTEGRATIVE BIOLOGY

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

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

**3:15 PM**

10.1 Introduction. Frank Booth, Univ. of Missouri, Columbia.


10.3 Gene-Activity/Inactivity Interaction. Flemming Dela. Univ. of Copenhagen, Denmark.

**4:20 PM**

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

10.5 Lifestyle Medicoparmacogenetics. William J. Kraus, Duke Univ. Sch. of Med.

### Symposia IV  
**Exercise Adaptations Track**

**11.0 ACETYLATION: LINKING CHANGES IN NAD TO METABOLISM AND GROWTH**

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

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

**3:15 PM**

11.1 Introduction. Keith Baar. Univ. of California, Davis.


11.3 Regulation of the Adaptive Response to Exercise by the Acetyltransferase GCN5. Keith Baar. Univ. of California Davis.

**4:20 PM**


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**Plan to Attend the Welcome and Opening Reception**

**Wednesday, October 10**

**6:00 – 10:00 PM**

**The Lake House**

---

C-36
### DAILY SCHEDULE

**FRIDAY, OCTOBER 12, 2012**

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<th>Time</th>
<th>Session</th>
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<td>8:30 AM</td>
<td>Symposium V</td>
<td>Cardiovascular Track</td>
<td>Fri., 8:30 - 10:45 AM, WB III/IV.</td>
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<tr>
<td>8:30 AM</td>
<td><strong>12.0</strong> CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM ANIMAL STUDIES</td>
<td>Fri., 11:00 - 12:30 Noon, Standley Ballroom.</td>
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<tr>
<td>10:05 AM</td>
<td>Symposium VI</td>
<td>Lipid Metabolism Track</td>
<td>Fri., 11:00 AM - 12:00 Noon, WB III/IV.</td>
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<tr>
<td>10:05 AM</td>
<td><strong>13.0</strong> FIT, FAT AND LEAN LIVER: EXERCISE ADAPTATIONS IN NON-TRADITIONAL TISSUES</td>
<td>Fri., 8:30 - 10:45 AM, WB III/IV.</td>
<td></td>
</tr>
<tr>
<td>1:50 PM</td>
<td>Symposium VIII</td>
<td>Lipid Metabolism Track</td>
<td>Fri., 1:15 - 3:30 PM, WB III/IV.</td>
</tr>
<tr>
<td>1:50 PM</td>
<td><strong>15.0</strong> CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM HUMAN STUDIES</td>
<td>Fri., 1:15 - 3:30 PM, Standley Ballroom.</td>
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<tr>
<td>1:50 PM</td>
<td><strong>15.3</strong> Improved Cardiac Function in Obese Adolescents: Reversal by Aerobic Interval Training.</td>
<td>Charlotte Ingul. Norwegian Univ. of Sci. &amp; Tech., Trondheim, Norway.</td>
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<tr>
<td>2:20 PM</td>
<td><strong>15.4</strong> Effects of Interventional and Lifelong Exercise on Left Ventricular Compliance and Diastolic Function in Aged Subjects.</td>
<td>Benjamin Levine. Texas Hlth., Presbyterian Hosp.</td>
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<td>2:20 PM</td>
<td><strong>15.5</strong> Exercise Attenuates the Premature Cardiovacular Aging Effects of Type 2 Diabetes Mellitus.</td>
<td>Amy Huenchmann. Univ. of Colorado Sch. of Med.</td>
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<tr>
<td>2:50 PM</td>
<td>Career Session</td>
<td>THE INS AND OUTS OF AUTHORSHIP</td>
<td>Fri., 3:45 - 4:45 PM, Standley Ballroom.</td>
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<tr>
<td>2:50 PM</td>
<td><strong>17.0</strong> THE INS AND OUTS OF AUTHORSHIP</td>
<td>Fri., 7:00 - 9:30 PM, WB I/II.</td>
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<tr>
<td>3:45 PM</td>
<td><strong>18.0</strong> MICROCIRCULATION</td>
<td>Fri., 7:00 - 9:30 PM, WB I/II.</td>
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**PLENARY LECTURE**

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<tr>
<td>11:00 AM</td>
<td>PLENARY LECTURE</td>
<td>Fri., 11:00 AM - 12:00 Noon, WB III/IV.</td>
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<tr>
<td>11:00 AM</td>
<td><strong>14.1</strong> Adaptations of the Heart: Traditional and Non-Traditional Research Approaches.</td>
<td>Leslie Leinwand. Univ. of Colorado, Boulder.</td>
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**SYMPOSIUM V**

- Chair: David Brown, East Carolina Univ.

**SYMPOSIUM VI**

- Chair: Espen Spangenberg, Univ. of Maryland, College Park.

**SYMPOSIUM VII**

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

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<tr>
<td>5</td>
<td>18.5</td>
<td>The Impact of Neuronal Nitric Oxide Synthesis Expression on Running Performance and the Capillary System in Skeletal Muscle of Mice. O. Baum, and H. Hoppeler. Univ. of Bern, Switzerland.</td>
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<tr>
<td>7</td>
<td>18.7</td>
<td>Chronic Heart Failure and Muscle Microvascular Oxygenation: Effects of Exercise Training. D. Hirai, S. Copp, S. Ferguson, C. Holdsworth, G. Sims, T. Musch, and D. Poole. Kansas State Univ.</td>
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<td>8</td>
<td>18.8</td>
<td>The Effects of Acute Dietary Nitrate Supplementation on Muscle Microvascular Oxygenation in Contracting Rat Muscle. S. Ferguson, D. Hirai, S. Copp, C. Holdsworth, T. Musch, and D. Poole. Kansas State Univ.</td>
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<td>9</td>
<td>19.0</td>
<td><strong>BLOOD FLOW REGULATION</strong> Fri., 7:00 - 9:30 PM, WB III.</td>
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**CARDIOVASCULAR** Fri., 9:30 - 11:30 AM, WB III.  

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<td><strong>CARDIOVASCULAR</strong> Fri., 7:00 - 9:30 PM, WB III.</td>
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**Don't forget to visit the Exhibits—open daily during the Poster Sessions**
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<tr>
<td>28.1</td>
<td>Acute Exercise and Activation of Nitric Oxide Synthase in Aorta of Rats: Role of Reactive Oxygen Species, Akt and AMP-Activated Protein Kinase.</td>
<td>C. De Souza, T. Luciano, S. Marques, D. Souza, and R. Pinho. Univ. do Extremo Sul Catarrinhense, Criciúma, Brazil.</td>
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<tr>
<td>29.1</td>
<td>Effects of Voluntary Wheel Running on Aortic Doxorubicin Accumulation and Dysfunction.</td>
<td>N. Gibson, S. Greufe, D. Hydock, and R. Hayward. Univ. of Northern Colorado.</td>
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<td>32.1</td>
<td>Chronic Low-Intensity Interval Exercise Training Increases Cardiac Torsion and is Associated with Enhanced Systolic and Early Diastolic Strain Rate in Mini-Swine with Compensated Heart Failure.</td>
<td>K. Marshall, C. Weimer, and C. Enter. Univ. of Missouri, Columbia.</td>
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<tr>
<td>35.1</td>
<td>Effects of High Intensity Intermittent Training on Aerobic Capacity, Endurance Capacity and Short Term Recovery.</td>
<td>J. Eigendorf, and N. Maassen. Leibniz Univ., Hannover, Germany.</td>
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<tr>
<td>36.20</td>
<td>Factors Limiting Aerobic Capacity: Cardiopulmonary or Peripheral? G. Crocker, and J. Jones. Univ. of California, Davis.</td>
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**CHO/LIPID METABOLISM**

**DAILY SCHEDULE**

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<td>38.1</td>
<td>Insulin Signaling in Myotubtes Derived from Obese Adults was not Impaired in Response to a Mixture of Fatty Acids Resembling that Found in Human Plasma.</td>
<td>A. Park, J. P. Gumucio, A. Hinko, S. A. Newsom, and J. F. Horowitz. Univ. of Michigan.</td>
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<tr>
<td>44.1</td>
<td>Acute Heat Treatment Alters Adipose Tissue Fatty Acid Handling. R. Rogers, M-S. Beaudoin, J. Wheatley, D. C. Wright, and P. C. Geiger. Univ. of Kansas Med. Ctr., and Univ. of Guelph, Canada.</td>
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<tr>
<td>45.1</td>
<td>The Upregulation of Genes Involved in Fatty Acid Oxidation is Depressed with Severe Obesity. J. Mangles, J. Brault, T. Weber, G. Battaglia, S. Alavi, G. Dubis, L. Consitt, and J. Howard. East Carolina Univ., Univ. of Illinois at Chicago, and Ohio Univ.</td>
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<tr>
<td>47.1</td>
<td>Activation of the Fat Metabolism by High-Intensity Sprint Exercise. M. Maassen, H. Starke, K. Sutro, M. Alexander, and G. Maassen. Leibniz Univ., Hannover, Germany.</td>
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<tr>
<td>48.1</td>
<td>Erythropoietin Increases Mitochondrial Capacity in White Adipose Tissue in Mice. V. Diaz, R. A. Jacobs, C. Lundby, and M. Gassmann. Univ. of Zurich, Switzerland.</td>
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22.0 MUSCLE INJURY
Fri., 7:00 - 9:30 PM, WB III.


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


23.0 MUSCLE FUNCTION AND ADAPTATION II
Fri., 7:00 - 9:30 PM, WB III.


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

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


24.0 EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE
Fri., 7:00 - 9:30 PM, WB III.

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

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<th>THE IMPACT OF HEAT SHOCK PROTEIN EXPRESSION ON MUSCLE METABOLISM, EXERCISE CAPACITY AND DISEASE PREVENTION</th>
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<th>INTEGRATED EXERCISE RESPONSE</th>
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30.0 SIGNALLING
Sat., 1:15-3:15 PM. WB I/II.


30.4 Aerobic Exercise Training Increases APPL1 Expression and Improves Insulin Signaling in the Liver of Obese Mice. R. Marinho, E. C. Ropelle, D. Cintra, L. Pauli, C. Souza, A. Silva, L. Moura, E. Ropelle, and J. R. Pauli. State Univ. of São Paulo, Rio Claro, Brazil, and Estate Univ. of Campinas, Limeira, Brazil.


30.6 Smad3 is Sufficient to Inhibit Protein Synthesis and Induce Muscle Fiber Atrophy In Vivo. C. Goodman, R. McNally, M. Hoffmann, and T. Hornberger. Univ. of Wisconsin, Madison.


31.0 INFLAMMATION
Sat., 1:15-3:15 PM. WB I/II.

31.1 PGC-1α is Required to Prevent an Age-Associated Increase in TNFa and for Decreased TNFa Protein in Skeletal Muscle with Combined Exercise Training and Resveratrol. J. Olesen, C. Brandt, J. Pedersen, K. Weihe, S. Ringholm, and H. Pleiggaard. Univ. of Copenhagen, Denmark.

31.2 Exercise Reverses High-Fat Diet Induced Neuropathy in Pre-Diabetic Mice. B. Guilford, A. Groover, J. Ryals, R. Swerdlov, and D. Wright. Univ. of Kansas Med.Ctr.


31.9 Estrogen Status and the IL-6 Response to Prolonged Endurance Exercise. A. C. Hackney, K. Kolunt, and A. Kallman. Univ. of North Carolina.


32.0 LATE BREAKING ABSTRACTS


32.2 Reductions of PEPCK in Adipose Tissues from CD36 KO Mice. Z. Wan, S. Matravadia, D. J. Philbrick, Graham P. Holloway, and D. C. Wright. Univ. of Alberta, Edmonton, Canada, and Univ. of Guelph, Canada.


32.7 Bronchodilation During Exercise in Patients with Cystic Fibrosis, Comparison to Albuterol Administration. M. C. McCue, C. M. Wheatley, S. E. Baker, M. A. Morgan, E. C. Wong, M. Sattler, and E. M. Snyder. Univ. of Minnesota.


32.9 Interlukin-6 and Adipose Tissue Insulin Resistance During the Recovery from Exercise. L. Castellani, C. G. R. Perry, J. Root-McCrae, and D. C. Wright. Univ. of Guelph, Canada, and York Univ. Canada.


32.11 Role of the Novel Tissue-Specific PGC-1 and ERR-Induced Regulator PERM1 in Muscle. Y. Cho, B. Hazen, A. Russell, and A. Kralli. Scripps Res. Inst., La Jolla, California, and Deakin Univ., Burwood, Australia.

Chair: P. Darrell Neuf, East Carolina Univ.


3:50 PM 33.3 Mitochondria, Hyperglycemia, Redox and Cardiac Dysfunction in Type 2 Diabetes. Miguel Aon. Johns Hopkins Univ.


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

3:15 PM 34.1 Introduction. Keith Baar. Univ. of California, Davis.

3:20 PM 34.2 The Role of mTOR in Skeletal Muscle Hypertrophy. Troy Hornberger. Univ. of Wisconsin, Madison.

3:50 PM 34.3 Myostatin and the Control of Muscle Size. David L. Allen. Univ. of Colorado.

4:20 PM 34.4 Satellite Cells as Mediators of Skeletal Muscle Hypertrophy. Marcus Bamman. Univ. of Alabama at Birmingham.

4:50 PM 34.5 Molecular Connections Underlying the Hypertrophic Response to Loading. Keith Baar. Univ. of California, Davis.
# Abstracts of Invited and Contributed Presentations

## Thursday, October 11

1.0  Integrating Human “Omics” to the Molecular Physiology of Exercise .................. C-46  
2.0  Mechanisms Behind Adaptations to Physical Activity/Inactivity ............................. C-46  
3.0  Genomics/Proteomics ............................................................................................... C-46  
4.0  Gender Differences .................................................................................................. C-47  
5.0  Physical Inactivity and Chronic Disease .................................................................. C-47  
6.0  Exercise and Drug Interactions .............................................................................. C-49  
7.0  Muscle Function and Adaptation I .......................................................................... C-50  
8.0  Molecular Regulatory Mechanisms ......................................................................... C-53  
9.0  Aging ....................................................................................................................... C-55  
10.0 Personalized Exercise: Prescription Based Upon Integrative Biology ....................... C-57  
11.0 Acetylation: Linking Changes in NAD to Metabolism and Growth .......................... C-58  

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12.0 Cardiovascular Benefits of Exercise: Insight from Animal Studies ......................... C-59  
13.0 Fit, Fat and Lean Liver: Exercise Adaptations in Non-Traditional Tissues ....................... C-59  
15.0 Cardiovascular Benefits of Exercise: Insight from Human Studies .............................. C-59  
16.0 Skeletal Muscle Lipid Droplet Biology in Exercise and Disease ............................... C-60  
18.0 Microcirculation ....................................................................................................... C-60  
19.0 Blood Flow Regulation ............................................................................................. C-61  
20.0 Cardiovascular ........................................................................................................... C-63  
21.0 CHO/Lipid Metabolism ............................................................................................. C-66  
22.0 Muscle Injury ............................................................................................................ C-69  
23.0 Muscle Function and Adaptation II ......................................................................... C-69  
24.0 Extracellular Matrix and Connective Tissue ............................................................ C-72  
25.0 Fatigue ..................................................................................................................... C-72  

## Saturday, October 13

26.0 Physical Inactivity is Necessary for Optimal Brain Function ..................................... C-72  
27.0 The Impact of Heat Shock Protein Expression on Muscle Metabolism, Exercise Capacity and Disease Prevention ................................................................. C-73  
29.0 Integrated Exercise Response ..................................................................................... C-73  
30.0 Signalling .................................................................................................................. C-79  
31.0 Inflammation ............................................................................................................ C-80  
32.0 Late-Breaking Abstracts ............................................................................................ C-82  
33.0 Hot Topics in Exercise Physiology ........................................................................... C-84  
34.0 Unified Cellular and Molecular Mechanism of Muscle Hypertrophy ......................... C-85  

**Author Index** .................................................................................................................. C-87
1.0: INTEGRATING HUMAN "OMIC" TO THE MOLECULAR PHYSIOLOGY OF EXERCISE

1.2 MODULATION OF SMALL MOLECULE METABOLITES IN PERIPHERAL BLOOD AND SKELETAL MUSCLE

Kim Huffman1,2
Mass spectroscopy-based quantification of metabolic intermediates, or metabolic profiling, is increasingly providing insight into the pathways and underlying mechanisms for exercise-mediated improvements in metabolic health. Metabolomic platforms can measure concentrations of metabolic intermediates including amino acids, fatty acids, and acylcarnitines, which are by-products of fatty acid and amino acid catabolism. Using plasma and skeletal muscle from participants of STRRIDE, a randomized controlled exercise training intervention, we are evaluating training-induced responses in metabolic intermediates. In this session, we will discuss analytic issues associated with tissue-based metabolomics. In this session, we will discuss analytic issues associated with tissue-based analyses and data complexity. We will summarize responses observed in metabolic intermediates as a result of exercise training and metabolic modulation relates to changes in insulin sensitivity after six months of exercise training or sedentary activity. For example, we found that reductions in plasma free fatty acids and increases in glycerol and proline are related to improvements in insulin action. Also, modulation of saccinate in skeletal muscle is associated with improvements in insulin action, identifying amino acid metabolism as a key component of metabolic adaptations to even aerobic exercise training. Last year we discussed how these findings might inform our understanding of how exercise training improves metabolic health and guide future studies to derive more knowledge about exercise-mediated metabolic benefits.

1.4 MODULATION OF THE PROTEOME BY EXERCISE

Dustin Hittel1, Jane Shearer2
1Kinesiology, Univ. of Calgary, 2500 University Dr. NW, Calgary, AB, T2N 1N4, Canada.
An integrative model of the molecular physiology of exercise needs to account for all concurrent processes in a cell, tissue or organism. This will only be possible when all biochemical interactions can be quantified in a single biological sample. In my talk I will discuss the many contributions and current limitations of proteomics as it is applied to our understanding of the biology of exercise. Specifically, I will discuss two current projects in my lab that attempt overcome the complexity of the proteome by focusing on the modulation of protein post-translational modifications. The first project involves the quantification of the phospho-proteome of muscle cells in response to the atrophy-inducing protein myostatin. The goal of this project is to use proteomics to better understand the cellular signaling events that govern both muscle atrophy and hypertrophy. The second project involves the quantification of O-linked N-acetylglucosamine (O-GlcNAc) on erythrocyte proteins in response to glycemic status and exercise. O-GlcNAc levels are in part, responsive to cellular glucose supplies and linked to metabolic diseases with perturbed glucose homeostasis such as type 2 diabetes. O-GlcNAc levels can also be modulated by exercise, as exercise results in a number of beneficial changes such as improved glycemic control. As such, we are currently determining if O-GlcNAc is more sensitive than HbA1c as an early marker for pre-diabetes.

2.0: MECHANISMS BEHIND ADAPTATIONS TO PHYSICAL ACTIVITY/INACTIVITY

2.2 ROLE OF PGC-1α IN EXERCISE-INDUCED ADAPTATIONS IN SKELETAL MUSCLE

Christian Handschin
Biozentrum, Univ. of Basel, Div. of Pharmacology/Neurobiology, Klingelbergstrasse 70, Basel, 4056, Switzerland.
Skeletal muscle cells exhibit high plasticity upon stimulation, e.g. a profound remodeling of myofilibril and metabolic properties induced by regular exercise. The transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) is one of the key regulators of endurance exercise adaptation in skeletal muscle. Many of the major signaling pathways that are activated in a contracting muscle fiber converge on PGC-1α by inducing gene expression, promoting posttranslational modifications of the PGC-1α protein, or by doing both. In turn, elevated expression and enhanced activity of PGC-1α result in the coordinated regulation of the transcriptional programs that mediate exercise adaptation in muscle. We now provide evidence that muscle-specific expression of PGC-1α is sufficient to promote an oxidative phenotype of skeletal muscle cells by remodeling of the neuromuscular junction, modulation of calcium homeostasis, coordinated regulation of catabolic and anabolic metabolic pathways and regulation of the contractile properties. Moreover, we delineated the transcriptional network that controls these adaptations involving the specific antagonistic action of coactivator and co-repressor protein complexes. These findings have important implications for our understanding of skeletal muscle cell biology, plasticity in inactive and trained muscle, as well as the therapeutic application of potential “exercise mimetics”, pharmacological agents that elicit exercise-like effects in muscle, in various muscle diseases. Supported by the Swiss National Science Foundation, Gebert-Rüf Foundation and the University of Basel. Summerratter, S. and Handschin, C. (2012) Int J Obes, epub ahead of print.

2.3 EXERCISE-INDUCED AUTOPHAGY IN SKELETAL MUSCLE ADAPTATION

Zhen Yan1, Vitor Liang2, Mitsuharu Okutsu3, Mei Zhang1
1Dept. of Med., Univ. of Virginia, 409 Lane Rd., Charlottesville, VA, 22903.
Autophagy, a catabolic process for clearance of aggregated proteins and damaged organelles (e.g. mitochondria), is required for normal muscle function. Acute exercise activates autophagy in skeletal muscle; however, it is unknown whether exercise training promotes autophagy and whether autophagy is required for skeletal muscle adaptation. Here, we report that long-term (4 weeks) voluntary wheel running promotes basal autophagy in recruited plantaris muscle in mice as shown by increased protein expression of autophagy regulatory genes (Atg6/Becn1, Atg7, Atg3) and increased autophagy flux (increased LC3-II and decreased p62/Sqstml). Similar directional changes were found when comparing slow-twitch, oxidative soleus muscle with intermediate plantaris and fast-twitch, glycolytic white vastus lateralis muscles. We also found that transgenic mice with muscle-specific overexpression of PGC-1α have increased basal autophagy with elevated Bnip3 expression, but not significant increases in Atg6 and LC3, suggesting that PGC-1α is sufficient to promote autophagy likely through other mechanism(s). Finally, voluntary exercise-induced improvement of endurance capacity is absent in heterozygous Atg6 knockout mice (Atg6+/−) along with attenuated increases in markers of mitochondrial biogenesis, autophagy and autophagy flux in plantaris muscle and blunted improvement of whole body glucose clearance. These findings suggest that endurance exercise training promotes basal autophagy in skeletal muscle and that autophagy is required for mitochondrial biogenesis, as well as improved exercise capacity and insulin sensitivity.

3.0: GENOMICS/PROTEOMICS

3.1 GLOBAL MUSCLE GENE EXPRESSION AFTER SHORT EXERCISE

Andreas Montelä1, Ilkka Rundvall2, Mona Essbjörnsson2, Eva Jansson2
Objective: We hypothesized that sprint exercise increases the transcription of a large number of genes due to the profound metabolic and endocrine stress. The objective of measuring global gene expression was to enable a broad assessment of the physiological responses to sprint exercise. Methods: Fourteen healthy subjects performed three 30-s sprints exercise with 20 minutes rest-in-between. Vastus lateralis samples were obtained at rest and 120 minutes after the third sprint. RNA was analyzed on Human Gene 1.0 ST Array. Differential expression was calculated by ANOVA. An FDR cutoff of 10% yielded 928 differentially expressed genes. Downstream analysis was performed using IPA (Ingenuity Pathway Analysis), comprising tests for canonical pathways, genetic networks and transcription regulators. Results: Gene ontology analysis revealed tissue remodeling processes, involving effects on gene expression, cell cycle, growth and proliferation. Pathway analysis pointed to changes in hormonal and cytokine signaling. A transcription factor activity analysis showed recurring physiological themes. The downstream gene list of HIF1A, CREB, NOTCH, FOXO2, BRAC1, affect energy metabolism, angiogenesis and mitochondrial biogenesis. Conclusion: Acute bouts of sprint exercise seem to initiate muscle tissue remodeling, possibly stimulated by hypoxia together with activity of growth factors and hormones.

3.2 MOLECULAR SIGNATURES OF ADIPOSE TISSUE IN AN OSSABAW SWINE MODEL OF CHILDHOOD OBESITY USING TRANSCRIPTOME ANALYSIS

Ryan Toedebusch1,2, Kevin Wellis3, Frank Booth4, J. Scott Reczek4
Childhood (6-11 yrs old) obesity has increased more than 3-fold in the U.S since 1980. The study objective was to gain an understanding for mechanisms by which adipose tissue expands in young growing animals as a result of a positive caloric balance. Juvenile (8-week old), female Ossabaw swine (n = 6/group) were fed either a high-fat, high-fructose (43.0% fat and 17.8% high fructose corn syrup) or low-fat (10.5% fat) diet for 16 weeks. The high-fat, high-fructose fed animals were fed ~2.5x the number of calories as fed animals (n = 3/group) provided an initial list of five enriched functional-related gene markers of mitochondrial biogenesis, autophagy and autophagy flux in plantaris muscle and blunted improvement of whole body glucose clearance. These findings suggest that endurance exercise training promotes basal autophagy in skeletal muscle and that autophagy is required for mitochondrial biogenesis, as well as improved exercise capacity and insulin sensitivity.
HABITUAL PHYSICAL ACTIVITY PREDICTS DIETARY FAT OXIDATION AND TRAFFICKING

Andrey Begaugman1, Iman Mohammad1, Edwina Amour1, Dale Schoeller1, Carine Platat1, Hubert Vidal1, Martina Leissl2, Flavie Legrain1, Chantal Nonon1, Stephen Briers1,

1DEPE, IPHC/CNRS, 23, rue Becquerel, Strasbourg, 67087, France, 2Dept. of Nutritional Science, Univ. of Wisconsin, 1415 Linden Dr, Madison, WI 53706, 1st Hospitalier Lyon Sud, Service d’Endocrinologie, Diabète, Nutrition, 165 Chemin du Grand Revoyet, Pierre Benite, F-69310, France.

INTRODUCTION: The relationship between energy and lipid balances suggests a key role of physical activity energy expenditure (PAEE) in dietary fat partitioning. This hypothesis still needs to be tested. METHODS: Sedentary (n=10) and active (n=9) lean men and women were trained during 2 months in a detraining condition. PAEE, tissue free fatty acids (FFA), hormone sensitive lipase (HSL), and plasma FFAs were measured at rest and during constant rate exercise (CREE) following a pre-training and 4 weeks post-training. RESULTS: There were significant main effects of time (pre=69.7±43.5, post=243.0±184.4 U/mL; time x sex interaction p<0.05) and gender (M=9.1±3.0, F=8.3±4.2 U/mL; x time interaction p<0.05) on PAEE. There were significant main effects of time (pre=9.1±0.3 Hz, post=7.0±0.3 Hz; time x sex interaction p<0.05) and gender (M=9.1±0.3 Hz, F=8.3±0.2 Hz; time x sex interaction p<0.05) on ventilation frequency (VR). The interaction time x gender was found for PAEE, tissue FFAs, HSL and plasma FFAs. CONCLUSIONS: The present armamentarium of pharmacologic agents can mimic many of these beneficial effects. The present armamentarium of pharmacologic agents can mimic many of these beneficial effects. This study was supported by Grants-in-Aid for Scientific Research. FUNDING: Fondation Coeur et Artères, Plan National de Recherche en Nutrition, CNRS, Université de Strasbourg and CNES.
agents that are like exercise and heat that can restore the low heat shock proteins state of diabetes. Exercise-hyperthermic mimetics improve glycemic control, reduce body weight, restore mitochondrial function, improve insulin signalling, reduce inflammatory cytokines, improve lipid parameters, enhance beta-cell function, and reduce diabetic complications. Recent in vivo and impaired cellular stress response of diabetes corrects a defect that is close to the very pathogenesis of the disease and spawns the development of therapeutic options that are both safe and effective.

5.4 COMPENSATORY RESPONSES OF INSULIN SIGNALING TO STORE MUSCLE GLUCOSE UPTAKE FOLLOWING LONG TERM INACTIVITY

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We investigated the role of muscle activity in maintaining normal glucose homeostasis via transection of the sciatic nerve, an extreme model of inactivity. Mice were sacrificed either 3 days, 10 days, 28 days or 56 days post transection or sham surgery. There was no difference in muscle mass between sham and transected limbs at 3 days post surgery, but there was a significant reduction following transection at the three other time points. Muscle weight stabilized by 28 days post-surgery with no further loss. Glucose uptake of isolated muscle was blunted 3 days after transection, but returned to normal at later time points. In transected muscle there was reduced expression for transcriptional regulators of metabolic genes (PGC-1α, PGC1β, PPARγ), glycogen synthesis (GYS1), fatty acid transport (M-CPT1), and mitochondrial oxidation (CS) genes at 3 and 10 days post-surgery, but this decrease was reached at 56 days. Western blot analysis showed reduced expression of AS160 in transected muscle with a compensatory increase in expression of AKT at 3 days, indicating inability to maintain glucose uptake and signalled reduced sensitivity. Replacement of normal glucose responses in muscle of insulin signaling normal function. These data suggest that necrosis and/or apoptosis may prevent an accurate assessment of the role of inactivity in maintaining glucose homeostasis. This work was supported by NIH grant number 1R15DK085 497-01.A1.

5.5 EFFECT OF CHRONIC SWIM EXERCISE ON ADIPOSITY AND METABOLIC FUNCTION IN MICE

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Diabetes is a major health concern today. Concomitantly, the American diet is composed more of fat and fructose. Chronic exercise has been recommended as a way to attenuate metabolic changes and prevent obesity. This study was undertaken to determine the effects of moderate swim exercise on body fat and metabolic parameters in response to a high fat/high fructose diet in mice. Mice were assigned to one of three groups: Control (standard chow, without exercise, n=10), Sedentary (fat/fructose, without exercise, n=9), and Exercise (fat/fructose, with exercise, n=9). In the Exercise group, mice swam 1 hour/day, 3 days/week for 8 weeks. In humans, this is equivalent to a low/moderate training program. The fat/fructose diet produced a syndrome similar to human diabetes. The sedentary mice developed hyperglycemia, insulin resistance, high body fat (up to 40 percent), and increased lipogenic hormones (insulin and leptin). The exercise paradigm prevented the pathological effects for glucose, insulin, leptin, and glucose tolerance. Exercise did not improve body fat or fat cell size. Glycogen storage and tissue morphology were examined in the liver. The high fat/fructose diet depleted glycogen and caused damage, effects which were partially corrected by the moderate exercise program. Results document the beneficial effects of even moderate exercise on diet-induced diabetes. This study was funded by NIH R01 HL093567.

5.6 INFLAMMATORY PATHWAYS LEADING TO NON ALCOHOLIC FATTY LIVER DISEASE ARE BLunted BY REGULAR RUNNING EXERCISE IN MICE

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Maintenance of normal body weight by being more physically active is associated with prevention of the pathological effects for glucose, insulin, leptin, and glucose tolerance. The exercise paradigm prevented the pathological effects for glucose, insulin, leptin, and glucose tolerance. Exercise did not improve body fat or fat cell size. Glycogen storage and tissue morphology were examined in the liver. The high fat/fructose diet depleted glycogen and caused damage, effects which were partially corrected by the moderate exercise program. Results document the beneficial effects of even moderate exercise on diet-induced diabetes. This study was funded by NIH R01 HL093567.

5.7 HIGH INTRINSIC AEROBIC CAPACITY IS ASSOCIATED WITH GREATER LIVER FATTY ACID OxidATION ADAPTABILITY

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High intrinsic aerobic capacity is inversely associated with diabetes and non-alcoholic fatty liver disease. We previously observed elevated hepatic fatty acid oxidation (FAO) in rats bred for high aerobic capacity [high capacity runners (HCR)] compared to rats bred for low aerobic capacity [low capacity runners (LCR)]. We hypothesized that high aerobic capacity would result in greater hepatic flexibility in lipid metabolism, in response to an acute high-fat diet (HFD) challenge. We examined FAO in liver homogenate and isolated mitochondria of HCR/LCR rats following a 3 day HFD (45% fat). In both strains, HFD resulted in increased daily weight gain (73% HCR, 1.5-fold LCR; p<0.05) and increased feeding efficiency (49% HCR, 2.5-fold LCR; p<0.05). In liver homogenates, HCR rats had 56% greater complete FAO to CO2 relative to diet (p<0.05). Also, HCR rats demonstrated a 15% increase in incomplete FAO on the HFD (p<0.05), with no change observed in LCR rats. In isolated hepatic mitochondria, HCR rats display 73% greater complete FAO compared to LCR (p<0.05), with HFD producing a 40% reduction in HCR rats (p<0.05) but no change in LCR rats. The reduced complete FAO in HCR mito- chondria on HFD was reversed with the addition of ADP or uncoupling agent FCCP to the assay. In conclusion, HCR rats show greater FAO and adaptability to a HFD than LCR rats suggesting that differences in intrinsic aerobic capacity confer differences in hepatic metabolic flexibility for lipid metabolism.

5.8 PHENOTYPIC DIFFERENCES BETWEEN GENERATION 8 RATS SELECTIVELY-BRED TO VOLUNTARILY RUN VERSUS LOW NIGHTLY DISTANCES WITH AN EMPHASIS ON USING VOLUNTARY RUNNING TO PREVENT THE DEVELOPMENT OF JUVENILE OBESITY

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We phenotyped generation 8 (G8) rats that possess high (HVR) versus low (LVR) moti- vations to voluntarily run under two conditions: a) those that voluntarily ran during 28-34 days of age (runners), or b) those that never run until sacrifice at 34 days of age (sitters). RNA-seq data from the nucleus accumbens of these animals will also be presented. HVR male runners ran longer (22.5 vs. 4.1 km, p<0.001), spent more time running (625 vs. 142 min, p<0.001), and ran faster (34.7 vs. 28.8 m/min, p<0.001) than LVR male runners. HVR female runners ran longer (28.3 vs. 5.9 km, p<0.001), spent more time running (770 vs. 194 min, p<0.001), and ran faster (36.2 vs. 29.5 m/min, p<0.001) than LVR female runners. Comparing RNA-seq body compositions (n = 5-7 families) revealed that LVR male and female sitters possessed a 14-26% higher body fat percentage than HVR male sitters (p = 0.003-0.11) despite similar body weights. Visceral adipose tissue weights were 1.5-5.0-fold greater in G8 HVR/LVR male and female sitters versus their runner counterparts. However, significantly reduced body fat percentages in both lines by 35-52% (p < 0.001). Importantly, while HVR runners ran 4.7-5.5-fold higher than LVR runners, body composition and visceral adipose tissue weights between lines were similar after the 6-day running period. Hence, these findings suggest that a range of physical activity is beneficial in preventing the onset of body fat accrual in young rats.

5.9 INTRAMUSCULAR EXPRESSION OF MECHANOSENSORS ANKRD2 AND MYOKINE ANGPTL4 DURING AN ACUTE BOUT OF INACTIVITY

Jacob Brown1, Michael Roberts2, Tom Childs2, Clayton Crabtree3, Frank Booth2


Aerobic capacity is inversely associated with diabetes and non-alcoholic fatty liver disease. We previously observed that HVR runners, with elevated hepatic fatty acid oxidation (FAO) in rats bred for high aerobic capacity [high capacity runners (HCR)] compared to rats bred for low aerobic capacity [low capacity runners (LCR)]. We hypothesized that high aerobic capacity would result in greater hepatic flexibility in lipid metabolism, in response to an acute high-fat diet (HFD) challenge. We examined FAO in liver homogenate and isolated mitochondria of HCR/LCR rats following a 3 day HFD (45% fat). In both strains, HFD resulted in increased daily weight gain (73% HCR, 1.5-fold LCR; p<0.05) and increased feeding efficiency (49% HCR, 2.5-fold LCR; p<0.05). In liver homogenates, HCR rats had 56% greater complete FAO to CO2 relative to diet (p<0.05). Also, HCR rats demonstrated a 15% increase in incomplete FAO on the HFD (p<0.05), with no change observed in LCR rats. In isolated hepatic mitochondria, HCR rats display 73% greater complete FAO compared to LCR (p<0.05), with HFD producing a 40% reduction in HCR rats (p<0.05) but no change in LCR rats. The reduced complete FAO in HCR mito- chondria on HFD was reversed with the addition of ADP or uncoupling agent FCCP to the assay. In conclusion, HCR rats show greater FAO and adaptability to a HFD than LCR rats suggesting that differences in intrinsic aerobic capacity confer differences in hepatic metabolic flexibility for lipid metabolism.
different between SED and WLO but decreased by WL5 and WL29, respectively. Wheel running increased PLI PPL mL/min at WLO, but values decreased to SED levels by WL5. These results, while not conclusive, show the potential importance and need to further study Ankrd2 and Angthrop gene expression during acute inactivity. Funded by anonymous gifts.

5.10 THE UBQUITIN-PROTEIN LIGASE NEDD4 CONtributes TO THE SKELETAL MUSCLE ATROPHY INDUCED BY 14 DAYS OF IMMobilization

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Research in physical activity induce skeletal muscle atrophy. The primary mechanism for protein breakdown is the ubiquitin-proteosome pathway, a process relying on ubiquitin ligases (E3s) to target specific proteins for degradation. Recent work shows that the E3 Nedd4 contributes to disease atrophy; however this has not been investigated in humans. PURPOSE: To investigate how disuse from immobilization affects Nedd4 gene expression and protein content. METHODS: Healthy men and women (10.9 ± 2.9) completed 14-d of leg immobilization. Muscle biopsies of the vastus lateralis collected before (PRE) and immediately after (POST) immobilization were processed to isolate protein and mRNA and quantified by Western Blotting and q-PCR. Immunohistochemistry confirmed protein changes and identified the predominant localization site. RESULTS: Following 14d of disuse Nedd4 protein content increased 24% (p < 0.01) compared to the 26% increase in total available mRNA (p < 0.001). Although mRNA levels POST were not different from PRE levels (p = 0.3), immunohistochemistry confirmed increased (3.5±fold) sarcoplasmic localization of Nedd4 (p = 0.03). CONCLUSION: These results suggest that Nedd4 continues to contribute to the total protein ubiquitination occurring after 2 weeks of disuse. This research was funded jointly by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Institutes of Health Research (CIHR).

6.0. EXERCISE AND DRUG INTERACTIONS

6.1 RAT METABOLIC RESPONSES DURING TREADMILL RUNNING FOLLOWING DOxorubicin INJECTIONS IN SEDENTary AND EXERCISE-TRAINED RATS

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The purpose of this study was to determine the effects of 10 weeks of treadmill training prior to doxorubicin (DOX) administration on resting metabolic and submaximal exercise metabolic parameters. Twenty male adult (~12 weeks of age) Sprague-Dawley rats were randomly assigned to one of four groups: 1) sedentary saline, 2) sedentary DOX, 3) exercise saline and 4) exercise DOX. Exercise groups underwent a 10-week progressive treadmill training protocol, and sedentary groups maintained normal cage activity for 10 weeks. Following the activity treatment period, baseline resting and submaximal exercise (50 cm/s) metabolic data were collected, and rats received either a bolus 15 mg/kg DOX injection or saline as a control. Seventy two hours after injection, resting and submaximal exercise metabolic data were collected. No group differences were observed at baseline. Likewise, 72 hours after injection, there was no exercise effect or exercise by treatment interaction, but there was a treatment effect between groups for VO2, VCO2 and energy expenditure (EE) (DOX groups, 12%, 20%, and 16% less, respectively). DOX injections resulted in a inability to match aerobic demands while running at 50 cm/s due to altered metabolic processes regardless of whether rats were exercised for 10 weeks prior to injection. Prior exercise did not protect against the DOX-induced metabolic disturbances observed during submaximal exercise.

6.2 A PILOT STUDY: ACUTE EFFECTS OF DOxorubicin ON HIND-LIMB GAIT KINEMATICS IN RATS

Jeremy Smith1, John Yaggi2, Noah Gibbon3, David Hydock4

1Sch. of Sport & Exercise Sci., Univ. of Northern Colorado, Biomechanics Lab, Greeley, CO, 80639.

The purpose of this study was to determine the effects of doxorubicin (DOX) on rat hindlimb mechanics, with specific focus on the accelerations and spatiotemporal characterisitcs of gait. Fifteen adult male Sprague-Dawley rats were randomly assigned and injected with saline, 10 mg/kg DOX, 12.5 mg/kg DOX, or 15 mg/kg DOX delivered as a bolus i.p. injection. Sagittal plane video was collected while rats walked on a treadmill (27 cm/sec) prior to injection (PRE) and 72 hours post-injection (POST). Two-factor ANOVAs with repeated measures showed no significant (p>0.05) dose effects for any of the kinematic or spatiotemporal variables. However, significant time by group interactions were observed for peak ankle vertical acceleration (p<0.05, ES=-1.02) and peak vertical foot acceleration (p<0.05, ES=-0.93). In both variables, the peak accelerations were decreased by ~14% in POST for all DOX groups compared to the saline group. Additionally, although not significant, similar interaction trends were observed for peak ankle external & internal rotations (p>0.05, ES=-0.88). DOX injections in limb accelerations occurred during swing when compared to a saline treated group. These reduced limb accelerations were consistent with reductions in isolated muscle force production previously reported (Hydock et al., 2011) suggesting muscle dysfunction due to DOX treatments may transfer to activities of daily living. Hydock DS, et al. (2011). Characterization of the effect of in vivo doxorubicin treatment on skeletal muscle function in the rat. Anticancer Res. 2011 Jun;31(6):2025-8.
Acute ethanol exposure inhibits muscle protein synthesis, while chronic ethanol exposure causes muscle wasting in humans and laboratory animals. In contrast, resistance exercise increases muscle protein synthesis and thus muscle mass, but few studies have addressed the interaction of ethanol and exercise. To assess this interaction, we overloaded the right plantar flexors by removal of gastrocnemius and soleus and then pair-fed the animals for five weeks on a nutritionally complete liquid diet in which ethanol contributed 36% of calories. Rats in the alcohol-treatment group were fed ad libitum while rats in the control group were pair-fed equal volumes of an isocaloric diet. Preliminary results (data not yet published) indicate that surgically overloaded plantaris muscles overexpressed several transcripts significantly and uniformly larger than contralateral, non-overloaded muscles. However, ethanol treatment had no significant effects on body mass, heart rate, or mass of either the overloaded or contralateral plantar. These results indicate that ethanol consumption is unable to prevent overload-induced hypertrophy in skeletal muscle. This work was sponsored by the Department of the Navy, Office of Naval Research, under Award # N00014-11-1-0359.

6.7 MAC25 PROMOTES MUSCLE HYPERTROPHY BY COORDINATING BOTH IGFII AND TGFb PATHWAYS

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The stimulation of the nitric oxide (NO)-3’5’-cyclic guanosine monophosphate (cGMP) signaling pathway results in vasodilation and increased NO production. Transgenic mice in which the catalytic (TAD) (TAD), a phosphodiesterase-5 inhibitor, reduces cGMP hydrolysis and might, to some extent, influence physiological responses to exercise. The aim of this study was to verify whether the oral administration of TAD influences physiological responses during submaximal exercise in healthy mice. Male C57BL/6J mice were randomly assigned to receive either two tablets of placebo (PLC) or TAD (20mg/kg) in a double-blind crossover design. After the administration of either PLC or TAD, the subjects performed a 30-min bout of exercise at anaerobic threshold on a cycle ergometer. Gas exchange measures and heart rate (HR) were recorded throughout, while blood lactate concentrations (Lac) and blood pressure responses (BP) were recorded every 5-min period. This study was designed according to the Declaration of Helsinki. Compared to PLC, the TAD condition did not differ for HR (139±13 vs. 142±13 bpm), systolic (145±17 vs. 143±26 mmHg) and diastolic blood pressure (58±15 vs. 64±13 mmHg), and Lac concentration (5.5±0.5 vs. 3.6±0.7, respectively for PLC and TAD). However, oxygen uptake was significantly higher in TAD (204±276 ±mL/min) compared with PLC (221±334 ±mL/min). In summary, the oral administration of TAD does not substantially influence physiological responses during submaximal exercise in normoxia. However, TAD might affect gas exchange responses to exercise.

6.10 NITROUS OXIDE NARCOSIS AND HYPERTHERMIA EFFECT THE PATTERN OF BREATHING DURING LIGHT EXERCISE

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HYPOTHESIS: It was hypothesized that breathing of normoxic 30% N2O during hypothermic exercise would give a deeper pattern of breathing.

METHODS: Six college-aged, healthy male participants volunteered for this SFU Office of Research Ethics approved study. Each participant rode a cycle ergometer at 50 W and ~70 rpm during 2 trials on separate days at ambient temperatures (Ta) of 18°C or 35°C. In each trial the participant breathed air at rest. Subsequently in 3 successive 10 min exercise periods inhalants were added (Air 1), normoxic 30% N2O and air (Air 2).

RESULTS: When Ta was 35°C, Tcore was significantly increased (p<0.0001) by ~1°C. During hypothermia pulmonary ventilation (Vt) increased (p=0.02) by ~6 L/min, improved flow (Vt/Ti) also increased, (p=0.08) and expiratory time (p=0.06). Inhales of N2O resulted in a reduction in Vt, Ti and Vt/Ti. 

CONCLUSION: Inhaled, light exercise with a superimposed hypothermic elicited hyperventilation whereas normoxic 30% nitrous oxide breathing during hypothermic exercise gave a deeper pattern of breathing. Supported by Canadian Foundation for Innovation and Natural Sciences and Engineering Research Council of Canada.

7.0 MUSCLE FUNCTION AND ADAPTATION

7.1 PROLONGED MECHANICAL VENTILATION RESULTS IN DIAPHRAGM HYPOXIA AND A DOWN-REGULATION OF RESISTANCE ARTERY ENOS EXPRESSION

Brad Behal1, Robert Davis II2, Christian Studzinski2

1Anesthesiology, UBC, 2School of Biomedical Sciences, Simon Fraser University, Burnaby, BC.

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7.3 THE COMBINED EFFECTS OF INSPIRATORY MUSCLE TRAINING AND CYCLING ON DIAPHRAGM MUSCLE ACTIVITY

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Inspiratory muscle training (IMT) is an intervention employed to improve the strength and performance of ventilatory muscles. The purpose of this study was to investigate whether sub-fatiguing IMT (40% maximal inspiratory pressure) would significantly increase inspiratory muscle activity above resting breathing and whether this effect would be additive to the effects of cycling. We measured DIA (DIA) muscle activity by surface electromyography (sEMG) in ten subjects (7 male, 3 female). Subjects performed IMT at rest or while cycling in either an upright or drops cycling posture. The addition of IMT in the upright posture during resting conditions significantly increased DIA sEMG, but the addition of IMT under other postural conditions did not lead to significant increases in sEMG. The addition of cycling significantly increased DIA sEMG above resting conditions independent of posture. During all cycling interventions, independent of IMT and posture, DIA sEMG was significantly greater than non-cycling conditions that did not incorporate IMT. Cycling in the drops position along with IMT significantly increased DIA sEMG activity above all non-cycling conditions tested. Significant differences in DIA sEMG activity were not observed between the upright and drops cycling postures. In support of our hypothesis, it appears that IMT and cycling have additive effects on DIA sEMG activity. Funding for this study was provided by the Mayo Clinic. The Mayo Clinic IRB approved all methods.

7.4 EFFECT OF INTERMITTENT ACTIVITY DURING CARDIO- RESPIRATORY STRESS ON HUMAN DIAPHRAGM MITOCHONDRIAL RESPIRATION

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Recent studies have shown that short periods of controlled mechanical ventilation (MV) use leads to ventilation induced diaphragmatic dysfunction. We examined the effect of intermittent diaphragm activity during cardiorespiratory stress on the human diaphragm by measuring mitochondrial respiration (MR) using high resolution respiratory fluxometry. In 5 patients (65 ± 6 yrs) undergoing lengthy thoracic surgery, the right or left phrenic nerve was randomly selected for 1 minute of stimulation every hour (30 pulses per minute, 15 msec pulse duration) during the surgery. Shortly before the surgery was completed, full thickness samples of diaphragm muscle were obtained from the anterior and lateral regions of both hemidiaphragms. The mean duration between the start of controlled MV and tissue harvest was 5.2 ± 1.0 hours. In the stimulated hemidiaphragm, the MR rate (pontol 02/sec kg wet weight) was 14.63 ± 3.31 during state 3 and 3.79 ± 1.09 during state 4, while in the unstimulated hemidiaphragm the MR rate was 11.78 ± 2.28 during state 3 and 2.38 ± 1.09 during state 4. The stimulated and control samples were different for state 3 and 4 activities, p < 0.05.

7.5 A 28 DAY SOJOURN TO 3454M DIMINISHES SKELETAL MUSCLE RESPIRATORY CAPACITY BUT ENHANCES EF- FICIENCY IN HUMANS

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Hypoxia-induced alterations in mitochondrial function are not well understood, and accordingly studies regarding mitochondrial modifications in human skeletal muscle following acclimatization to high altitude are seemingly inconsistent. We previously demonstrated that despite the loss of several mitochondria-specific proteins, 9-11 days of exposure to high altitude did not markedly modify integrated measures of mitochondrial functional capacity in skeletal muscle, though oxidative phosphorylation capacity tended to decrease. The aim of this study was to examine mitochondrial function following a more prolonged exposure to high altitude. Skeletal muscle biopsies were obtained from 8 lowland natives prior to and again after 28 days of exposure to 3454m. High-resolution respirometry was performed on the muscle samples to compare indices of respiratory control and capacity. Respirometric analysis revealed that mitochondrial-specific respiratory capacity decreased the capacity for fat oxidation, complex I-specific respiration, complex II-specific respiration, and oxidative phosphorylation capacity. Some indices of respiratory chain function were also altered, as controlling protein improved in response to high altitude exposure. This data suggests that chronic exposure to high altitude reduces respiratory capacity in human skeletal muscle, however the efficiency of electron transport improves.

7.6 ACUTE IN VITRO STATIN EXPOSURE ALTERS MITOCHONDRIAL FUNCTION IN PERMEABILIZED SKELETAL MUSCLE FROM HEALTHY HUMANS

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Statins are widely-used in the treatment of cardiovascular disease, are associated with potential adverse side effects in skeletal muscle. Data from cell culture studies suggest statin-induced myopathy may be initiated by altered mitochondrial function. To further examine the potential impact of statins, various aspects of mitochondrial function were assessed in human permeabilized skeletal muscle fiber bundles (PMF) exposed (30 min) in vitro to atorvastatin (ATOR, 10 mM) or simvastatin (SIM, 10 mM), in PMF from healthy subjects after acute (2h) and/or chronic (once/d for 7d) treatment with ATOR (80 mg/d) or SIM (40 mg/d). In vitro exposure of PMF to ATOR and SIM decreased both complex I and II supported respiratory capacity (O2.), whereas only SIM decreased complex I supported mitochondrial calcium retention capacity (sCa2+). Neither acute nor chronic in vivo treatment with ATOR or SIM altered O2. or Ca2+ - dependent mitochondrial H2O2 emission potential (sE2O2) in the presence of complex I or multiple substrates was not altered by in vitro or in vivo exposure to either statin, both in vitro and acute in vivo exposure to SIM decreased complex II sE2O2. These findings in-vitro both ATOR and SIM are capable of directly impacting mitochondrial function in human PMF exposed in vitro. The acute and chronic impact of in vitro statin exposure on skeletal muscle mitochondrial function is less clear and will require further study. R01 DK074825.

7.7 ACUTE EXPOSURE TO LOVASTATIN DIMINISHES TENSION DEVELOPMENT IN INTACT ISOLATED MYOFFIBERS

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Statins are widely-prescribed cholesterol-lowering drugs shown to cause skeletal muscle myopathy. In particular, the lipophilic statins (e.g. lovastatin, simvastatin, atorvastatin, cerivastatin) can induce skeletal muscle toxicity, which often presents as muscle weakness, fatigue, and pain. The objective of the present study was to determine the effects of acute exposure to lovastatin on muscle contractile function using intact isolated skeletal muscle fibers. All procedures were approved by the UCSD IACUC. Intact muscle fibers were isolated from Xenopus laevis, electrically stimulated and tension development recorded. After incubating fibers in 10 mMLovastatin for 1 h, tension development at submaximal and maximal frequencies of stimulation (30-150 Hz) was reduced by 50% and demonstrated slower peak rates of contraction and relaxation compared to preincubation values. The addition of 1 mM Ca2+ fully restored the maximal tetanic tension development with lovastatin, but did not restore the slowed relaxation rate. Although the overall time-to-fatigue was not affected by the acute lovastatin treatment, the work performed was smaller in the lovastatin-treated fibers. In conclusion, acute exposure to lovastatin causes a reduction in tension development and slows the rate of muscle contractile activation and relaxation in single myofibers, and our results suggest that this effect is mediated through intracellular calcium handling. Funded by NIH grants NIAIMS AR04155 and NHLBI HL91830.

7.8 THREE-DIMENSIONAL DYNAMIC ORGANIZATION OF MITOCHONDRIA IN SKELETAL MUSCLE: EFFECTS OF A SINGLE BOUT OF VOLUNTARY EXERCISE

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Mitochondria undergo fusion and fission events that are frequent and easily observable in proliferating cultured cells, but whether mitochondria undergo morphology transitions in terminally differentiated muscle fibers in vivo remains unclear. Furthermore, the effect of exercise on mitochondrial dynamics is unknown. Here, using a combination of freeze-fracture scanning EM and transmission EM in both transverse and longitudinal planes, we characterized the morphology of subsarcomemal (SS) and intermyofibrillar (IMF) mitochondria. High resolution micrographs were traced and analyzed for mitochondrial size and shape descriptors. In sedentary mice, IMF mitochondria were elongated and branched whereas SS mitochondria were mostly spherical. Electron-dense mitochondrial contact sites consistent with events of outer mitochondrial membrane fusion and fission were also visualized. In exercising mice, a large bout of voluntary wheel running decreased blood glucose levels (-38%, p<0.05) as well as the amount and size of intramyocellular lipid droplets (p<0.001), attesting to an increased in muscular metabolic demand. Although neither mitochondrial size nor morphology significantly differed post-exercise, electron-dense mitochondrial contact sites were more frequent (+130%, p<0.05) in exercising animals. We postulate that electron dense contact sites consist in pre-fusion events - a single bout of exercise may prime mitochondria for morphological change, but does not immediately alter mitochondrial size or shape.

7.9
GlycOlytic Skeletal MyFibers Display Higher P/O Ratios Than Cardiac MyFibers Due to Adenylyl Kinase: Preliminary Findings Using a Novel Oxi-fluorometer Apparatus

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Oxidative tissues such as myocardium rely heavily on fatty acids for mitochondrial ATP production; however, accumulation of fatty acids has been shown to uncouple oxidative phosphorylation and induce protein-mediated (e.g. UCPT, ANT) and indirect pathways and lead to lower metabolic efficiency (i.e. decreasing P/O ratio). We therefore hypothesized that the efficiency of oxidative phosphorylation (P/O ratio) is: 1) lower in oxidative muscle than in glycolytic muscle and 2) lower during lipid oxidation than carbohydrate oxidation. To test these hypotheses using an enzyme-coupled assay system, we simultaneously measured ATP production (JATP) and oxygen consumption (JO2) in peronealized mouse soleus and tibialis anterior during 4 hours of exercise. The results of this study demonstrate that 1) the P/O ratio is highly conserved in muscle mitochondria, 2) adenylyl kinase is a major producer of ATP in glycolytic muscle and 3) palmitoyl-carnitine does not promote mitochondrial uncoupling in myocardium under the conditions tested. Funded Sources: R21 HL098780 and R01 DK073488.

7.10
Effects of Aerobic Training and Overtraining on DNA Damage and Oxidative Stress in SwIcE Mice

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We aimed to verify aerobic training and overtraining protocol effects on DNA damage of blood and skeletal muscle cells in mice. To relate possible alterations of these parameters with oxidative stress status, we measured reduced-glutathione (GSH) levels in blood, and GSH levels and lipid peroxidation in gastrocnemius. Rodents were divided into control (C), trained (TR) and overtrained (OTR) groups. All experiments were in accordance with the American Physiological Society “Guiding Principals in the Care and Use of Animals”. Incremental load test (ILT) and exhaustive test (ET) were used to measure performances before (i.e. week 0) and after (i.e. week 8) exercise protocols. 24h after ET, gastrocnemius was collected and used for comet assay. For comet assay, the results were expressed in terms of % tail DNA. All experiments were in accordance with the American Physiological Society “Guiding Principals in the Care and Use of Animals”. The ILT and ET parameters showed intra and inter-groups significant differences. OTR group showed a significant increase in tail DNA in the tail compared to C and TR groups. GSH levels were significantly lower in OTR group compared to C and TR groups. OTR group showed significantly higher levels of TBARS compared to C and TR groups. In conclusion, overtraining, but not high intensity exercise is related to DNA damage and oxidative stress. Financial support from FAPESP (2011/20520) and 2010/08239-4.

7.11
Sarcopl in Ablation Does Not Affect Exercise-Induced Adaptation of Oxidative Metabolism in Skeletal Muscle

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Calcium signaling plays a role in mediating exercise-training-induced mitochondrial biogenesis in skeletal muscle. Furthermore, modulation of activity of sarco (endoplasmic reticulum Ca2+)-ATPases (SERCA) which as serve vital controllers of intracellular Ca2+ in skeletal muscle. To investigate the potential role of SLN in the adaptive response of skeletal muscle mitochondria to endurance training, mice without (SLNKO) underwent endurance training for 8 weeks (TR) and were compared to their untrained (UT) counterparts. A total of 36 mice (18 SLNKO and 18 wild type (WT)) were randomly assigned to TR and UT groups. Soleus (SOL) and extensor digitorum longus (EDL) muscles were collected from all groups at matching time points following the endurance training to determine the relative abundance of cytochrome-c (cyt-c), adenine nucleotide transporter (ANT) and cytochrome c oxidase IV (COXIV) using Western blotting. TR mice had increased cyt-c content (p<0.05) in both SOL and EDL compared to their UT counterparts. ANT and COXIV content were higher (p<0.05) in TR EDL compared with UT EDL. A similar trend was observed for the COXIV (p=0.1) but not ANT in TR SOL (p>0.1). There were no differences (p>0.1) between SLNKO and WT for any of the mitochondrial proteins analyzed. Our results show that SLN ablation did not affect the adaptive response of skeletal muscle to increase oxidative capacity with endurance training. This study was funded by CIHR and NSERC.

7.12
NFATC3 Regulates Muscle Fiber-Type Transition Independently from the Activation of Calcineurin (Can) During Long-Term Endurance Training in Rats

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Regulation of sarco (endoplasmic reticulum Ca2+)-ATPases (SERCA) is part of the complex including physical interaction with sarcoplasmic (SLN) and phospholamban (PLN). Muscle skeletal muscle only expresses SLN in slow-twitch type I (ST) fibers. To understand the physiological effect induced by dual expression of SLN and PLN, we examined mice with targeted overexpression of PLN in ST fibers. Methods: Soleus, extensor digitorum longus (EDL), and diaphragm were excised from 20 mice (10 wild-type [WT], 10 PLN overexpression [PLN OE]) mice. Immunofluorescent staining was done to characterize fiber types in each muscle. Sub-maximal VO2, VO2 max, and times to exhaustion during treadmill exercise were also recorded. Results: The body weights, EDL weight, and VO2 max between PLN OE and WT mice were not significantly different, whereas soleus weight was significantly lower (p<0.0001) in PLN OE (3.6 ± 0.2) vs WT (5.7 ± 0.2). Immunofluorescent staining in soleus and diaphragm reveal elevated proportions of atrophied ST fibers and hypertrophied type IIA fibers. A trend (p=0.09) was seen with PLN OE mice having higher sub-maximal VO2 (6716 ± 185.7 ml/kg/hr) than WT (6242 ± 196.1 ml/kg/hr). Time to exhaustion was shorter in PLN OE mice (82.3 ± 7.4 min) vs WT mice (125.9 ± 9.6 min; p<0.003). Conclusion: In summary, muscles of mice expressing both SLN and PLN underwent physiological changes, and both traditional characteristics of myopathy, which likely contributed to reduced exercise capacity.

7.13
Phospholamban Overexpression Causes Irregular Distribution and Size of Slow-Twitch and Fast-Twitch Fibres in Mouse Soleus and Dia Phragm

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Regulation of sarco (endoplasmic reticulum Ca2+)-ATPases (SERCA) is part of the complex including physical interaction with sarcoplasmic (SLN) and phospholamban (PLN). Muscle skeletal muscle only expresses SLN in slow-twitch type I (ST) fibers. To understand the physiological effect induced by dual expression of SLN and PLN, we examined mice with targeted overexpression of PLN in ST fibers. Methods: Soleus, extensor digitorum longus (EDL), and diaphragm were excised from 20 mice (10 wild-type [WT], 10 PLN overexpression [PLN OE]). Immunofluorescent staining was done to characterize fiber types in each muscle. Sub-maximal VO2, VO2 max, and times to exhaustion during treadmill exercise were also recorded. Results: The body weights, EDL weight, and VO2 max between PLN OE and WT mice were not significantly different, whereas soleus weight was significantly lower (p<0.0001) in PLN OE (3.6 ± 0.2) vs WT (5.7 ± 0.2). Immunofluorescent staining in soleus and diaphragm reveal elevated proportions of atrophied ST fibers and hypertrophied type IIA fibers. A trend (p=0.09) was seen with PLN OE mice having higher sub-maximal VO2 (6716 ± 185.7 ml/kg/hr) than WT (6242 ± 196.1 ml/kg/hr). Time to exhaustion was shorter in PLN OE mice (82.3 ± 7.4 min) vs WT mice (125.9 ± 9.6 min; p<0.003). Conclusion: In summary, muscles of mice expressing both SLN and PLN underwent physiological changes, and both traditional characteristics of myopathy, which likely contributed to reduced exercise capacity.
ASSOCIATION OF HYPERSERUM  CORTICOSTEROID LEVELS WITH PEOPLE WITH DIABETES MELLITUS

Tim Griffin, Joanna DeMoor, Wun-Pin Chang, Mark Barton Frankel, Melissa Belusk, Eren Hutchinson

1Free Radical Biology and Aging, Oklahoma Med. Res. Fdn., 825 NE 13th St., MS 21, Oklahoma City, OK, 73104, 2Biochemistry and Molecular Biology, Reynolds Oklahoma Cancer Institute, Univ. of Oklahoma Health Sci. Ctr., 4900 N. Western Ave., MS 19, Oklahoma City, OK, 73104, 3Arthritis and Clinical Immunology, Oklahoma Med. Res. Fdn., 825 NE 13th St., MS 58, Oklahoma City, OK, 73104. Obesity increases the risk of knee osteoarthritis (OA) presumably by increasing local biomechanical factors and systemic inflammatory factors. Although exercise increases joint loading, we have recently shown that it lessens metabolic inflammation and OA in mice. PURPOSE: To determine the effect of a high-fat diet and wheel-running exercise on the differential expression of genes in knee cartilage and subchondral bone using whole-genome microarrays. METHODS: Male C57BL/6J mice were fed either a 10% or 60% kcal fat diet from 16-20 wks of age. Half of the mice were housed with running wheels (n=5 per group). RNA was isolated from knee femoral and tibial cartilage and subchondral bone and quantified using a whole-genome mouse BeadChip Array (Illumina). Differentially expressed genes (q<0.05) were further analyzed using Ingenuity Pathway Analysis in diet-matched sedentary vs. exercised animals. RESULTS: 162 genes, including 41 transcriptional regulators, were differentially expressed (>1.25 fold) with exercise in mice fed a high fat diet compared to 35 genes in control diet mice. Pathway analysis predicted that exercise increased nitric oxide signaling and inhibited Myc family target genes in high-fat but not control mice. CONCLUSION: Dietary fat content profoundly alters the effect of short-term exercise on genetic regulators of cartilage and bone inflammation and growth, suggesting a role for diet-specific molecular targets in treating OA. Support: Arthritis Foundation & NIH.

8.2 SKELETAL MUSCLE MASS REGULATORS WITH AND WITHOUT CONTRACTILE ACTIVITY IN SPINAL CORD-INJURED VS. ABLE-BODIED INDIVIDUALS

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1Cellular, Developmental, and Integrative Biology, Univ. of Alabama at Birmingham, 1720 University Blvd., Birmingham, AL, 35294, Ctr. for Exercise, Phys. Activity, UAB, Birmingham, AL, 35294, 2Physical Therapy, UAB, SHPB 3600, Birmingham, AL, 35294, Surgical, UAB, Kirklin Clinic, 5th Fl., Birmingham, AL, 35294. Spinal cord injury (SCI) is known to induce substantial skeletal muscle atrophy, which progresses rapidly for the first several weeks and appears to regress more slowly but remains approximately 17-18 months post-injury. The mechanisms responsible for this early phase atrophy, as well as this plateau, are incompletely understood. Regardless, it has been shown that SCI muscles even several years post-injury are responsive to hypertrophic stimuli. For example, neuromuscular electrical stimulation (NMES)-induced resistance exercise has been shown to induce muscle regrowth in SCI. However, there is a limited understanding of the mechanisms responsible for NMES myofiber hypertrophy in both SCI and able-bodied (AB) individuals. The two-fold purpose of this project is thus to establish the basis for SCI and AB muscle mass regulation and to assess the relative importance of SCI and AB muscle mass regulation. Support: NIDRR.

8.3 GROWTH HORMONE DEFICIENCY HAS TISSUE-SPECIFIC EFFECTS ON PROTEIN SYNTHESIS

4.1 ACID INHIBITS CERAMIDE BIOSYNTHESIS IN SKELETAL MUSCLE

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1Health and Exercise Sci., Colorado State Univ., 220 Moby B Complex, Fort Collins, CO, 80523, 2Dept. of Pathology and Geriatrics Ctr., Univ. of Michigan, 109 Zina Pitcher Pl., Ann Arbor, MI, 48109. Sarcopenia is associated with a decrease in muscle function and exercise capacity and is associated with a decrease in growth hormone (GH). GH administration has been suggested as a means by which to promote skeletal muscle protein synthesis (PS) and exercise capacity but has shown mixed results. Less is known about anabolic effects of GH in other tissues. Understanding how growth hormone (GH) regulates PS in other tissue is important. We hypothesize that the cellular compartments in a variety of tissues could provide valuable information about the long-term outcomes of GH therapy. Small Dwarf (SD, n=10) mice, which are GH deficient, and wild type control mice (C57, n=10) were given 8% D Glucose as drinking water for 4 weeks. Gastronomers complex (SMX) and heart (Hrt) were harvested, homogenized, and fractionated into mixed (Mx), cytosolic (Cyto), and mitochondrial-enriched (Mito) fractions. Fractional synthesis was determined by the D dilution of lanthanum incorporated into tissue protein during the labeling period. Protein synthesis was decreased in all tissue fractions with the exception of the heart (Mx: Con=0.73±0.02, SD=0.55±0.02; Cyto: Con=0.81±0.02, SD=0.61±0.02; Mito: Con=0.55±0.03, SD=0.39±0.02). Ht showed decreased protein synthesis in Mx (Con=0.88±0.03, SD=0.73±0.04) and Cyto (Con=0.98±0.01, SD=0.88±0.04) fractions but Mito synthesis was maintained (Con=0.79±0.02, SD=0.76±0.02). The difference in tissue specific responses illustrates the need to consider tissues beyond skeletal muscle. Further understanding of how...
differential protein synthesis is regulated between tissues could improve how exercise adaptations are interpreted and lead to the development of better treatments for sarcopenia and growth-related pathologies.

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The sphingolipid ceramide is increased in hyperlipidemic states and is known to elicit a host of adverse cardiac outcomes. In contrast, AMPK has long been studied for its effects on metabolism and substrate utilization, acting as the critical mediator for several stimuli that induce fatty acid oxidation. We sought to understand the direct effect of AMPK activation on ceramide metabolism in skeletal muscle, a highly active site of both ceramide biosynthesis and fatty acid oxidation. AICAR treatment, known to activate AMPK, induced a significant reduction in ceramide levels in muscles treated with high levels of palmitate. This observation was further supported by the finding that AICAR treatment, but not AICAR + Compound C, an AMPK inhibitor, significantly reduced expression of serine palmitoyltransferase (SPT) 2, the rate-limiting step in the de novo ceramide synthesis.

Subsequently, we sought to determine whether the ceramide-specific effects of AMPK were relevant in an in vivo model. Male rats were fed a standard or high-fat diet, with a subset receiving daily AICAR injections. Similar to myotubes, animals receiving AICAR treatments tended to have reduced soleus SP2 expression and reduced ceramide content. These findings identify ceramide synthesis as a novel therapeutic target of AMPK activation.

8.5 MODULATION OF CARDIAC MITOCHONDRIAL BIOENERGETICS BY ENDURANCE TRAINING AND INTERMITTENT HYPOBARIC HYPOXIA
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Intermittent hypobaric hypoxia (IHH) and endurance-training (ET) are cardioprotective strategies against several stress-stimuli. Modulation of mitochondrial bioenergetics appears to be an important step of the process. This study aimed to analyse whether a combination of these approaches provides additive or synergistic effects by improving heart-mitochondrial and cardiac function. Wistar male rats were: normoxic-sedentary (NS), normoxic-exercised (NE, 1h/d/5wks treadmill-running), hypoxic-sedentary (HS, 6000m, 5h/d/5wks) and hypoxic-exercised (HE). In vitro cardiac mitochondrial O2 consumption, complex-II subunits. ANT increased in HE. HE presented normalized ventricular-arterial heart-mitochondrial contractility and cardiac function. Wistar male rats were: normoxic-sedentary (NS), normoxic-exercised (NE, 1h/d/5wks treadmill-running), hypoxic-sedentary (HS, 6000m, 5h/d/5wks) and hypoxic-exercised (HE). In vitro cardiac mitochondrial O2 consumption, complex-II subunits. ANT increased in HE. HE presented normalized ventricular-arterial heart-mitochondrial contractility and cardiac function.

The results of previous investigations suggest that the combination of both strategies, although not additive, seem to modulate cardiac mitochondria bioenergetics although without visible addictive effects. It is suggested that the combination of both strategies, although not additive, seem to translate into improved cardiac function.

8.6 OVARIECTOMY INCREASES HEPATIC MITOCHONDRIAL ROS PRODUCTION IN MICE
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We have previously shown that loss of ovarian function leads to the disruption of lipid metabolism regulators in hepatic tissue, thus increasing the susceptibility for developing hepatic steatosis. PURPOSE: To determine if the loss of ovarian function in female mice results in increased triacylglycerol (TAG) storage, impaired hepatic mitochondrial metabolism, and whether any of these changes resulted from altered sirtuin (SIRT) function. METHODS: Female C57BL/6 mice were divided into two groups SHAM or bilateral ovariectomy (OVX). Mitochondrial function was assessed by measuring oxygen consumption, reactive oxygen species (ROS) production, and mitochondrial protein content from isolated hepatic mitochondria. In addition, mitochondrial acetylation status and sirtuin 1/3 (SIRT) protein content were assessed. RESULTS: Compared to SHAM mice, hepatic mitochondrial antioxidant enzymes, OXV mice exhibited no differences in oxygen consumption, in either state 3 or 4 conditions, but did exhibit increased ROS production. In addition, no differences in mitochondrial protein content, acetylation status or total SIRT 1/3 content were detected between groups. OXV mice exhibited a non-significant increase in hepatic TAG compared to SHAM mice. CONCLUSION: The data suggest that ovariectomy contributes to impaired hepatic mitochondrial function by increasing ROS production, which is not a result of altered SIRT function. This work was funded by the Baltimore DRTC (NIH-P60DK079637).

8.7 TREATMENT OF CULTURED MYOTUBES WITH RAPAMYCIN ACTIVATES AMP-ACTIVATED PROTEIN KINASE
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Exercise is one of the best understood and most effective interventions to attenuate chronic diseases associated with aging. Aerobic exercise activates AMP-activated protein kinase (AMPK) while simultaneously downregulating mammalian target of rapamycin (mTOR), both of which have been shown to promote longevity in various human and animal models. While evidence for rapamycin activating AMPK is evident in cancer models, little data exists suggesting the mTOR inhibitor can activate AMPK in postmitotic tissues such as skeletal muscle. Treatment with rapamycin could stimulate pathways sensitive to energetic stress to elicit cellular effects similar to endurance exercise. The purpose of this study was to determine whether rapamycin can exhibit exercise-like effects through the inhibition of mTOR and activation of AMPK in skeletal muscle cells. Treatment of C2C12 cultured myotubes with 10nM rapamycin for 24 hours significantly activated AMPK, as assessed by phosphorylation of Thr172; while also inhibiting mTOR signaling, as assessed by the hypophosphorylation of ribosomal protein S6 (pS6). Addition of metformin, a known AMPK agonist, did not enhance the ability of rapamycin to activate AMPK. These results suggest rapamycin could be utilized to understand the mechanisms by which exercise activates AMPK. Furthermore, rapamycin-induced cellular energetic stress to identify potential treatments which mimic the benefits of aerobic exercise. Ongoing experiments are focused on determining the role of autophagy with rapamycin and metformin treatment, and whether the beneficial effects of these pharmaceutical interventions can influence healthspan and longevity.

8.8 SKELETAL MUSCLE ADAPTATION IN RESPONSE TO MECHANICAL STRESS IN P130CAS−/− MICE
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Mammalian skeletal muscles undergo adaptation in response to alteration in functional demands involving mechanical stress-induced cellular signaling called mechano-transduction. We hypothesized that p130Cas which has been reported to act as a mechanosensor, transducing mechanical extension into cellular signaling, plays an important role in maintaining and promoting skeletal muscle adaptation in response to mechanical stress via p38 MAPK signaling pathway. We observed that muscle-specific p130Cas−/− mice have normal expressions of contractile protein in skeletal muscle. Furthermore, muscle-specific p130Cas−/− mice showed normal mechanical stress-induced muscle adaptations including exercise-induced IIb-to-IIa muscle fiber type transformation and hypertrophy as well as disease-induced muscle atrophy. Finally, we showed evidence that exercise-induced p38 MAPK signaling did not impaired by muscle specific deletion of the p130Cas. We conclude that p130Cas play limited role in mechanical stress-induced skeletal muscle adaptation.

8.9 PHOSPHATIC ACID AND MECHANICAL STIMULI ACTIVATE MTOR SIGNALING VIA AN ERK-INDEPENDENT MECHANISM
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Signaling by mTOR is both necessary and sufficient for the induction of hypertrophy in response to mechanical overload. Recently it has been suggested that mechanical stimuli (MS) induce mTOR signaling via a mechanism that requires phosphatidic acid (PA). The mechanism via which PA activates mTOR signaling is not clear, but at least two models have been proposed; 1) direct binding of PA to mTOR, or 2) PA-induced activation of MEK which then stimulates mTOR. In order to define the role of ERK in the regulation of mTOR by PA and MS, we first performed experiments in which C2C12 myoblasts were stimulated with exogenous PA. The results indicated that PA was sufficient to induce signaling through both ERK and mTOR; however, inhibition of ERK with UO126 did not prevent the ability of PA to induce mTOR signaling. Next, we performed experiments in which mouse EDL muscles were subjected to intermittent stretch as a source of MS. The results indicated that MS was sufficient to induce an increase in PA, as well as, signaling through both ERK and mTOR, however, inhibition of ERK with U0126 did not prevent the ability of MS to induce mTOR signaling. Finally, we performed in vivo mTOR kinase activity assays and found that PA could directly activate mTOR signaling. Taken together, these results demonstrate that both exogenous PA and MS induce mTOR signaling through an ERK-independent mechanism that potentially involves a direct interaction of PA with mTOR. Support: NIH grant AR057347 to TAH.

8.10 MTOR PATHWAY ACTIVATION IN THE DESMIN KNOCKOUT MOUSE

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that exercise training prior to hindlimb unloading is not protective against losses of HU+EX was also elevated with a blunted FSR; supporting prior research suggesting a competitive inhibitor of mTOR, was accompanied by reduced FSR. Reambulation after exercise during recovery, or with a subsequent HU bout (2HU or 2HU+EX).

DEPTOR EXPRESSION IS ALTERED BY MECHANICAL ambulation following 1HU, with (1HU+EX) or without (1HU+REC) chronic re-sistance training prior to long-duration unloading offered no protective effects. This study determined if a specific modulator of mTOR, called DEPTOR, played a role in the muscle adaptation response to unloading. Male Sprague-Dawley rats (6mo) were either exposed to one or two bouts of 28d hindlimb unloading (1HU, 2HU), or with 56d of re-

8.12 TARGETED INHIBITION OF CALCINEURIN SIGNALING WITH THE CA-2-BUFFERING PROTEIN PARVALBUMIN REDUCES UTPHIN A EXPRESSION AND EXACERBATES THE DYSTROPHIC PATHOLOGY IN MDX MICE We have shown utrophin A, a therapeutically relevant protein that can compensate for the lack of dystrophin in dystrophic mouse muscles, to be regulated by calcineurin (Ca) signaling (PNAIS 2003. Hum Mol Gen 2004 d 2006). We set out to determine the impact of interfering with Ca-dependent signaling in targeted dystrophic-deficient myofibers. We thus crossbred mdx mice with transgenic mice expressing the Ca--buffering protein parvalbumin (PV), driven by the fiber-specific Troponin I slow promoter. This approach forced expression of this non-native fast Ca--regulatory protein in slow fibers thus lowering Ca in fiber regions of the absence of any fiber type conversions. Consistent with impairments in Ca, nuclear localization of NFATc1 was reduced in slow fibers from mdx/PV mice. We also observed significant reductions in utrophin A mRNA and protein in targeted fibers of crossbred mice. In accordance with lower levels of utrophin A, we noted a clear exacerbation of the dystrophic phenotype in mdx/PV slow fibers as exemplified by several pathological indices. These results further establish Ca--MAM-based signaling as key to regulating expression of utrophin A in skeletal muscle. Moreover, they illustrate the therapeutic potential of targeting Ca--Ms-based signaling intermediates in muscle as well as strategies aimed at promoting the slow oxidative myofiber program as effective countermeasures for Duchenne muscular dystrophy. Funded by CIBHR, NSERC and CRC.

8.13 DEPTOR EXPRESSION IS ALTERED BY MECHANICAL LOADING IN SKELETAL MUSCLE OF RATS Prior work in our lab has demonstrated that muscle mass can be restored to control levels following re-

Supported by NIH AG032127.


David Russ1, Jodi Krause2, Allison Wills2, Emily Klein2

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1Human Performance Lab., Ball State Univ., 2000 W. University Ave., Muncie, IN, 47306.

The main purpose of this investigation was to explore the fiber type-specific expression of genes involved in skeletal muscle oxidative capacity at rest and in response to 45 min of non-exhaustive (72±1% VO2max) cycling in recreationally active men (n=6, 25±1y, 54±1kg kg<sup>−1</sup> min<sup>−1</sup>). Gene expression was assessed by qPCR in slow (MHC I) and fast (MHC IIa) fibers isolated from vastus lateralis muscles harvested at rest and 2h after exercise. Of the 16 genes examined, basal expression of NRF-1 and β-HAD mRNAs was higher (P<0.05) in MHC I fibers, while UCP3 mRNA was higher (P<0.05) in MHC Ila fibers. Due to vast individual variability, only PGC-1α mRNA in-

9.0: AGING

9.1 MARKERS OF "SR STRESS" IN AGING AND EXERCISED MUSCLE

David Russ1, Jodi Krause2, Allison Wills2, Emily Klein2

1,2


Purpose: Impaired sarcoplasmic reticulum (SR) function has been associated with reduced muscle force generation and locomotor function. This study was conducted to de-
termine the extent to which aging increased SR stress markers, and the extent to which volitional exercise affected them. Methods: Gastrin-releasing peptides were harvested from adult (8 months; n = 8), aging (24 months; n = 8) and F344/BN rats that aged with wheel access for 16 months (24 months; n = 4). SR calcium handling assays and immunostaining (Calsequestrin and LC3) were performed on crude homogenates and SR-enriched microsomal fractions. Results: Aging was associated with increased Calsequestrin 12 and SR dysrin, as well as a reduced LC3HI ratio and impaired calcium release. Wheel running partially restored SR calcium release and dysrin toward younger levels, despite no increases in Calsequestrin 12. Of note, the LC3HI ratio was also partially restored in the running group, suggesting increased autophagy. Discussion: These results suggest that impaired SR function with aging is associated with age-related increases in SR stress, possibly related to reduced autophagy. Long-term volitional exercise reduces SR stress markers and markers of autophagy, suggesting that running contributed a beneficial stress that differed from the “distress” of sedentary aging. Conclusion: Age-related SR dysfunction may be partially explained by decreased autophagy increasing SR stress.

9.2 IDENTIFICATION OF DIFFERENTIALLY EXPRESSED MRNAS BETWEEN YOUNG AND OLD RATS DURING MUSCLE REGENERATION
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Adult skeletal muscle has a remarkable regenerative capacity. However, skeletal muscle regeneration is markedly impaired with age. We hypothesized that during muscle regeneration the mRNA for regeneration potentiating factor would be present in the damaged muscle of young (3- to 6-mo-old) but reduced in old (30- to 32-mo-old) Fischer 344 x Brown Norway rats. Gene expression levels of >31,000 transcripts were determined by using Affymetrix GeneChip Rat Genome 230 2.0 Array in homogenate tissue samples obtained at 24h, 48h, and 7 days following injury. Each muscle sample was applied to an independent set of arrays. Analysis of microarray data revealed that 301 mRNAs were significantly altered by using two-way ANOVA. Fourteen of the 301 mRNAs were upregulated in young damaged TA muscles more than 10-fold change) but no increase during regeneration in the old damaged TA muscles (less than 2-fold change), including muscle-specific the MLH1 transcription factor myogenin, cyclin-dependent kinase inhibitor 1 (p21), and muscle ankyrin repeat protein family member Ankrd1/CARP. The mRNAs that were differentially expressed during regeneration in young and old rats could modulate muscle regeneration, and highlight new candidate mechanisms to explain the impaired muscle regenerative capacity with age.

9.3 RAGE AND STAT3 SIGNALING IN CHRONIC AICAR-TREATED YOUNG ADULT AND OLD SKELETAL MUSCLE
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We examined the role of RAGE and STAT3 signaling in a mouse model of chronic exercise training. AICAR (6-azauridine 5’ -monophosphate) is an AMP mimetic, which activates AMPK. AMPK is an important regulator of energy metabolism, and is of potential importance in the development of exercise training as a treatment for sarcopenia. Previous studies have shown that chronic AICAR treatment increases muscle mass, strength, and endurance in rodents. However, the underlying mechanisms mediating these effects are not clear. The current study aimed to evaluate the role of RAGE and STAT3 signaling in the skeletal muscle of chronically AICAR treated mice. Methods: Both young (3-4 mo) and old (12 mo) C57BL/6 mice underwent 3x/week AICAR (100mg/kg, i.p.) treatment for 12 weeks. Controls were untreated. Results: RAGE expression was increased 2.5-fold in young AICAR-treated mice, but not in old AICAR-treated mice. In contrast, STAT3 expression was increased nearly 3-fold in old AICAR-treated mice, but not in young AICAR treated mice. Chronic AICAR treatment led to an increase in muscle mass in young mice, but not in old mice. Chronic AICAR treatment increased muscle strength, and increased muscle endurance, in both young and old mice. We found that AICAR treatment increased skeletal muscle Akt phosphorylation of the RAGE target STAT3. RAGE protein expression was 218% higher in young (3-4 mo-old) but reduced in old (30- to 32-mo-old) Fischer 344 x Brown Norway rats. Gene expression levels of >31,000 transcripts were determined by using Affymetrix GeneChip Rat Genome 230 2.0 Array in homogenate tissue samples obtained at 24h, 48h, and 7 days following injury. Each muscle sample was applied to an independent set of arrays. Analysis of microarray data revealed that 301 mRNAs were significantly altered by using two-way ANOVA. Fourteen of the 301 mRNAs were upregulated in young damaged TA muscles more than 10-fold change) but no increase during regeneration in the old damaged TA muscles (less than 2-fold change), including muscle-specific the MLH1 transcription factor myogenin, cyclin-dependent kinase inhibitor 1 (p21), and muscle ankyrin repeat protein family member Ankrd1/CARP. The mRNAs that were differentially expressed during regeneration in young and old rats could modulate muscle regeneration, and highlight new candidate mechanisms to explain the impaired muscle regenerative capacity with age.

9.4 RMS INCREASES IN FUNCTIONAL CAPACITY IN THE AGED ELDERLY:
2012 APS Intersociety Meeting: The Integrative Biology of Exercise-VI
ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS
Matthew Harbour1, Adam Kononock1, Miranda Underh1, Matthew Hinkle1, Keri Minchev1, Leonard Kaminski2, Todd Trappe2, Scott Trappe2
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To examine potential age-specific adaptations in skeletal muscle size and myofiber contractile physiology in response to aerobic exercise, seven young (YM; 20±1 yr) and six older (OM; 74±3 yr) men performed 12 weeks of cycle ergometer training. Muscle biopsies were obtained from the vastus lateralis to determine size and contractile properties of isolated slow (MHC I) and fast (MHC IIa) fibers. Aeric capacity was higher (P<0.05) after training in both YM (16±2%) and OM (13±3%). Quadriceps muscle volume was 5±1 and 6±1% greater (P<0.05) after training for YM and OM, respectively, which was associated with an increase in MHC 1 fiber cross-sectional area (CSA) and an independent increase in MHC I peak power was higher (P<0.05) after training for both YM and OM while MHC IIa peak power was increased (P<0.05) with training in OM only. MHC I and MHC IIa fiber peak and normalized (P<0.05) force were preserved in training with OM while MHC I isoforms and MHC IIa peak force were lower (P<0.05) after training in YM. These data suggest improvements in muscle size and aerobic capacity are similar between YM and OM while adaptations in myofiber function showed a general improvement in OM. Training-related increases in MHC I and MHC IIa peak power reveal that skeletal muscle of OM is responsive to aerobic exercise training and further support the use of aerobic exercise for improving cardiovascular and skeletal muscle health in older individuals. Supported by NIH AG032127 & NASA NNJ06HF59G.

9.5 CHANGES IN MUSCLE STRENGTH AND BONE MINERAL DENSITY FOLLOWING EXERCISE TRAINING IN OLD ADULTS
Michael Welsch1, Neil Johannsen2, Daniel Credeur2, Brandom Holli3, Timothy Church4, Eric Ravussin5, Jason Allen6

Purpose: To determine effects of 8wks of progressive whole-body training, preceded by 4wks of regional (RS) or aerobic exercise training (AE), on bone mineral density (BMD)and muscle strength. Methods: Subjects were ~70yrs and randomized to AE or RS for the first 4 wks (Phase 1). AE consisted of 60min of walking/biking at 40-60% of HRR, 3 d/wk. RS consisted of 3-5min of exercise specific to lower and upper body parts, 12 wks of training. Results: Groups were similar in age and weight. There was a main effect for pelvis BMD (p=0.003). Conclusion: Progressive whole-body training results in significant gains in strength and BMD. The gains after phase 2 were superior in those who used RS during phase 1. These results suggest RS serves as a primer for musculoskeletal gains in the elderly.
The purpose of this study was to determine (1) differences between 4 weeks of a regionally specific training stimulus (RST) versus standard aerobic exercise training (AET) on VO2peak and combined muscle group IRM strength (CIRM); (2) the effects of subsequent 8 weeks of progressive whole-body training protocol on VO2peak and CIRM. Trial (walked between 218-400yds in 6 min) subjects >70 yrs were randomized to 4wks of AET (60min of walking/biking at 40-60% of HRr, 3xwk) or RSTS (specific muscle groups exercised focused on the calf, thigh, buttocks, arms, shoulders, and torso, performed for 3 to 5 min, at ~40-70% of the MVC (60 min total), 3xwk) (Phase 1). All subjects then advanced to a well-rounded, whole-body exercise program according to ACSM guidelines (Phase 2). VO2peak and CIRM were examined at baseline and after phases 1 and 2. Both groups included 54 subjects (RSTS=14 men; AET=16 men), age ~76±5yrs. After adjustment for baseline (16.9ml/kg/min), there was a group*time effect in favor of RSTS for VO2peak following phase 2 (P<0.005). Both RSTS also showed greater gains in CIRM following both phase 1 (+47l/min vs. +7l/min, p<0.01) and phase 2 (+51l/min vs. +39l/min, p<0.01). These results suggest initial RSTS may serve as an effective modality for enhancing strength and aerobic fitness in the elderly.

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9.8 LONG-TERM CREATINE SUPPLEMENTATION COMBINED WITH RESISTANCE TRAINING IMPROVES FUNCTIONAL CAPACITY BUT NOT MAXIMAL STRENGTH IN OLDER WOMEN
Renee Jamesil, Andrea Aquea, Raymundo Piesc Juncal, Aline Mendes Genez, Fabíola Chacra Pinho, Madeleine Arrauto Amorato da Nascimento, Edilenor Serrano Cervino


This study examined the effects of long-term creatine supplementation combined with resistance training (RT) on the one-repetition maximum (IRM) strength, motor functional performance (e.g., 30+ chair stand, arm curl, and getting up from lying on the floor tests) and body composition (using DEXA scans) in older women. Eighteen healthy women (64 ± 5.0 yrs) were randomly assigned in a double-blind fashion to a creatine (C, N=9) or placebo (PL, N=9) group. Both groups underwent a 12-wk RT program (3d wk-1), consuming an equivalent amount of either creatine (5g × 4) or placebo. This study was conducted in accordance with procedures as set forth in Declaration of Helsinki. After 12 wk, the CR group experienced a greater (P<0.01) increase in training volume (Δ%, CR: 294.1 vs. PL: 129.9), fat-free mass (Δ%, CR: 3.2 vs. PL: no change) and muscle mass (Δ%, CR:3.7 vs. PL:0.9) and were more efficient in performing submaximal strength functional tests than the PL group. However, there was a similar increase in muscle mass when the groups were compared using the IRM bench press and curl knee extension pre- to post-test. No changes (P>0.05) in body mass or % body fat were observed. The results indicate that long-term creatine supplementation combined with RT improves the ability to perform submaximal-strength functional tasks and promotes a greater increase in fat-free mass and muscle mass in older women. However, creatine supplementation fails to promote additional benefits to maximal strength.

9.9 EFFECT OF INCREASING ESSENTIAL AMINO ACID AVAILABILITY FOLLOWING RESISTANCE EXERCISE ON SKELETAL MUSCLE LET-7 MRNA EXPRESSION IN OLDER MEN
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We have previously observed that relative to young individuals, older adults have an im- paired muscle protein anabolic response to resistance exercise (RE). However, provision of essential amino acids (EAA) postexercise overcomes this impairment. In addition, older adults have a higher basal expression of skeletal muscle Let-7 microRNAs (miRNAs), which is indicative of impaired cell growth, proliferation and cell cycle function. We hypothesized that increasing EAA availability following resistance exercise would reduce skeletal muscle Let-7 miRNA expression concomitant with increased expression of genes associated with satellite cell regulation and muscle protein anabolism (Pax7, MyoD) in older adults. Older men performed a bout of high-intensity resistance exercise and an 1h postexercise ingested 10g of EAA. Muscle biopsies (vastus lateralis) were obtained at rest and 2, 5 and 24h postexercise to examine miRNA and mRNA ex- pression. Let-7a, -7b, and -7e expression was reduced by ~10% at 2 and 5h and by ~15% at 24h, with Let-7e showing the greatest reduction at all timepoints. MyoD expression ~4 fold; PLA had less than two -fold increases in all measured genes. In conclusion, aerobic exercise combined with EAA supplementation enhances the expression of select AA transporter mRNA in the skeletal muscle of older adults. Future work will identify whether enhanced AA transporter expression is linked to mTOR signaling and muscle growth during aerobic exercise training.

NIH/NSF R01 AG03070.

9.11 AEROBIC EXERCISE ATTENUATES THE AGE-ASSOCIATED DETERIORATION OF HUMAN SKIN
Justin Crane, Lauren MacNeil, Bilal Braun, Daniel Ogborn, Mark Tamakolpour


Exercise is associated with a lower risk of cancer, neurological disease and diabetes, suggesting systemic benefits that may oppose the aging process. In order to better understand the underlying mechanism(s) for this reduction in disease incidence, we in- vestedigated the effects of long-term (~10 years) and short-term (3 months) aerobic exercise (AE) on the biological aging of human skin. Skin biopsies were acquired from the sun naive upper buttocks of individuals throughout the lifespan (20-86 y) that regularly exer- cised (N=51, ACT) as well as those who remained largely sedentary (N=56, SED). A subset of SED older adults (~64 y) underwent 5 months of AE training. Epidemiological studies have shown that exercise increases telomere length, age, was higher in SED compared to ACT subjects and short-term AE reduced SC thickness in SED older adults (P<0.05). Dermal collagen content was reduced with age, was higher in ACT subjects vs. SED and increased with AE training in elderly, SED subjects (P<0.05). Similarly, average skin telomere length was higher in ACT vs. SED (P<0.05) and tended to increase with AE in older adults (P<0.08). Overall, these results demonstrate that aerobic exercise can mitigate the effects of aging on skin when performed habitually as well as partially reverse these alterations in previously inactive older adults. Supported by NSERC.

10:0 PERSONALIZED EXERCISE PRESCRIPTION BASED UPON INTEGRATIVE BIOLOGY
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The response of VO2-max and cardiometabolic risk factors to exercise training is charac- terized by a significant genetic component. Transcriptomics and genomics can be used to investigate the molecular basis of this variation. Whole-genome transcriptomics from skeletal muscle yielded a panel of 29 transcripts whose abundance profile accounted for 58% of the variance in VO2-max gains among 24 sedentary men trained for 6 weeks. A genomewide association study in the HERITAGE Family Study was based on 324,611 single-nucleotide polymorphisms (SNPs). The top 21 SNPs explained 49% of the vari- ance in VO2-max trainability. The sum of favorable alleles was used as a genomic pre- dictor score, with a theoretical range from 0 (no beneficial alleles) to 42 (2 copies of the beneficial allele). Individuals in VO2-max groupings of those carrying 9 or less of these alleles and those carrying 19 or more represented a 3-fold range. An examination of the response distribution for risk factor traits in HERITAGE yielded suggestive evidence that there were adverse responders. Exploration of adverse responses in 5 other exercise intervention cohorts confirmed that the prevalence reached about 10% for any given risk factor with about 7% experiencing multiple adverse re- sponses. The identification of transcriptomic and genomic predictors of the ability to re- spond to regular exercise will illuminate the underlying biology and provide screening tools to potentially harm reduce the risk of adverse responses.
A family history of type 2 diabetes (e.g., first degree relatives, FDR) and low birth weight (LBW) are risk factors of type 2 diabetes and prediabetes to type 2 diabetes via genetically and environmental susceptibility, respectively. Providing a careful matching (e.g., age, habitual physical activity, body composition etc) these two groups represents very useful “models” for studying the influence of genes and environmental factors on responses to alterations in the daily physical activity level. Severe physical inactivity could possibly unmask their predisposition and reveal a larger vulnerability to physical inactivity than those without preexisting risk factors. Furthermore, comparisons between FDR and LBW may provide insights into the determinants of body weight and obesity. We have studied young men before and after a ten-day bed rest intervention study, which was followed by a four wk re-training program. Thirteen FDR (age: 26 ± 1 yr; body weight 80 ± 3 kg; BMI: 25 ± 1; VO2max: 44 ± 3 ml/min/kg) and twenty healthy controls (CON) (age: 25 ± 1 yr; body weight 72 ± 3 kg; BMI: 23 ± 1; VO2max: 44 ± 3 ml/min/kg) was included in the study. Imitation secretion and action, endothelial function, inflammation, and muscle transcriptional and translational changes was studied in a comprehensive experimental program. (Sonne MP, Albiggenov AC, Højbjerg L, Vaag A, Stallknecht B and Dela F. Effect of 10 days of bedrest on metabolic and vascular insulin action: a study in individuals at risk for type 2 diabetes. J Appl Physiol 108: 830-837, 2010.)

11.4 HIGH RESOLUTION PHYSIOLOGICALLY-BASED PHENOTYPING ALONG WITH AN INTEGRATED MEDICAL RECORD SYSTEM TO PROVIDE INSIGHT ABOUT INDIVIDUAL PATIENTS

Michael Joyner

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It is hoped that genetic information on individual patients will yield insights into pathophysiology and disease risk for both common and uncommon diseases. If successful then so-called “individualized medicine” will emerge. In this context, population based genetic studies on issues related to disease risk sometimes use data gleaned from medical records to add to their effort to identify heritable variants with disease phenotypes. In this talk, I will review the types of information available in typical medical records systems and the many limitations with it. I will also discuss issues related to data curation and other challenges associated with using essentially clinical tools for research purposes. These challenges are amplified by the loss of what might generally be described as “clinical phenotypes” of the patients’ expertise and capabilities at many (most) medical institutions. Several recent examples of how high resolution phenotyping of humans along with genetic data have yielded insights into disease risk will be discussed.

10.5 LIFESTYLE MEDICOPHARMACOGENETICS

Will Kraus

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There are very important interactions between genetic variation, exercise and pharmacologic therapies when considered with respect to therapeutic interventions for a variety of health and disease conditions. The concept that exercise is the best of all medicines has been developing over the past decade, leading to the Exercise is Medicine(TM) initiative being led by the American College of Sports Medicine. However, as will be discussed in this presentation, just as is the case with pharmacologic therapy, there is a wide range of responses—not all positive—when exercise is directed at improving a specific medical issue. What is relatively understudied is the variation in responses that are observed when exercise as a lifestyle medicine agent is combined with medical therapy, especially when directed at specific disease conditions. As an example of how different exercise intensities and their interactions with medications is of potential import, we have observed that women on combined hormone replacement therapy had a robust improvement in insulin-induced uptake of glucose into skeletal muscle in response to vigorous intensity exercise training, whereas women not on hormone replacement therapy had almost no improvement—on average—in these responses. In contrast, moderate intensity exercise effects were relatively invariant to hormone replacement effects in women. What is known about the three-way interactions of genetic variants, exercise as a therapeutic intervention (lifestyle medicine) and pharmacologic therapy will be discussed. Ref: Huffman KM, Slentz CA, Johnson JL et al., Mediators of exercise training-induced improvements in insulin action for sedentary overweight men and post-menopausal women. Metabolism 57:688-695, 2008.

11.6: ACETYLATION: LINKING CHANGES IN NAD TO METABOLISM AND GROWTH

11.2 PATHOPHYSIOLOGICAL SIGNIFICANCE AND THERAPEUTIC POTENTIAL OF NAMPT-MEDIATED NAD+ BIO-SYNTHESIS IN METABOLIC DISEASES

Jim Yoshino

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Sedentary lifestyles and calorie-rich diets have overwhelmed our adaptive metabolic pathways, contributing to the current epidemic of obesity and type 2 diabetes (T2D). In mammals, one such adaptive metabolic response is mediated by nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting NAD+ biosynthetic enzyme, and the NAD+-dependent deacetylase SIRT1. An accumulating body of evidence suggests that NAMPT-mediated NAD+ biosynthesis and SIRT1 together play a pivotal role in numerous biological processes, such as metabolism, stress response, and inflammation. Previously we discovered that NAMPT and SIRT1 comprise a novel transcriptional-enzymatic feedback loop for the regulation of circadian rhythm, thus demonstrating an interesting connection between metabolism and physiological rhythm. We have recently found that NAMPT-mediated NAD+ biosynthesis is severely compromised in metabolic organs of high-fat diet-induced T2D mice. Remarkably, nicotinamide mononucleotide (NMN), a product of NAMPT reaction, ameliorates glucose intolerance and insulin resistance by restoring NAD+ levels and SIRT1 activity. Furthermore, NIMN improves metabolic complications in age-induced T2D mice. These findings will provide great insights into the development of “nutriceutical” interventions, using key NAD+ intermediates, against metabolic diseases. REFERENCES: Yoshino J, Mills KF, Yoon M, Imai S. “Nicotinamide mononucleotide, a key NAD+ intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice.” Cell Metab. 2011;4(4):526-36.

11.3 REGULATION OF THE ADAPTIVE RESPONSE TO EXERCISE BY THE ACETYLTRANSFERASE GCN5

Andrew Phillips

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In the last decade, reversible acetylation of protein lysine residues has garnered significant attention as a fundamental means of modulating cellular metabolism. Protein acetylation status represents a balance between the activity of acetyltransferases that add acetyl groups to proteins, and deacetylases (that remove acetyl groups). Whilst the majority of work within this field has focused on the sirtuin (SIRT) family of protein deacetylases, little attention has been given to understanding the reciprocal role of acetyltransferases. The acetyltransferase, general control of amino acid synthesis 5 (Gcn5), has been implicated in the regulation of mitochondrial biogenesis and its ability to acetylate and suppress the activity of the transcriptional co-activator, PGC-1α. In this talk, the role and regulation of GCN5 will be discussed in the context of mitochondrial metabolism, with particular focus on recent data from our laboratory indicating novel regulation of GCN5 (and acetyltransferase activity) in response to endurance exercise. This talk will also discuss the therapeutic potential of targeting GCN5 in order to modulate mitochondrial function.

11.4 SIRTUINS: REGULATING METABOLISM WITHIN THE MITOCHONDRIA

Matthew Hirschey


Sirtuins are a family of NAD+-dependent protein deacetylases that have been shown to regulate cell survival and longevity, and have important metabolic effects. SIRT3 is localized to the mitochondria and regulates the acetylation status of several proteins. Acetylation is increasingly recognized as an important post-translational protein modification, particularly in metabolic regulation, and over one-third of all proteins in the mitochondria are acetylated. SIRT3 is upregulated during fasting, and plays an important role in nutrient sensing and energy homeostasis under metabolically stressed conditions. During high-fat diet feeding, SIRT3 is down regulated, and hepatic mitochondrial protein acetylation is elevated. Mice lacking SIRT3 (SIRT3KO) placed on a high-fat diet show accelerated obesity, insulin resistance, hyperlipidemia, and steatohepatitis compared to wild type mice. We further identify a single nucleotide polymorphism in the human SIRT3 gene that shows a strong genetic association with the metabolic syndrome. New post-translational acyl modification can also regulate metabolism. Our findings show loss of SIRT3 and dysregulation of mitochondrial protein acetylation is a hallmark of the metabolic syndrome and occurs in both mice and in humans. (Work supported by AHA 12SDG8840004 and 12RIRG0910008). References: Anderson, K. A. & Hirschey, M. D. Mitochondrial protein acetylation regulates metabolism. Essays Biochem. 52, 23–35 (2012); Hirschey, M. D. et al. SIRT3 Deficiency and Mitochondrial Protein Acetylation Accelerate the Development of the Metabolic Syndrome. Mol Cell 44, 177–190 (2011); Hirschey, M. D. et al. SIRT3 Deficiency and Mitochondrial Protein Hyperacetylation Accelerate the Development of the Metabolic Syndrome. Mol Cell 44, 177–190 (2011); Hirschey, M. D. et al. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacylation. Nature 464, 121–125 (2010).

11.5 THE HISTONE DEACETYLASE SIRT6, A CRITICAL MODULATOR OF GLUCOSE METABOLISM AND TUMORIGENESIS

Raul Mestaslovsky1, Lei Zhong2, Carlos Sebastián3, Debabrata Toh9, Jean-Pierre Etchegaray4, Barbara Martínez4, Sofia Gacsa5, Daline Silverman6, Carolin Costantino7


Efficient glucose metabolism is critical for maintaining cellular viability. Under hypoxia or nutrient stress, metabolism is switched to glycolysis, increasing lactate production and reducing mitochondrial respiration, a switch known to play an important role in cancer cell survival. As defined by Otto Warburg in the 1920s. Little is known about how glucose metabolism changes in response to metabolic stress. We have discovered that the mammalian SIRT6 is a chromatin acetyltransferase that influences glucose metabolism and DNA repair. In mice, SIRT6 deficiency promotes a profound and lethal hypoglycemia which culminates in accelerated death. At the cellular level, SIRT6 inactivation leads to increased cellular glucose uptake, higher lactate production and decreased mitochondrial activity. SIRT6 directly regulates expression of several key glycolytic genes. In this context, SIRT6 functions at chromatin to co-repress Hif1α, acting as a histone H3 lysine 4 (H3K4) deacetylase to inhibit expression of HIF1α target genes (Zhang et al., 2011). Strikingly, our new studies indicate that SIRT6, in contrast to other HDACs, appears to regulate transcriptional elongation, a novel function for histone deacetylases. Furthermore, the “glycolytic switch” observed in the absence of...
SIRT6 provides a unique growth advantage in the context of tumorigenesis, suggesting that SIRT6 might play a critical role in modulating the Warburg effect.

12.0: CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM ANIMAL STUDIES

12.2 EXERCISE AND CARDIAC ARRHYTHMIA

George Billman

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Sudden cardiac death resulting from ventricular tachyarrhythmias remains the leading cause of death in industrially developed countries. Yet, despite the enormity of this problem, both the identification of factors contributing to ventricular fibrillation as well as the development of safe and effective anti-arrhythmic agents remains elusive. Alterations in cardiac autonomic regulation that occur as a consequence of cardiac disease increase the risk for malignant ventricular arrhythmias. In particular, a subnormal cardiac parasympathetic regulation coupled with an elevated cardiac sympathetic activation following myocardial infarction can lead to intracalcellum calcium dysregulation and arrhythmias (1).

As it is well established that exercise training improves cardiac autonomic balance (increasing cardiac parasympathetic regulation and restoring a more normal beta-adrenergic balance), this intervention could protect against life-threatening changes in cardiac rhythm (1). Indeed, a growing body of experimental and epidemiological data suggests that aerobic exercise conditioning can dramatically reduce cardiac mortality in both healthy individuals and patients with pre-existing cardiac disease (1). Conversely, a sedentary lifestyle is strongly associated with an enhanced risk for chronic debilitating diseases (1). Thus, prudently designed exercise training programs may reverse the autonomic imbalance and lethality induced by cardiac disease thereby enhance the arrhythmia stability of the heart in individuals shown to be at an increased risk for sudden cardiac death. [Reference: 1. Billman GE, Am J Physiol Heart Circ Physiol 297:H1171-H1193, 2009].

12.4 EXERCISE, SARCOLEMMA KATP CHANNELS AND CARDIOPROTECTION

Leonid Zingman

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Physical activity is one of the most important determinants of cardiac function. The ability of the heart to increase delivery of oxygen and metabolic fuels relies on an array of adaptive responses necessary to match bodily demand while avoiding exhaustion of cardiac resources. The ATP-sensitive potassium (K_{ATP}) channel has the ability to adjust cardiac membrane excitability in accordance with the metabolic status of the cell, and up-regulation of its expression that occurs in response to exercise could represent a critical element of this adaptation. However, the mechanism by which K_{ATP} channel expression changes result in a beneficial effect on cardiac excitability remains to be established. We demonstrate that an exercise-induced rise in K_{ATP} channel expression enhanced the rate and magnitude of action potential shortening in response to heart rate acceleration. This adaptation in membrane excitability promoted significant reduction in cardiac energy consumption. Genetic disruption of normal K_{ATP} channel pore function abolished the exercise-related improvement in action potential duration adjustment and caused increased cardiac energy consumption. Thus, an exercise-driven enhancement in the ability of K_{ATP} channels to respond to alterations in cardiac workload represents a previously unrecognized mechanism for adaptation to physical activity and a potential target for cardioprotection. NIH HL093368. Zingman LV, Zhu Z, Sierra A, Stepniak E, Burnett CM, M. Czajkowski G, Anderson ME,. Coetzee WA, Hodgson-Zingman DM. Exercise-induced expression of cardiac K_{ATP} channels promotes action potential shortening and energy conservation. J Mol Cell Cardiol. 51:72-91, 2011.

12.5 CARDIAC KATP CHANNELS AND EXERCISE CARDIOPROTECTION

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Ischemic heart disease is a leading cause of morbidity and mortality in industrialized nations, while exercise is an important countermeasure against ischemic heart injury. Exercise induced cardioprotection research reveals that multiple cellular mechanisms mediate protection against ischemia-reperfusion injury (IR). Within exercised hearts, protective mechanisms appear to be unique to major clinical benchmarks of IR injury in that different mechanisms protect against IR-induced ventricular arrhythmias, contractile dysfunction, and tissue death. Amongst recently studied cardioprotective mechanisms are the ATP-sensitive potassium channels (KATP) located in the sarcolemma and inner membrane of the mitochondria. Mitochondrial KATP channels appear to mediate protection against ventricular arrhythmias experienced during IR, while sarcolumellar KATP channels are responsible for partially preventing tissue death in exercised hearts. Observations of tissue sparing efficacy following experimental IR challenges promote myocardial tissue necrosis, but not apoptosis. Preliminary evidence also suggests that both mitochondrial and sarcolumellar KATP channel activity within exercised hearts may improve cardiac tissue viability through preservation of autophagy in the hours immediately following IR.

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

13.3 INTRINSIC FITNESS AND EXERCISE PREVENT HEPATIC LIPOTOXICITY

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Hepatic steatosis, the excessive storage of lipids in the liver, increases risk for liver injury (steatohapatitis and cirrhosis), and is also linked to hepatic insulin resistance and the metabolic syndrome. Both physical inactivity and low aerobic fitness are linked to increased prevalence of steatosis, while exercise is an effective treatment, however, liver specific mechanism(s) for these associations remain poorly understood. We have shown that a physical activity (voluntary wheel running) both effectively prevents and treats hepatic steatosis in a hyperphagic, obese rat model. We have also shown that sedentary rats bred to have reduced fitness (low capacity runners (LCR)) display increased susceptibility to hepatic steatosis and aging induced liver injury compared to sedentary rats bred for high fitness (high capacity runners (HCR)). In both cases, daily physical activity or high aerobic fitness is associated with higher hepatic mitochondrial content and complete fatty acid oxidation, suggesting that these factors play a role in susceptibility for steatosis. Current studies are testing if there are differential responses in lipid metabolism between low fit-LCR and high fit-LCR rats with acute and chronic high fat diets known to induce steatosis and if genetically altering mitochondrial content and function modifies these responses.

13.4 EXERCISE, IL-6 AND ADIPOSE TISSUE METABOLISM

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Obesity is a dysfunctional metabolic alteration characterized by the excessive expansion of the white adipose tissue (WAT) that develops as a result of prolonged positive energy balance. Therefore, strategies aimed at depleting the fat content of the WAT are of great relevance for the treatment of obesity and its co-morbidities. In this context, several studies have demonstrated that metabolism of the WAT can be remodelled to increase its ability to dissipate energy within itself and reduce lipid storage. Studies in rodents show that this can be achieved through chronic pharmacological activation of the cellular energy sensor AMP-activated protein kinase. This approach up-regulates the oxidative machinery of the WAT, increases spontaneous physical activity and whole-body energy expenditure, and reduces adiposity. More recently, it was also demonstrated that chronic endurance exercise induces the expression of thermogenic genes in the WAT conferring to it a phenotype typical of brown adipose tissue. Interestingly, these effects seem specific to subcutaneous fat depots, since visceral fat depots show very limited ability to acquire a “brown-like” phenotype under chronic endurance training conditions. Unraveling the mechanisms by which pharmacological agents and endurance exercise remodel WAT metabolism may lead to the development of new strategies to improve the long-term success rate in the treatment of obesity and its co-morbidities. Reference: Gadhou MP, Frontini A, Hung S, Pistor K, Cinti S, Ceddia RB (2011) Chronic AMP-kinase activation with AICAR reduces adiposity by remodeling adipocyte metabolism and increasing leptin sensitivity. J Lipid Res. 52(9):1702-11.

15.0: CARDIOVASCULAR BENEFITS OF EXERCISE: INSIGHT FROM HUMAN STUDIES

15.5 EXERCISE ATTENUATES THE PREMATURE CARDIOVASCULAR AGING EFFECTS OF TYPE 2 DIABETES MELLITUS

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Type 2 diabetes mellitus (T2D) is an example of a disease process that results in decreases in function additional to those imposed by the inexorable 'primary aging' process.
These decrements due to disease, rather than primary aging, can be termed 'secondary aging', and include the premature development (as early as adolescence) of asymptomatic preclinical cardiovascular abnormalities (e.g. endothelial dysfunction, arterial stiffness, diastolic dysfunction), as well as impaired exercise performance. These abnormalities are important, as the combination of greater cardiovascular morbidity and mortality in people with and without T2D. A better understanding of the pathophysiology of secondary cardiovascular aging in people with T2D is warranted, and an evaluation of the benefits of existing treatments for these abnormalities is useful (e.g. exercise training).

The focus of this review is to discuss the data relevant to the following key postulates: (a) Excess accumulation of lipids in oxidative tissues in obesity and diabetes can cause cellular damage in tissue, and this may be deleterious to cell survival and function. Partial, IMCL in skeletal muscle is responsible for the development of muscle insulin resistance and mitochondrial lipotoxicity. (b) Cardiac muscle but due at least in part to alterations in LD function. To directly examine the relationship between myocardial lipotoxicity and dysfunction is not simply due to the presence of LDs in cardiac muscle but due at least in part to alterations in LD function. To directly examine the function of cardiac LDs by overexpressing perilipin 5, a lipid droplet associated protein, and member of the perilipin protein family. To investigate perilipin 5 function in vivo, we obtained transgenic mice with heart-specific perilipin 5 over-expression (MHC-Plin5). These mice have a strong cardiac LD phenotype. Hearts from MHC-Plin5 mice expressed at least 20-fold higher levels of Plin5 and exhibited a 3.5-fold increase in triglyceride content versus transgenic littermates. Cardiac excess accumulation of LDs was found to result in mild heart dysfunction with decreased expression of a subset of PPARα target genes, decreased mitochondrial function and left ventricular concentric hypertrophy. Lack of more severe heart function complications may have been prevented by the strong increased expression of oxidative induced genes via NF-E2-related factor 2 pathway. Our results suggest that perilipin 5 plays an important role in stabilizing cardiac LDs and promote cardiac steatosis without major heart function impairment. NHI002, RO1 DK 075017, AHA Grant in Aid 11GRNT670027, P50 DK072488-01, VA GRECC.

18.0: MICROcircULATION
18.1: CHRONIC (-)EPICATECHIN ADMINISTRATION DOES NOT CHRONICALLY ALTER SKELETAL MUSCLE MICRO-VASCULAR OXYGENATION

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2The flavanol (-)epicatechin is a naturally occurring component of cocoa, consumption of which is associated with numerous cardiovascular health benefits. Chronic EPI reportedly augments skeletal muscle capillarity and mitochondrial density (Nogueira et al., J Physiol, 589, 2011). These effects may translate to improved skeletal muscle oxidative capacity, O2 delivery-utilization matching (i.e. mitochondrial O2 pressure (PmO2)) during contractions. We tested the hypothesis that EPI would elevate PmO2 at rest and during contractions. Rats were administered EPI (2mg/kg, n=5) or water (CON; n=5) via oral gavage twice daily for 21 days. PmO2 was measured via phosphoreseence quenching in the spinotrapezius muscle at rest and during 180 s of 1 Hz twitch contractions. PmO2 did not change resting baseline PmO2 (PmO2=29±4; C=30±2 mmHg; p>0.05). Following the onset of contractions the time delay (EPI=9±1; C=8±2 s; p>0.05) and time constant (time to 63% of transient response, EPI=16±4; C=23±3 s; p>0.05) of the PmO2 fall were not altered by EPI nor was contracting steady-state PmO2 (EPI=18±4; C=19±2 mmHg; p>0.05). Despite previous reports of the efficacy of EPI to improve the O2 transport pathway, the present data indicate that chronic EPI treatment (2mg/kg) does not improve skeletal muscle microvascular oxygenation at rest or during contractions. (Funding: ACSM, AHA Midwest Affiliate 0750090Z, NIH HL-108328).

18.2: RELATION OF ARTERIO-VENOUS DIFFERENCES IN NITRATE AND NITRITE TO OXYGEN CONTENT AND ACID BASE STATUS
Norbert Maasen1, Katja Sutsmeller1, Heiner Stadler1, Mirja Maasen2, Dimitrios Tsikas2

We had two aims with the study 1) To evaluate the influence of acid base state and the oxygenation of the blood on the Nitrate and Nitrite concentration 2) To test whether NO3 and NO2 in arterialized blood of a superficial hand vein differs from arterial blood.

METHODS: 5 subjects (5 males and 2 females) took part in the study. No prescription related to food intake was given. Blood was sampled from the arteria radialis, a cubital vein and a superficial hand vein. The hand was warmed by a heating pad. Acid base status was measured by an ABL 520 and plasma NO2 and NO3 by mass-spectroscopy.

RESULTS: Oxygen saturation was 98 % (art), 58 % (cub), and 90% (hand). The respective [NO3] were 51.53, 47.14, and 50.35 μM/μl. Cub was significantly lower than art (p<0.02). The differences between hand and art were not significant (p<0.76). [NO2] were 0.98 (art), 0.98 (cub), and 0.95 mmol/l (hand). None of the differences between the sampling sites was significant. No meaningful correlation between NO3 and HBO2, PCO2, and pH could be found. The same holds true for [NO2]. There was no significant correlation between [NO3] and [NO2] blood from an arterialized hand vein corresponds to arterial blood.

18.3: FOXO1 AND FOXO3A ARE INVOLVED IN THE REGULATION OF EXERCISE INDUCED ANGIOGENESIS
Dara Slapok1, Sammy Li2, Emilie Roudier1, Olivier Binot3, Andreas Morel-Moula2, Tomas Gustafsson1, Tina Hans1

The Forkhead Box “O” (FOXO) family of transcription factors are known to be anti-angiogenic. We hypothesized that downregulation of FOXO1 and FOXO3a in capillaries in response to repeated aerobic exercise contributes to the typically observed angiogenic response. In mice exercised on a treadmill, both FOXO1 and FOXO3a protein in plantaris muscle was increased in response to repeated aerobic exercise contributes to the typically observed angiogenic response. In mice exercised on a treadmill, both FOXO1 and FOXO3a protein in plantaris muscle was increased. These results are consistent with previous observations that exercise training reduces FoxO proteins in skeletal muscle, and that further reduction in FoxO proteins accelerates the angiogenic response. Conditional deletion of FoxO1,3,4 (MxCre:FoxO1,3,4fl/fl) in mice resulted in reduced vascular endothelial expression of FoxO1 and 3a, and promoted an earlier increase in capillary number, which was detectable after 7 days of training compared to 14 days in wildtype littersmates. We assessed FOXO protein levels in humans in response to prolonged (6 weeks) training. These subjects were classified retrospectively as high or low responders based on their % increase in VO2 max. Following training, FoxO1 and FoxO3a levels were elevated in the high but not the low responder group. Our results demonstrate that FoxO1 and FoxO3a are down-regulated in response to short term training, and that further reduction in FoxO proteins accelerates the angiogenic response. In contrast, an increase in FoxO proteins following prolonged training, as seen in the human high responder group, correlates with markers of matrix synthesis and may indicate a role for FoxO proteins in stabilizing the newly expanded vascular network. Funded by CIHR.

18.4: MYOCEDELIVERED VEFG REGULATES ADAPTATIONS TO INCREASED BLOOD FLOW IN SKELETAL MUSCLE

2012 APS Interociety Meeting: The Integrative Biology of Exercise-VI
ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS
18.5 THE IMPACT OF NEURONAL NITRIC OXIDE SYNTHASE (NOS) EXPRESSION ON NUTRITION AND PERFORMANCE: THE CAPILLARY SYSTEM IN SKELETAL MUSCLE OF MICE

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Given the sarcocerebral development of neuronal nitric oxide synthase (nNOS), we hypothesized that nNOS-generated NO might be involved in the communication between muscle fibers and the central nervous system to influence performance. We therefore subjected male wild type (WT) mice and nNOS-knockout (KO) littermates (n=8 in both strains) at the age of 12 weeks to an incremental and a run-to-exhaustion (conducted at 70% of maximal velocity) exercise test on a treadmill. Peak power (±8.3%) as well as time to exhaustion (±7.8%) and distance (±16.9%) were not significantly different between the NOS-KO mice and WT mice. Both the C/F-ratio (±12.1%; p≤0.05) and the mean cross-sectional fiber area (±25.9%; p≤0.05) were significantly lower in the extensor digitorum longus muscle (EDL) of nNOS-KO mice than in that of their WT counterparts. Not surprisingly, therefore, the number of capillaries was higher in the EDL of the nNOS-KO mice than in that of the WT mice (±15.9%; ns). Finally, the capillaries in the EDL of both mouse strains subjected to a morphometric analysis at transmission electron microscopy level. Mean cross-sectional capillary area, volumes densities and the surface-to-volume ratios of the capillary fractions (lumen, endothelial cells, pericytes, basement membrane) differed only non-significantly between the nNOS-KO mice and the WT mice. In summary, we conclude that EDL muscle fibers from mice lacking nNOS are smaller and more richly supplied with capillaries than those of WT mice.

18.6 AMELIORATIVE EFFECTS OF ANTIOXIDANT ASTAXTHAN IN CAPILLARY REGRESSION IN HINDLIMB UNLOADING-INDUCED ATROPHIED MUSCLE

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PURPOSE: Oxidative stress is proposed as the initial pathologic step of skeletal muscle atrophy. In order to investigate the ameliorative effects of astaxathin (ASX), an antioxidant, on capillary regression in the soleus muscle during hindlimb unloading (HU) and to elucidate the regulations of pro- and anti-angiogenic factors. METHODS: Twenty-four adult male Wistar rats were assigned randomly either to a control, control treated with ASX, HU, or HU treated with ASX group. RESULTS: HU for 7 days resulted in a decrease in muscle weight, capillary number and volume in the atrophied muscle. In addition, the accumulation of pro-angiogenic oxygen species, the overexpression of SOD-1, a decrease in the level of VEGF and its receptors and angiopoietins, and an increase in the level of thrombospordin-1 (TSPI), an anti-angiogenic factor, were observed in the atrophied muscle. Administration of ASX attenuated the changes in SOD-1, VEGF, TSPI-1, and other angiogenic factors, and prevented the capillary regression in the atrophied muscle. Furthermore, the VEGF-to-TSPI-1 ratio was higher in the ASX treated groups than in the control and HU groups. CONCLUSIONS: These results suggest that ASX may be an effective treatment to counter a chronic decrease in the capillary network in skeletal muscle, and associated with angiogenic factors. Supported by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

18.7 CHRONIC HEART FAILURE AND MUSCLE MICROVASCULAR OXYGENATION: EFFECTS OF EXERCISE TRAINING

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Vascular endothelial growth factor (VEGF) is a key regulator of vascular remodeling, and can be produced by both mesenchymal and endothelial cells. Skeletal muscle angiogenesis can be initiated by either metabolic or hemodynamic stimuli. Skeletal muscle VEGF is required for exercise-induced angiogenesis. We hypothesized that muscle-derived VEGF is not required for vascular adaptations to increased blood flow. Myocyte-specific VEGF deleted (mVEGF−/−) mice or wildtype littermates were treated with prazosin for 14 days to induce a sustained increase in blood flow. The baseline capillary to fiber ratio, vascular area and number of small smooth muscle actin positive vessels were reduced in the EDL muscles of mVEGF−/− vs. WT littermates (p<0.01, n=3-7 per group). Prazosin treatment resulted in an increase in vascular area in the EDL of WT but not mVEGF−/− mice, suggesting that angiogenesis was inhibited by the muscle VEGF deletion (p<0.05, n=3 per group). Preliminary evidence also indicates that arteriolar remodeling may not occur in the mVEGF−/− mice treated with prazosin, as the number of large smooth muscle actin positive vessels tended to increase in the WT but not mVEGF−/− mice (p<0.05). Our results show that lack of myocyte-derived VEGF impairs development of an appropriate microvascular network and prevents vascular adaptations to increased blood flow within skeletal muscle. Funded by NSERC and the Heart and Stroke Foundation of Canada.

18.8 THE EFFECTS OF ACUTE DIETARY NITRATE SUPPLEMENTATION ON MUSCLE MICROVASCULAR OXYGENATION IN CONTRACTING RAT MUSCLE

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Nitric oxide (NO) bioavailability modulates the O2 supply/utilization matching (PO2mv) within the muscle microvasculature. Recently, increased NO via dietary nitrate supplementation has been shown to decrease the O2 cost of submaximal exercise in humans. However, the effects of nitrate supplementation on the PO2mv remain uncertain. We tested the hypothesis that acute dietary nitrate supplementation via beetroot juice (BR) would improve muscle microvascular oxygenation during metabolic transitions. Young male Sprague-Dawley rats were randomized into control or nitrate-supplemented groups. Either untreated (control, n=11) or nitrate supplemented (1 mmol/kg/day BR, n=8) distilled water was available ad libitum for 5 days and consumption monitored. PO2mv was measured in the spinotrapezius muscle using phosphorescence quenching at rest and during 1 Hz twitch contractions. The time delay preceding the fall in PO2mv at contractions onset was longer in BR (Control: 7.1s; BR: 13.2±s, p<0.05). BR also had a slower rate of PO2mv fall (mean response time: Control: 17.2s; BS: 26.3±s, p<0.05) and lower PO2mv amplitude (Control: 17.1s; BR: 11.1±s, p<0.05). Dietary nitrate improves microvascular oxygenation throughout contractions suggesting that BR elevates muscle O2 delivery relative to O2 demand. The BR induced enhanced driving pressure for transcapillary O2 flux constitutes a potential mechanism for improved metabolic control and exercise tolerance. NIH HL-108328, AHA Midwest Affiliate 0750090Z, NIH HL-108328.
19.2 ALTERATIONS IN CEREBRAL BLOOD FLOW DURING EXERCISE AT HIGH ALTITUDE
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We examined changes in regional cerebral blood flow (CBF) and arterial blood gases at rest and during supine incremental cycling exercise to exhaustion at sea level (SL) and high altitude (HA; 2000 m). Blood flow in the internal carotid (QICA) and vertebrobasilar (QVA) artery (vascular ultrasound) and velocity (transcranial Doppler) was monitored in distal cerebral arteries (middle [MCV] and posterior [PCV]). Arterial blood pressure, arterial PO2 (PaO2) and arterio-venous PO2 difference (PaO2-PCO2) were sampled during steady state changes at 20, 40, 60, 80 and 100% of the maximum achieved wattage (% Wmax) at each condition. Regional cerebral oxygen delivery (DO2) was calculated as the product of arterial O2 content (CaO2) and CBF and O2 uptake (VO2). Blood flow changes were compared with normoxic conditions (P<0.05) using DO2 and CBF calculated in all cerebral arteries (ICA, VCA and PCA) at 40%, 60%, 80%, 90% and 100% Wmax. Overall, CBF remained constant during HA, whilst VO2 decreased during HA (P<0.05). Regional cerebral oxygen delivery at 100% Wmax was lower during HA compared with SL (P<0.05). Blood flow to the brain was reduced during exercise at HA (P<0.05), which likely helped to maintain effective cerebral O2 delivery. During exercise at HA compared with SL, there were greater (range, 27±3 % to 40±5 %; P<0.05) reductions in CBF (QICA and QVA) for the same increase in exercise intensity.

19.3 EFFECT OF PCO2 CLAMPING ON BRAIN BLOOD FLOW, OXYGENATION AND PERFORMANCE DURING 15 KM TIME TRIAL CYCLING IN SEVERE HYPOXIA
Sui Liu¹, Emi², Nicole Bourdillon², Benet Kaspar³
During exercise in hypoxia, hyperventilation-induced hypocapnia leads to cerebral vasodilation and a reduction in cerebral blood flow (CBF). This impairs cerebral O2 delivery and could account for the reduced exercise performance in hypoxia. We measured end-tidal PCO2 (PETCO2), ventilation (VE), middle cerebral artery velocity (MCV; index of CBF), brain and muscle oxygenation ([O2Hb] and cerebral PO2) and cerebral blood flow (SMBFV; Doppler ultrasound) were measured during 25 min of an 80% Wmax exercise. We hypothesized that cerebral blood flow (CO) would be reduced during exercise in hypoxia, presumably due to a greater vasodilatory effect of the hypoxic stimuli. These findings refute the hypothesis.

19.4 CONTRIBUTION OF NITRIC OXIDE TO EXERCISE HYPEREMIA IN OBESE ADULTS
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INTRO: Previous research indicates obese adults exhibit impaired endothelial dependent dilation due, in part, to reduced nitric oxide (NO) bioavailability in resting skeletal muscle. The contribution of NO to exercise hyperemia in young obese adults is currently unknown. We hypothesized the relative contribution of NO to exercise hyperemia would be lower in young obese adults when compared to lean adults. METHODS: Three healthy lean (23±2 yrs, BMI=24±1) and 3 obese adults (25±3yrs, BMI=39±6) performed 10 minutes of dynamic forearm exercise (20 contractions/minute) at 15% of maximal voluntary contraction. A brachial artery catheter was used for continuous blood pressure (BP) measurements and local infusion of the NO synthase inhibitor, L-NAME (10 μM) during the final 5 minutes of exercise. Forearm blood flow (FBF) was measured using laser-Doppler flowmetry, and forearm vascular conductance (FVC) was calculated (FBF/ΔP). RESULTS: Steady state FBF was similar between lean and obese adults (201±183 ml/min/100mmHg). Infusion of L-NAME, lean subjects’ FVC decreased by 29±6% (P=0.02) and FBF by 28±6% (P=0.01). FVC was also decreased in FBF after β-adrenergic receptor inhibition (propranolol). FBF was similar between groups (~26 % vs 24% respectively). CONCLUSION: The effect of NO synthase inhibition on exercise hyperemia appears to be similar between groups, suggesting the contribution of NO to exercise hyperemia remains intact in young obese adults. Support: NIH R01 grant #HL05820.

19.5 EFFECT OF β-ADRENERGIC BLOCKADE ON EXERCISE HYPEREMIA IN METABOLIC SYNDROME
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In younger healthy adults, β-adrenergic mediated vasodilation does not contribute to moderate intensity exercise hyperemia. Adults with metabolic syndrome (MetSyn) exhibit greater sympathetic nerve activity which may activate this vasodilator system during exercise. We hypothesized MetSyn adults would demonstrate a significant reduction in steady state exercise hyperemia after β-adrenergic blockade. We studied 14 adults with metabolic syndrome (31.3±y; 16 healthy controls (351±y). Forearm blood flow (FBF, Doppler ultrasound) and blood pressure (MAPB) were measured during 4 minutes of dynamic forearm exercise at 15% maximal voluntary contraction under control conditions and after non-specific β-adrenergic receptor inhibition (propranolol). Propranolol was infused via brachial arterial catheter. Due to higher MAPB in MetSyn, FBF was normalized for perfusion pressure by calculating forearm vascular conductance (FVC = FBF / MAPB). Changes in steady-state FVC with propranolol infusion were assessed. The rise in FVC with exercise was greater in adults with MetSyn when compared with healthy controls. There was no significant effect of propranolol infusion on FVC in either group. β-adrenergic receptor-mediated vasodilation is not obligatory to moderate intensity exercise hyperemia in metabolic syndrome adults. Funding: AHA 10PRE3870000, NIH R01HL105820.

19.6 EFFECT OF ENDURANCE TRAINING ON SPLANCHNIC CIRCULATION DURING HEAD-UP TILT
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Endurance training (ET) has been reported to increase orthostatic intolerance. The splanchnic circulation contains up to ~30% of blood volume and receives ~25% of cardiac output at rest. Moreover, upon standing vasocostriction of the splanchnic bed contributes to increased peripheral resistance. The aim of this study was to determine the effect of ET on superior mesenteric (SM) vascular responses to orthostatic stress. It was hypothesized that SM vasoconstriction would be attenuated after ET.

19.7 VASOCONSTRICTOR RESPONSIVENESS DURING HYPERBARIC HYPOXIA IN CONTRACTING HUMAN MUSCLE
Dawson Casey¹, Michael Joyner², Paul Claret³, Maureen Bagley³, William Paquet³, Timothy Carey³
¹Anesthesiology, Mayo Clinic, 200 First St. SW, Rochester, MN, 55905, ²Preventative, Occupational, & Aerospace Med., Mayo Clinic, 200 First St. SW, Rochester, MN, 55905. We tested the hypothesis that sympathetic vasomotor tone (blunting of β-adrenergic vasoconstriction) is attenuated during hyperoxic exercise. Nine male subjects (28±1y) performed forearm exercise (20% of maximum; 70 mmHg) in a hyperbaric chamber under normoxic (1 ATA while breathing 21% O₂) and hyperoxic (2.82 ATA while breathing 100% O₂) conditions. Forearm blood flow (FBF; ml/min) was measured using Doppler ultrasound. Forearm vascular conductance (FVC) was calculated from FBF and blood pressure (mmHg; brachial arterial catheter). Vasoconstrictor responsiveness was de-termined with intra-arterial infusion of the final 3 min of rest and each exercise bout. FBF and FVC were ~20% lower during hyperoxic exercise compared to normoxic. At rest, vasoconstrictor responsiveness did not differ between normoxic and hyperoxic conditions. However, during exercise at 1ATA, vasoconstrictor responsiveness was greater during hyperoxic compared to normoxic (P=0.02). During exercise at 2.82ATA, vasoconstrictor responsiveness was greater during hyperoxic compared to normoxic (P=0.001). Thus, the attenuated forearm vascular conductance of hyperoxic exercise was significantly greater at 2.82ATA. During exercise at 1ATA, vasoconstrictor responsiveness did not differ between normoxic and hyperoxic conditions.

19.8 ALTERATIONS IN ENDOThelial FUNCTION WITH PHYSICAL INACTIVITY: A PRELIMINARY REPORT
2012 APS Intersociety Meeting: The Integrative Biology of Exercise-VI

ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS

Leryn Boylei, Daniel Creedz, Seth Holwerda, Heather Leidy, Jaime Padilla, John Thybuln, Paul Fude
Nutrition & Exercise Physiology, Univ. of Missouri, 106 Mckee Gym, Columbia, MO, 65211, Medical Pharmacology & Physiology, Univ. of Missouri, 1 Hospital Dr, Columbia, MO, 65211, Biomedical Sciences, Univ. of Missouri, 65211. Previous bed rest studies have reported impaired endothelial function. However, the early effects of a transition from high (>10,000 steps/day) to low ambulatory activity (~5,000 steps/day) on endothelial function are unknown. Thus, we sought to examine the time course of change in endothelial function following 5 days of inactivity, and after 1 day return to activity (RA) in young, healthy men. Four recreationally active men (26±3 yrs, 20±1.8% body fat) performing ~10,000 steps/day underwent 5 days of reduced ambulatory activity (~5,000 steps/day), followed immediately by RA (~10,000 steps/day). Endothelial function was assessed in the arm (brachial) and leg (popliteal) using flow-mediated dilation (FMD) at baseline, 1, 3, and 5 days following inactivity, and RA. Subjects consumed a standardized diet throughout. Brachial FMD normalized to shear stimulation was not significantly altered over 5 days of inactivity or following a 1 day RA. However, popliteal FMD normalized to shear appeared lower following inactivity and was maintained with RA: baseline 5: 0.52±0.25, inactivity 1: 0.46±0.22, inactivity 3: 0.21±0.09, inactivity 5: 0.10±0.05, RA 0.17±0.08, p<0.05). These preliminary findings suggest that short term reductions in daily ambulatory activity impairs leg but not arm endothelial function. Furthermore, a 1 day RA did not appear to be sufficient to return endothelial function to pre inactivity values. Funded by HL-093167 (PJF) & 5 T32 AR048523 (LJB).

20.0: CARDIOVASCULAR

20.1 REGULAR EXERCISE REVERSES SUPPRESSIONS OF SERCA ACTIVITY AND β-MHC EXPRESSION IN THE HEART OF ORCHIDECTOMIZED RAT

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A high incidence of heart disease by hypogonadal men indicates a crucial role of male sex hormones in cardiac function. Suppressions of both cardiac systolic and diastolic functions have been reported in orchectomized (ORX) rat. We have also found decreases in SERCA activity and β-MHC expression in ORX rat heart which could be reversed by testosterone supplement. Unfortunately, the use of testosterone is precluded in some patients. We then tested whether regular exercise could prevent the systolic and diastolic dysfunction in ORX rat. With the protocol approval by Experimental Animal Committee, Faculty of Science, Mahidol University, in accordance with guidelines of Guiding Principles for the Care and Use of Animals, adult male rats were divided into sham and ORX rats with/without regular exercise. One week after sham-operation or orchectomcy, exercised rats were subjected to a nine-week treadmill running program with moderate intensity. Results showed an induction of cardiac hypertrophy in both sham and ORX rats after regular exercise. Using triple enzyme assay, the suppressed maximum SERCA activity detected in the heart of sedentary ORX rat was disappeared in exercised ORX rat. Regular exercise also completely normalized the enhanced β-MHC sensitivity of SERCA observed in OVX rat heart. Moreover, the shift of α-MHC toward β-MHC observed in the heart of ORX rat was also abolished by regular exercise. This study was granted by Mahidol University.

20.2 REGULAR EXERCISE PREVENTS THE CARDIAC MYOFILAMENT Ca2+-HYPERSENSITIVITY IN GASTROINTESTINAL INJURY-FUSED OVA RIECTOMIZED RAT

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The myofilament Ca2+-hypersensitivity detected in ovariectomized (OVX) rat heart was further enhanced after chronic AII infusion. We therefore tested in this study whether the preventive effect of regular exercise on changes in cardiac myofilament activity observed in OVX rat also extends to the heart of all-infused OVX rat. With the protocol approval by Experimental Animal Committee, Faculty of Science, Mahidol University, in accordance with guidelines of Guiding Principles for the Care and Use of Animals, adult female rats were divided into two main groups, exercise and sedentary, with four subgroups: sham and sham rats without/AII infusion, in each main group. One week after sham-operation or ovaritectomy, exercised rats were subjected to a nine-week treadmill running program with moderate intensity. All was infused using mini-osmotic pump throughout the last four weeks of 10-week study duration. As expected, the cardiac myofilament Ca2+-hypersensitivity detected in OVX rats/AII-infused, and all-infused OVX rats was all disappeared after regular exercise. An increased tropomyosin phosphorylation in OVX rat hearts but a decreased regulatory light chain phosphorylation in all-OVX rat hearts was also completely normalized by regular exercise. Surprisingly, exercise only reversed a shift of Ca2+ in the heart of OVX but not all-OVX rats. This work was granted by Faculty of Science, Mahidol University.

20.3 SARCOLIPIN (SLN) AND PHOPHOLAMBAN (PLN) PROTECT SARCOMERONEPLASMATIC RETICULUM CA2+ATPASE (SERCA) FUNCTION DURING HEAT SHOCK

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Mitochondrial permeability transition pore (MPTP) opening is an important triggering event for inducing apoptotic cell death. This study aimed to analyse whether a combination of intermittent hypobaric-hypoxia (IHH) and endurance-training (ET), two effective non-pharmacological cardioprotective strategies, afford synergistic effects to a more resistant phenotype against heart mitochondrial-driven apoptosis. Wistar rats were: normoxic-sedentary (NS), normoxic-exercised (NE, 1 h/d treadmill running), hypoxic-sedentary (HS,600m,5h/d) and hypoxic-exercised (HE). In vitro susceptibility to calcium-induced MPTP, CypD, ANT, Bax, Bcl2, MDA, –SH contents, caspase 3, 8, 9, aconitase, MnSOD activities, and HIF-1α gene expression were determined. The susceptibility to MPTP decreased in NE, HS and HE vs. NS and even further in HE. ANT increased in HE. Bc-2/Bax ratio increased in HE and HS. Decreased caspase 3 activity in HE vs. NS and HS and caspase 9 in HE vs. NS and NE were observed. Aconitase activity increased in HE and HS vs. others. No significant differences between groups were observed regarding MnSOD and caspase 8 activities, MDA and –SH contents. IHH and ET synergistically modulate heart mitochondria into a more resistant phenotype against calcium-induced MPTP opening and apoptotic signaling although without visible additive effects. JUP-71-2009; FCT-PDI/DCES/113580/2009.

20.5 ENDURANCE-TRAINING IN EARLY LIFE RESULTS IN LONG-TERM PROGRAMMING OF CARDIAC HYPERTHROPHY IN RATS

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This study examined the impact of short-term endurance-training early in life on cardiac hypertrophy in adulthood. Male WKY rats were allocated to sedentary (SED) or exercise group either early in life (Early Ex) or later in life (Late Ex) (N=10/group). The rats ran on a motorised treadmill 1h/d, 5d/wk for 4 wks. The Early Ex group trained at 5.9 wks, the Late Ex trained at 20-24 wks, with all rats killed at age 24 wks. The study was approved by the University of Melbourne ethics committee and conformed to the APS guidelines for the Care and Use of Animals. Compared to SED rats, there was a significant (P<0.05)~10% increase in relative heart mass (heart/body mass) in Early Ex and Late Ex at 24 wks. Consistent with exercise-induced cardiac hypertrophy, whole-genome expression (Illumina Inc.) in the heart found, compared to SED, both Early Ex and Late Ex rats had significantly increased (~20-40%) expression of many genes involved in protein transcription and translation (ribosomal proteins, elongation/initiation factors, mitochondrial ribosomal proteins), contraction (myosin, troponin and actin), energy production (ATP synthase, cytochrome oxidase, creatine kinase) and antioxidant defence (superoxide dismutase 1, glutathione-S-transferase). These findings suggest long-term and perhaps permanent cardiac programming by endurance-training during juvenile cardiac development. This study was funded by the Australian NHMRC, HF and The University of Melbourne.
Reduced cardiac glucose uptake and mitochondrial dysfunction are thought to promote cardiac dysfunction in diabetes. However, changes in heart metabolism during insulin resistance (IR) remain unclear. We investigated early cardiac metabolic changes in middle-aged (12mo) male LDLR−/− mice fed chow or high fat diet (HFD) for 3 months. HFD induced systemic IR and hyperinsulinemia, but dramatically increased posterior position tomography-assessed cardiac glucose uptake (2.9 fold). HFD also increased mitochondrial respiration and ATPO ratios in isolated mitochondria measured with respirometry. Shift to glucose utilization is thought to be associated with cardiac dysfunction; however echocardiography showed no contractile impairment. Insulin signaling (p-AKT, p-IRS1 and p-GSK3b) measured by Western blotting was increased in HFD-fed mice, even under fasting conditions. To test whether the hyperinsulinemia drives glucose uptake in the insulin-sensitive hearts of these mice, we induced insulin deficiency using Strep-tozotocin (STZ). STZ reduced cardiac glucose uptake and mitochondrial function, but was rescued by treatment with exogenous insulin, indicating that hyperinsulinemia drove the HFD-induced changes. In conclusion, the heart retains insulin sensitivity during systemic IR and increases its glucose uptake due to IR-induced hyperinsulinemia, resulting in an early adaptive change that may preserve mitochondrial and cardiac function in the face of obesity-related stress.

20.7 APOCYNIN PREVENTS EXERCISE-INDUCED CARDiac DYSFUNCTION AND Ca2+ LEAK FROM THE SARCOSPLASMIC RETICULUM AT MYOCARDIAL ARTERIES

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This study examined the effects of in vitro NADPH Oxidase (NOX) inhibition on isolated perfused heart function and sarcoplasmic reticulum (SR) Ca2+ handling following acute exhaustive exercise. Male Sprague-Dawley rats (20-23 wks) were given tap water or tap water supplemented with 1.5 mM apocynin (APO), a NOX inhibitor, for 3 days prior to random group assignment. The control groups (CTL & CTL-APO) only participated in the base line determinations and the exercise groups (EX & EX-APO) performed a single running bout (5 grade, 20 min/m) to exhaustion. In animals that were given tap water, left ventricular developed pressure (LVDP) was reduced immediately after exercise (CTL 137±4 vs EX 118±5 mmHg). APO did not alter LVDP under control conditions (CTL-APO 135±3 mmHg). Interestingly, NOX inhibition preserved LVDP in the EX-APO group (EX 118±5 vs EX-APO 135±4 mmHg). Rates of maximal Ca2+-ATPase activity was assessed in vitro from LV homogenate and was not different between groups. Similarly, oxalate-supported SR Ca2+ uptake was not affected by exercise in the absence or presence of NOX inhibition. However, the rate of Ca2+ leak from the SR was 44% greater in the EX group, an effect that was not observed in the EX-APO group. These results suggest that NOX generation of superoxide radical during exhaustive exercise caused greater SR Ca2+ leak, which may reduce SR Ca2+ load and depress left ventricular contractility. Supported by NSERC.

20.8 POST-EXERCISE FLOW-MEDIATED DIATION IS INFLUENCED BY RETROGRADE AND OSCILLATORY SHEAR

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We tested the hypothesis that elevated doses of retrograde shear rate (SR) in the brachial artery during lower body supine cycle exercise would attenuate post-exercise flow-mediated dilation (FMD) in a dose-dependent manner. Twelve men completed 3 exercise sessions (90 W, 20 min). One brachial artery was exposed to augmented oscillatory and retrograde shear (BA) and femoral artery (FA) diameter, wall thickness, and wall:lumen ratio prior to and after the stretching exercise. Results: The baPWV significantly decreased at 45 minutes before and immediately after the stretching exercise as well as 15, 30, 45, and 60 minutes after the stretching exercise. Results: The baPWV significantly decreased at 45 minutes after stretching exercise (P=0.05). Although systolic blood pressure increased and heart rate decreased after stretching exercise in both groups, changes were greater at baseline levels within 30 min after stretching exercise (P=0.05 in both). The trends of changed parameter in both groups responded in a similar fashion to stretching exercise (no group - by - interaction was detected). CONCLUSION: These results suggest that stretching exercise acutely decreases arterial stiffness regardless of flexibility levels.

20.11 LONG-TERM AEROBIC AND RESISTANCE TRAINING DIFFERENTIALLY IMPACT CONDUIT ARTERY STRUCTURAL PROPERTIES


The purpose of this study was to determine the impact of long-term aerobic (AT) or resistance exercise training (RT) on conduit artery characteristics in previously sedentary adults with the metabolic syndrome. After obtaining written informed consent, participants from the Studies of Targeted Risk Reduction Interventions through Defined Exercise (N=23; age, 49±2 yrs; BMI, 31±1 kg/m2; blood pressure, 120±3/87±2 mmHg; VO2peak, 27±1 ml/kg/min) were randomized to 8 months of AT (14 kcats/kg/wk, 65- 80% of VO2peak) or RT (3 sets, 12-16 repetitions, 4 upper and lower body exercises, 3d/wk). Dopper ultrasound and DICOM-based software were used to measure brachial (BA) and femoral (BF) artery diameter, wall thickness, and wall:lumen ratio prior to and after 48 weeks intervention. Resting BA and BF lumen diameter increased by 6.1±2% (P=0.01 vs. baseline) and 7.1±3% (P=0.005 vs. baseline) in AT and by 4.8±2% (P=0.06) and 5.3±3% (P=0.19) in RT, respectively. Wall thickness decreased by 1.3±1% (P=0.56) and 13.8±5% (P=0.11) in AT and by 5.5±5% (P=0.25) and 11.6±1% (P=0.12) in the BA and FA. The BF and FA wall:lumen ratio decreased by 6.3±3% (P=0.05) and 21.7±3% (P=0.03) in AT and by 2.5±3% (P=0.04) in RT. In conclusion, only AT resulted in significant changes in BA and FA lumen diameter and wall:lumen ratio, suggesting that long-term AT and RT differentially effect conduit artery structural properties in previously sedentary adults with the metabolic syndrome. Support: AHA 11POST440017, NIH HL-57534.
Functional responses of isolated mouse hearts (8-10 wks old) subjected to 1R (25 min ischaemia/45 min reperfusion) via Langendorff perfusion showed that 14-days of wheel running improved left ventricular developed pressure recovery from 48% to 58% (21% increase). Detraining occurred rapidly, returning to baseline levels after 7-days. 3 days of running returned protection to 58% (37% increase). Whole genome transcriptome analysis showed that transcriptional changes are associated with DOX treatment and is independent of its accumulation. We hypothesized that exercise exerts cardioprotection via pro-survival signal transduction during ischemia-reperfusion injury in various time points of brief (2-days; 2EX), moderate (7-days; 7EX) to extended (30-days; 30EX) training. Functional responses of isolated mouse hearts (8-10 wks old) subjected to 1R (25 min ischaemia/45 min reperfusion) via Langendorff perfusion showed that 14-days of wheel running improved left ventricular developed pressure recovery from 48% to 58% (21% increase). Detraining occurred rapidly, returning to baseline levels after 7-days. 3 days of running returned protection to 58% (37% increase).

20.15 CHRONIC LOW-INTENSITY INTERVAL EXERCISE TRAINING INCREASES CARDIAC TORSION AND IS ASSOCIATED WITH ENHANCED SYSTOLIC AND EARLY DIASTOLIC STRAIN RATE IN MINI-SWINE WITH COMPENSATED HEART FAILURE

Kurt Marshall1, Cary Weinreb1, Craig Entner2


Increased or preserved left ventricular (LV) torsion and strain at rest is a defining clinical feature of heart failure with preserved ejection fraction (HFpEF). We have shown chronic low-intensity exercise conserves normal diastolic function and contractile reserve in aortic-banded (AB) miniature swine. Alterations to the magnitude or rate of mechanical deformation during the cardiac cycle underlie the exercise-dependent improvements in LV function. The purpose of this study was to measure LV torsion, strain, and strain rate in AB sedentary (AB-S, n=5), AB exercise trained (AB-TR, n=5) and control sedentary (CON, n=4) male Yucatan mini-swine using 2D speckle-tracking echocardiography. Torsion was increased in AB-TR compared to AB-S and was positively correlated with ejection fraction and tau Glantz. Torsion in AB-TR was associated with increased systolic transverse strain and displacement, increased apical systolic radial and circumferential strain rate, and increased early diastolic apical radial and circumferential strain rate. In contrast, late diastolic longitudinal and mitral valve radial strain rate was increased in AB-S. Conclusion, chronic exercise after mechanical properties of the LV that may benefit systolic emptying and diastolic filling. Our data suggest 2D speckle tracking echocardiography may reveal a novel set of diagnostic criteria that can differentiate between pathologically and physiologically elevated cardiac torsion in HFpEF.

20.17 EFFECTS OF DEPLOYMENT-RELATED EXPOSURES ON CARDIOPULMONARY FUNCTION

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High-levels of particulate matter that exceed current environmental exposure guidelines have been reported in the deployment environments of Afghanistan and Iraq (OEF/OIF). Post-deployment, veterans endorse respiratory symptoms and limitations to exercise may be the result of these exposures. However, the extent and severity of respiratory problems are not well understood. 20 male veterans who self-reported exposure to airborne particulates and were deployed to OEF/OIF for a period of 1-5 months (n = 16-8.7 yrs; Low-Exposed) or 6+ months (n = 14-35.4 yrs; High-Exposed) volunteered for this study. All veterans participated in a standard treadmill-based exercise challenge with spirometry before and after exercise. We observed no differences in spirometry obtained at rest, but 31% of the High-Exposed group exhibited exercise-induced bronchoconstriction (i.e. greater than 15% drop in FEV1 at 20 minutes post-exercise) as compared to 0% of the Low-Exposed group. Further, 38% of the High-Exposed group exhibited ventilatory limitation to exercise (i.e. VE/MVV > 85%), but no limitations were observed in the Low-Exposed group. We observed airflow restriction in High-but not Low-Exposed veterans, we emphasize cautious interpretation as sample size was low and groups were of unequal size. Future studies on cardiopulmonary fitness in deployed veterans are warranted.

20.18 MODERATE-INTENSITY RESISTANCE TRAINING IMPROVES VASCULAR FUNCTION IN OBSESE WOMEN

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Obesity contributes to impaired vascular function (VF), a precursor to cardiovascular disease. Resistance training (RT) is recommended for obesity management and is associated with favorable effects on VF; however, previous studies show that acute resistance exercise impairs VF in sedentary lean adults. Therefore, we sought to determine if acute resistance exercise impairs VF in obese adults and if 8 wks of RT is vasculoprotective.
Ten obese young women were evaluated at four time points before (wks 0 and 4), during (wk 8), and after (wkr 12) participation in an 8-wk moderate-intensity RT intervention. The primary aim of this study was to examine alterations in insulin signaling in myotubes derived from muscle of obese adults in response to 12h incubations in lipids containing the most abundant fatty acids in human plasma (i.e., oleate, palmitate, linoleate, and linolenate). We compared: 1) a "normal" physiologic mixture of these fatty acids (NORM, 40% saturated), 2) a mixture very high in saturated fatty acids (HSFA; 60% saturated), and 3) 100% palmitate (PALM) At 0.4mM, PALM markedly suppressed insulin-stimulated phosphorylation of Akt (pAktSer473) and AS160 (pAS160Thr642) (both P<0.001), but impairments in insulin signaling were not found with NORM at this concentration. Doubling the concentration of NORM to 0.8mM still did not impair insulin signaling. In contrast, 0.8mM HSFA reduced pAktSer473 and pAS160Thr642 (both P<0.004), suggesting the "saturation-state" of available fatty acids may impair insulin signaling in primary human skeletal muscle cells. However, because the proportion of saturated fatty acids in our HSFA solution was far greater than that ever observed in vivo, further study is needed to examine the effects of a more physiologic elevation in saturated fatty acids. The main findings from this study indicate that the robust impairment in insulin signaling with palmitate incubation was not found when myotubes were exposed to a mixture of fatty acids resembling that commonly found in human plasma.

21.3 SKELETAL MUSCLE FATTY ACID SYNTHASE MODULATES SARCOPLASMIC RETICULAR MEMBRANE PHOSPHOLIPID COMPOSITION TO REGULATE INSULIN SENSITIVITY AND MUSCLE STRENGTH

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Abnormal lipid metabolism is implicated in the pathogenesis of skeletal muscle insulin resistance. Endogenous fat production is not thought to impact muscle insulin resistance, but we recently reported (Diabetes 61: Suppl 1, 102-OR, 2012) that the lipogenic enzyme fatty acid synthase (FAS) was increased in skeletal muscle of mice with diet-induced obesity. Moreover, FAS knockout in skeletal muscle (FASKO) mice were protected from diet-induced muscle resistance. Dogma holds that FAS is cytoplasmic, but we discovered a pool of sarcoplasmic reticulum (SR) resident FAS that modulates sarco/endoplasmic reticulum calcium ATPase (SERCA) activity. In muscle cells deficient in SR, decreased SR phosphatidylethanolamine and increased SR phosphatidylcholine was associated with lower SERCA activity. The reduction in SERCA activity in FAS deleted muscles led to calcium-mediated activation of AMP-activated protein kinase (AMPK) signaling that was abolished with overexpression of SERCA1. Elevated AMPK likely explains the increased insulin sensitivity phenotype of FASKO mice, but decreased SERCA activity also led to muscle weakness. Thus, inhibition of skeletal muscle FAS prevents obesity-associated diabetes in mice, but comes at the expense of decreased muscle strength, suggesting that mammals have retained the capacity for lipogenesis in muscle to preserve physical performance in the setting of disrupted metabolic homeostasis. Funding sources: NIDDK, AHA and ADA.
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diet group were sedentary (LFD-SED & HFD-SED), and the others performed 2h of exercise (LFD-EX & HFD-EX). At 3h post-exercise (3hPEX), both epididymal adipose tissues from each rat were isolated. Paired muscles were incubated with [3H]-2-deoxyglucose±100µM insulin. Insulin-stimulated muscles from HFD-SED vs. LFD-SED rats had low values for SGL and PpA. At 3hPEX, BGLI in muscles from HFD-EX rats was increased sufficiently to attain values that were similar to the LFD-SED group even though exercise did not elevate PA160 in HFD-EX rats. For muscles from LFD-EX rats, SGLU and PA160 were elevated to attain values that were greater than the HFD-SED group. These results indicate that exercise may enhance mitochondrial function, but further research is needed to understand the mechanisms involved.

21.5 PERILIPIN 2 AND 5 ARE NOT MODULATED BY PHYSIOLOGICAL STRESSORS AFFECTING TRIACYLGLYCEROL STORAGE OR UTILISATION IN SKELETAL MUSCLE

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We have previously shown that chronic exercise training improves whole-body and skeletal muscle insulin resistance and results in a decrease in epididymal adipose tissue (AT) mass. The purpose of the present study was to examine the effects of an acute heat treatment on lipolysis in multiple AT depots. Male Wistar rats consumed a high-fat (HF) or Chow diet for 6 weeks. After 6 weeks, rats were exercised either 20 min at 37 °C (heat) or 20 min at 20 °C (basal) treatment. Heat treatment reduced basal fatty acid re-esterification in SCAT. Heat treatment reduced Epi-stimulated fatty acid re-esterification in nPWSAT but not sPWSAT. Heat treatment increased heat shock protein 72 (Hsp72) expression in all AT depots and increased citrate synthase and total AMPK expression in rpWAT. In conclusion, acute heat treatment altered fatty acid re-esterification and lipid handling in AT in a manner that may decrease lipogenesis, while increasing the ability to oxidize fatty acids. NIH AG031575.

21.7 THE UPREGULATION OF GENES INVOLVED IN FATTY ACID OXIDATION IS DEPRESSED WITH SEVERE OBESITY

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PURPOSE: Severe obesity individuals are unable to increase fatty acid oxidation (FAO) in response to dietary lipid, which may contribute to positive lipid balance and weight gain. The purpose of the present study was to determine whether fatty acids differentially regulate genes that play a role in human skeletal muscle FAO in response to dietary lipid. METHODS: mRNA content was measured using real-time PCR in HSAMC from 9 lean (BMI= 22.8 kg/m² ± 2.2; Age= 23.4yrs ± 4.6) and 10 severely obese (BMI= 41.3 kg/m² ± 9.4; Age= 30.2yrs ± 8.3) Caucasian women following a 48hr incubation in 1) lipid (100µM oleate:palmitate) or 2) 5% BSA (control). RESULTS: The lipid-induced responses of critical genes that play a role in FAO were significantly (obese vs. lean, all p<0.05) dampened with obesity: PPARα obese 0.85- vs. lean 1.30-fold increase; PPARδ obese 1.52-fold increase (in response to lipid); NRF-1 obese 0.90- vs. lean 1.59-fold increase; and NRF-2 (GABPA) obese 0.49- vs. lean 1.56-fold change. CONCLUSIONS: The induction of broad transcriptional regulators such as the PPARs and NRF-1 and -2 was reduced in HSAMC from severely obese individuals. The inability to activate these critical genes during periods of increased lipid presence, such during an overnight fast or the dietary consumption of lipid, could contribute to the depressed FAO evident with severe obesity. Funding support provided by NIH Grant AG025205.

21.10 POSTPRANDIAL HEPATIC TRIACYLGLYCEROL SECREATION AND FATTTY ACID OXIDATION ARE NOT ALTERED BY PRIOR AEROBIC EXERCISE

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Postprandial triglyceride (TAG) concentrations are reduced in humans when prior aerobic exercise is performed, but the mechanisms are unknown. We hypothesized aerobic exercise would shift hepatic fatty acid partitioning away from TAG synthesis and secretion and toward fatty acid oxidation (FAO) in obese-susceptible Sprague-Dawley rats fed a normal chow (NC) or high fat (HF) diet. Thirty rats were randomized into one of four groups including 1) NC, 2) NC-acute exercise (NC-Ex), 3) HF, and 4) HF-acute exercise (HF-Ex). Rats in the Ex groups performed 1hr of treadmill exercise (12.6 mm/min) without electric shock at 2200-2300 h. At 0800 h the next day, the rats
were intravenously injected with Tylcopol (lipoprotein lipase inhibitor) 30 min prior to oral gavage with a 20% calorie meal (40% fat, 45% carbohydrate, and 15% protein) to assess postprandial hepatic TAG secretion in vivo. Blood was taken via tail vein at baseline and every hr for 4 hr to assess TAG secretion. A week later, the same rats performed the acute exercise bout again, and hepatic FAO was measured with $^{13}$C-MET. Acute aerobic exercise did not alter postprandial hepatic TAG secretion or FAO in either diet group, however, secretion rates were higher in NC compared to HF fed rats, regardless of acute exercise (P<0.05). Reduced postprandial hepatic TAG secretion is not a mechanism by which acute exercise reduces postprandial TAG levels.

21.11 ACTIVATION OF THE FAT METABOLISM BY HIGH-INTENSITY SPRINT EXERCISE

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INTRODUCTION: To investigate the behaviour of the fat metabolism after short exercise with maximal intensity we performed 2 repeated Wingate tests (WT) series, one on a cycle ergometer and the other with a forearm ergometer. METHODS: Series 1) 13 subjects performed both WT separated by a break of 60 s. The WT were followed by the rest period of 30 min. In arterialized blood [Lac] and [Glu] and in cubital venous blood free fatty acid base status, [Lac], [Glu], and fat metabolites were determined. Series 2) 9 subjects performed the WT with handgrip exercise. Arterialized blood was sampled from a heated hand vein. Blood draining the working muscle was collected from the cubital vein to determine PCO$_2$, [Lac], [Glu], [FFA], [lactate], pHb, Hct. Blood flow was determined pletysmographically. RESULTS: Cycling [Lac] increased to 13.6±2.6 (p<0.001) and [Glu] decreased to 0.39±0.22 (p<0.001) and [FFA] from 0.36±0.33 to 0.50±0.04 (p<0.001). Hand grip: Immediately after the second WT pH in venous blood decreased to 7.10±0.03, and PCO$_2$ increased to 103.3±12.9 Torr (both p<0.001). After termination of the WT [Glu] and [FFA] increased (p<0.03). During the recovery phase a significant release of [Glu] from the forearm occurred (p<0.001). Simultaneously there was an increase in FFA uptake (p<0.001). CONCLUSION: Both series show that short exercise of maximal intensity activates the fat metabolism.

21.12 ERYTHROPOIETIN INCREASES MITOCHONDRIAL CAPACIT Y IN WHITE ADIPOSE TISSUE IN MICE

Victor Diaz, Robert Jacoby, Lars Lundby.

INTRODUCTION: Erythropoietin (Epo) has been shown to exert effects beyond just the regulation of red blood cell production. There is increasing evidence for a link between Epo and metabolic pathways. We hypothesized that Epo administration would result in an increase of mitochondrial capacity in white adipose tissue (WAT) by a mechanism independent of anaerobic metabolism. METHODS: C57B6 female mice were assigned to the following groups: low fat diet (LFD, n=6), high fat diet (HFD, n=5), LFD with voluntary wheel running (LFD + WR, n=6), HFD with voluntary wheel running (HFD + WR, n=5), and Epo treatment of LFD mice (TgEPO, n=4). After euthanasia, WAT was harvested and mitochondrial capacity was determined in mitochondria isolated from this tissue. RESULTS: Mitochondrial capacity expressed as a maximum oxygen consumption rate was significantly increased in the Epo treated LFD group compared to the LFD and HFD groups. Furthermore, treatment with Epo increased the expression of ANT1, a mitochondrial import protein. CONCLUSION: Epo increases mitochondrial capacity in WAT, although further investigations are needed to elucidate the relevance and importance hereof.

21.13 RESVERATROL SUPPLEMENTATION IMPROVES GLUCOSE HOMEOSTASIS AND WHITE ADIPOSE TISSUE METABOLISM IN A DEPOT-SPECIFIC MANNER IN ZUCKER DICTYOTELIC FATTY (ZDF) RATS

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2Resveratrol (RSV) is a polyphenol suggested to have anti-diabetic properties. This study examined the effects of RSV on whole-body and white adipose tissue (WAT) metabolism. Five-week old ZDF rats were fed a diet rich in (ZDF RSV) or without (ZDF chow) resveratrol (200 mg/kg body weight). 6 weeks after diet start, blood glucose, insulin, adiponectin and hepatic CIDEA and CIDEC expression were assessed. Blood glucose values during an oral glucose tolerance test were significantly higher in ZDF RSV compared to ZDF chow (p<0.05). Adiponectin secretion was elevated in scAT from RSV-fed rats. In vitro treatment of scAT with RSV (30 mmol/L) also tended to increase PDK4 (p=0.08) and PEPC (p=0.06) mRNA expression at 6 h. Overall, this study suggests that RSV may modulate glucose homeostasis in ZDF, through at least in part, increases in glycogenolysis, respiration and adiponectin release in scAT. Funded by NSECR and OGS.

21.14 HEMOLYSIS DUE TO LACTATE INFUSION: IS pH OR OSMOLARITY THE CULPRIT?


CONCLUSION: It has been suggested that hemolysis is due to a combination of low pH and high osmolarity. We recommend further studies are needed to determine the optimal pH and osmolality for high performance sport athletes in various sports.

21.15 VERIFICATION OF AN INTRACELLULAR LACTATE SHUTTLE IN HUMAN SKELETAL MUSCLE

Robert Jacoby, Anne-Kristine Meinild, Nikolai Nordsborg, Bengt Saltin, Carsten Lundby.

INTRODUCTION: Human skeletal muscle mitochondria are capable of oxidizing lactate independent of exogenous LDH. The mechanism for this could be a functional lactate oxidation complex in human skeletal muscle mitochondria. METHODS: Blood lactate, oxygen consumption and pH were measured during 1 min of intense sprint exercise on an arm ergometer in series 1) 9 subjects (Series 1) and on a cycle ergometer in series 2) 13 subjects.RESULTS: Lactate was oxidized in both series. Oxygen consumption was significantly increased in series 1) (3.9±0.6 vs. 16.2±5.4 ml/min, p<0.001) and in series 2) (3.7±0.5 vs. 17.9±2.3 ml/min, p<0.001). Oxygen consumption increased maximally when the pH decreased by 0.1 units. CONCLUSION: Oxygen consumption was maximally increased by 1 unit decrease in pH. Low pH is a more significant factor than osmolality in causing hemolysis. These results demonstrate that human skeletal muscle mitochondria are capable of oxidizing lactate independent of extramitochondrial conversion to pyruvate and verify the existence of an intracellular lactate shuttle and a functional lactate oxidation complex in human skeletal muscle mitochondria.

21.16 EFFECTS OF DIETARY INDUCED OBESITY AND EXERCISE TRAINING ON HEPATIC CIDE EXPRESSION

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The cell death-inducing DFF45-like effector (CIDE) family of proteins plays an important role in lipid droplet formation and triglyceride storage in both adipocytes and hepatocytes. The purpose of the present study was to determine the effects of dietary-induced obesity and voluntary wheel running (WR) on the expression of CIDE and CIDE in liver. C57B6 male mice were assigned to the following groups: low fat diet sedentary (LFDSED), high fat diet sedentary (HFDSED), and HFDWR. Following 10 weeks of the respective treatments, insulin sensitivity, adiposity, and hepatic CIDEA and CIDEC expression were assessed. Blood glucose values during an oral glucose tolerance test were significantly higher in HFD compared to LFD. Exercise and hepatic CIDE and CIDEC expression were measured. Blood glucose values during an oral glucose tolerance test were significantly higher in HFD compared to LFD and this effect was prevented by WR. The expression of insulin sensitivity due to a HFD and WR was associated with changes in body weight and adipose tissue mass. The expression of CIDEA and CIDEC mRNA levels were significantly lower in livers of HFD compared to LFD mice and this effect was also prevented by WR. The expression of PPARa and RiP10, nuclear receptors that regulate CIDEs, were significantly elevated in livers of HFD compared to LFD mice, a
response that was not altered by WR. These results indicate that CIDEs are important for storing excess triglycerides in the liver during dietary obesity, but how CIDEs are regulated by exercise remains to be established.

22.0: MUSCLE INJURY

22.1 ROLE OF LKBI IN SKELETAL MUSCLE REGENERATION AFTER INJURY

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During skeletal muscle regeneration satellite cells are activated and proliferate before differentiating into myotubes and/or fusing with existing myofibers. Liver kinase B1 (LKB1) has been shown to be an important role in skeletal muscle differentiation in culture. Our purpose was to determine the role LKB1 plays in 1) myogenic regulatory factor expression in skeletal muscle and 2) muscle regeneration after cardiotoxin (CTX)-induced damage. We found protein content for Myf-5, Myf-6 and MyoD were 47%, 45% and 29% lower, respectively, in gastrocnemius muscles from skeletal muscle-specific LKB1 knockout (KO) vs. control (C) mice (n=6/group). To induce muscle damage, C and KO mice were injected with CTX into the right tibialis anterior (TA) muscle. The left TA served as a control. The mice recovered for 7 days after which both TAs were harvested and prepared for immunohistochemistry. Hematoxylin and cosin staining showed that the percentage of muscle fibers with centralised nuclei in un-injured muscles was similar between C (2.9%) and KO (2.3%), but after CTX injection was lower in KO (9.0%) vs. C (23.7%). Muscles, suggesting a defect in muscle regeneration in the absence of skeletal muscle LKB1. Our findings demonstrate the importance of LKB1 in normal muscle regeneration after acute muscle injury. Funded by NIHMS Grant AR-51928 and BYU Mentoring Environment Grants.

22.2 MESENCHYMAL STEM CELLS CONTRIBUTE TO EXERCISE-INDUCED SKELETAL MUSCLE HYPERTROPHY AND STRENGTH

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We have demonstrated that mesenchymal stem cells (mMSCs) accumulate in skeletal muscle overexpressing the α7 integrin (α7Tg) and α7Tg mice exhibit increased muscle growth following exercise. PURPOSE: The purpose of this study was to determine whether mMSCs isolated from α7Tg muscle contribute to exercise-induced growth. METHOD: Cells were isolated from α7Tg mice and cocultured with C57BL/6-FVB muscle. Recipient C57BL/6-FVB mice were injected with CTX into the right tibialis anterior (TA) muscle. The left TA served as a control. The mice recovered for 7 days after which both TAs were harvested and prepared for immunohistochemistry. Hematoxylin and cosin staining showed that the percentage of muscle fibers with centralised nuclei in un-injured muscles was similar between C (2.9%) and KO (2.3%), but after CTX injection was lower in KO (9.0%) vs. C (23.7%). Muscles, suggesting a defect in muscle regeneration in the absence of skeletal muscle LKB1. Our findings demonstrate the importance of LKB1 in normal muscle regeneration following CTX injection.

22.3 PROLIFERATION OF HUMAN MYOBLASTS CULTURED IN SERUM OBTAINED AFTER SPURT EXERCISE

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Maintenance and repair of skeletal muscle is strongly related to the function of satellite cells (SaCs). Systemic and local environmental factors seem to be important for proliferation and differentiation of SaCs. However, the function of the human SaCs and the influence of environmental factors are largely unknown. It has previously been shown that sprint exercise increases growth factors such as growth hormone and insulin. Hence, the aim of the present study was to determine the proliferation of cultured SaCs in serum supplemented with serum from subjects performing sprint exercise. Method: 18 subjects (8 F and 10 M) at the age of 20 – 30 yrs performed three 30s all out sprints with 20 min rest between each sprint. Serum were withdrawn from forearm vein at rest, 5 min after second and third sprint and one and two hours after third sprint. SaCs were extracted from vastus lateralis biopsies from one healthy male subject aged 25 years. Cells were cultured in medium containing 20% sera at different cell concentrations in triplicate and cell proliferation was measured with BrdU-ELISA kit. A significant decrease in cell proliferation rate in cells grown with sera obtained up to two hours following the three bouts of sprint exercise. Conclusion: There was no improved proliferation among satellite cells cultivated in sera obtained up to two hours after sprint exercise, despite the earlier observed increase in growth factors as a result of such exercise.

23.0: MUSCLE FUNCTION AND ADAPTATION II

23.1 SPACE RADIATION ENVIRONMENT CREATES ION-SPECIFIC INCREASES IN MUSCLE MASS IN SIMULATED LUNAR GRAVITY

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The impact of galactic cosmic radiation (GCR) exposure during long duration spaceflight on skeletal muscle is relatively understudied. Even less is known about any concurrent effects that may occur in conjunction with partial weight-bearing, as one might encounter in the Lunar and Martian environments. The focus of this study was to examine the effects of simulated GCR, using either 56Fe or 109Si in conjunction with partial loading similar to that experienced on the Lunar surface. Female BalbC/ByJ mice were separated into 5 partial weight-bearing or partial suspended groups. Groups were further divided by radiation species, receiving 90Gy of either 56Fe or 109Si. There was no significant difference in body weight or body mass index. The group exposed to partial weight-bearing following 21d of simulated Lunar gravity in non-irradiated controls. In the presence of 56Fe, GAST mass increased with an altered protein concentrations, suggesting an increase in muscle tissue. Animals subjected to 109Si had an increase in GAST mass in the Lunar group but exhibited a decreased protein concentration, indicating non-muscle protein additives in the tissue. This work may be the first to demonstrate an ion-specific increase in muscle mass, with varying effects resulting.

23.2 SHORT-TERM INTENSE EXERCISE TRAINING REDUCES MARKERS OF CELLULAR STRESS IN HUMAN SKELETAL MUSCLE

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The purpose of this study was to examine the influence of short-term intense exercise training on molecular factors related to skeletal muscle stress, oxidative damage and protein turnover. Ten recreationally active subjects (47.2 ± 2 kg·m², 25.2 ± 1 yr, 79.3 ± 1 kg) completed a 12-day study protocol, during which subjects performed steady state (45-min run at ~78% VO2max) or high intensity (4 x 5 min bouts at ~91% VO2max) running sessions on alternating days, for 11 consecutive days. Skeletal muscle biopsies were obtained from the vastus lateralis at rest on days 1 (D1) and 12 (D12) to measure protein content and mRNA expression. SAPK/JNK phosphorylation was 23% ± 11% lower (P < 0.05) on D12 compared to D1 suggesting a reduced skeletal muscle cellular stress. Muscle protein oxidation, measured using the Oxylab technique, was unaltered following the cycling protocol. Training tended (P < 0.08) to increase protein content for markers of cell protection (MnSOD, 63% ± 30% and HSP70, 14 ± 7%). MfSa-1 mRNA was 75% ± 24% higher (P < 0.05) and myostatin mRNA transcripts were 55% ± 22% lower (P < 0.05) on D12, which is consistent with increased muscle protein turnover. Collectively, these data provide a molecular basis for the increase in skeletal muscle protein turnover following exercise training and suggest that short-term intense training reduces basal cellular stress and creates a cellular environment that may be conducive for adaptation.

23.3 EFFECTS OF 12-WKS OF AEROBIC EXERCISE TRAINING ON SKELETAL MUSCLE INSULIN SENSITIVITY, MITOCHONDRIAL BIOENERGETIC, SUBSTRATE UTILIZATION, AND ENERGY EXPENDITURE IN PREMENOPAUSAL WOMEN

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Background: Aerobic exercise can improve skeletal muscle insulin sensitivity (SI), mitochondrial function, and increases energy expenditure (EE), however whether improvements in SI and mitochondrial function are due to negative energy balance (EB) induced by the exercise training remains to be determined. Purpose: To assess SI, mitochondrial bioenergetics, substrate utilization, and EE under rigorously controlled EB conditions pre- and 12-weeks post aerobic exercise training (AET) in premenopausal women. Methods: Eight women (age 52 ± 3 yr, 79 ± 3 kg) performed 12 weeks of AET (32-40 min at 75%±11 kg·BMI ± 28±2 kg·m²) at baseline and 12-wks post-AET. Room calorimetry was used for 24-hs to determine EE, and to insure EB prior to euglycemic hyperinsulinemic clamp measures for SI. Muscle biopsies were obtained, and in situ mitochondrial function was determined in permeabilized muscle fibers using high-resolution respirometry. Results: Mitochondrial bioenergetic analyses are ongoing. A significant improvement in SI occurred following AET (baseline SI clamp = 7.9 ± 3.1; 12-wks-post = 11.2 ± 5.1; P < 0.05). The 24-hr respiratory quotient significantly decreased following AET (0.92 ± 0.03 to 0.87 ± 0.05; P < 0.05). Importantly there was no significant increase in muscle energy intake and EE at baseline compared to 12-wks post AET. No significant changes in EE occurred following training. Conclusion: These preliminary data suggest that increases in SI following 12-wks of AET occur when changes in EB do not occur.

23.4 SKELETAL MUSCLE OF EXTREMELY OBESE WOMEN IS INSENSITIVE TO ATPROCHIM STIMULI
Atrogin-1 and MuRF-1 mRNA. Protein turnover, is markedly impaired in skeletal muscle of extremely obese women, 

protein concentration was reduced. Thus, MET and RSV administration evokes alterations in the acti-
tation of AMPK and regulates a basal metabolic property of skeletal muscles. Microarray analysis revealed that miR-23a was highly expressed in slow muscle compared to fast muscle. We analyzed muscle phenotype of miR-23a transgenic (miR-
23a) and control (C) mice. In the transgenic mice, mitotic proliferation was not affected. In the other hand, the amount of mitochondria and PGC-1α expression were significantly de-
creased in miR-23a-Tg mice. An online database predicted several binding sites for miR-
23a on the 3’ UTR of PGC-1α. We then subcloned the 5’ UTR into downstream of luciferase reporter vectors. Luciferase activity was markedly reduced when the miR-23a expression vector was co-transfected. In contrast, luciferase activity was markedly in-
creased when the miR-23a expression was knocked down. We next assessed exercise-induced 
muscle adaptation of miR-23a-Tg mice. Unexpectedly, muscle adaptation of miR-
23a-Tg mice was comparable to that of WT mice. These results suggest that miR-23a targets PGC-1α and regulates a basal metabolic property of skeletal muscles.

23.8
PGC-1α IS REQUIRED FOR EXERCISE TRAINING AND RESVERATROL INDUCED EFFECTS ON OXIDATIVE CAPACITY OF MICE SKELETAL MUSCLE
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Aim: The aim was to test the hypothesis that beneficial effects of Resveratrol are medi-
ated through peroxisome proliferator-activated receptor-γ co-activator (PGC)-1α. Methods: Old (15 month of age) whole body PGC-1α knockout (KO) and wildtype (WT) littermates were either exercise trained in running wheels from 3 month of age or seden-
tary and given either resveratrol supplementation or standard chow. Young (3 month of age) sedentary mice on standard chow served as controls. Skeletal muscles were obtained at respective ages. Results: Capillary/fiber (C/F) ratio of triceps was increased with training and resveratrol supplementation in WT but not in KO mice and the C/F ratio was overall 27% lower in KO mice than in WT mice in all groups. There was no significant ef-
fect of training and/or resveratrol on quadriceps cytochrome (Cyt) C protein content but Cyt C was significantly lower in KO old than in WT old mice. Citrate synthase (CS) ac-
tivity and protein content of pyruvate dehydrogenase (PDH) E1α and hoxkinesin (HK) E1α were increased with training in WT but not in KO mice. Conclusion: The combination of 

training and resveratrol supplementation increased capillarization of triceps muscle in a PGC-1α-dependent manner. While resveratrol had no effect, PGC-1α was required for lifelong exercise training increased content/activity of CS, PDH-E1α and HKII.

THROMBOSPONDIN-1 INFLUENCES SKELETAL MUSCLE MITOCHONDRIAL RESPIRATORY ENZYME ACTIVITY
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Measuring the metabolic demands of skeletal muscle during exercise is critical for healthy muscle function. The multi-domain, multifunctional protein thrombospondin-1 (TSP-1) has been implicated to be vital in regulating pathological and exercise induced skeletal muscle angiogenesis. Recently, it has also been shown that TSP-1 KO mice have in-
creased mitochondrial density and biogenesis. With this new evidence, we hypothesized that TSP-1 KO mice would have increased mitochondrial enzyme activity, while those given a chronic dosage of the potent TSP-1 mimetic ABT-510 would have decreased enzyme activity. We studied 2.5 month old male WT mice (WT), TSP-1 KO (KO), and WT mice given a chronic dose of TSP-1 mimetic ABT-510 (30mg/kg/day) via mini osmotic pump for 14 days (ABT). In the gastrocnemius, we found that under basal conditions KO mice had a 46% increase while ABT mice had a 24% decrease in Complex I activity compared to WT. We also found that KO mice had a 36% increase and ABT had a 24% decrease in Complex II activity compared to WT. Complex III was unchanged between groups. These support the notion that TSP-1 may influence mitochondrial function, adding to its importance in regulating skeletal muscle adaptive response to stress, such as exercise.

23.10
ALPHA-ACTININ-3 ATTENUATES M-TOR SIGNALING IN HUMAN SKELETAL MUSCLE AFTER SPONTANEOUS EXERCISE
Barbara Norman1, Mona Elshajjermanns2, Ted Österlund3, Håkan Rundqvist4, Eva Jansson1, 

Polymorphism (R577X) in the ACTN3 gene causes a complete loss of α-actinin-3 protein in homozygous individuals (XX genotype). α-Actinin-3 is a structural component of the Z-disks in type II skeletal muscle fibers and loss of α-actinin-3 has been shown to alter the elastic properties of the sarcomeres. Lack of α-actinin-3 has also been shown to be associated with smaller muscle fiber size. It is possible that the α-actinin-3 loss could lead to more rapid r-hypertrophy signaling during muscle contraction, is affected by the altered properties
of the Z-disks which may have implication for muscle growth. The aim of the study was therefore to elucidate if altered signaling via the Akt/mTOR pathway can contribute to explain the ACTN3 associated differences in muscle mass. 18 healthy subjects with different ACTN3 genotype (4 RR, 7 RX and 7 XX) performed three bouts of 30-s sprint exercise every 40 min of rest for a total of 120 min of exercise between subjects. Muscle biopsy samples were obtained at rest and 140 min after the last sprint. Phosphorylation of Akt, mTOR, p70S6K, rpS6 and AMPK was analyzed by Western Blot. The exercise-induced increase in phosphorylation of mTOR and p70S6K was smaller in XX than in RR/RX (p = 0.06 and p = 0.03 respectively) while there was no difference in increase of Akt, rpS6 and AMPK across genotypes. Results of the present study suggest that differences in the regulation of mTOR by mechanically induced signaling events, may contribute to explain the ACTN3 associated differences in muscle mass. 23.11 RESISTANCE EXERCISE ACETYLATES INDUCES THE UNFOLDED PROTEIN RESPONSE IN SKELETAL MUSCLE. Daniel Osborn1, Bryon McKay2, Justin Crane3, Gianni Parigi4, Mark Tunnacliffe4 1Med Sci, McMaster University, 1280 Main St. West, Hamilton, ON, L8S 4L8, Canada, 2Kinesiology, McMaster University, 1280 Main St West, Hamilton, ON, L8S 4L8, Canada, 3Med Sci, McMaster University, 1280 Main St West, Hamilton, ON, L8S 4L8, Canada. The unfolded protein response (UPR) acts to sequester recently synthesized proteins that are misfolded or unfolded to minimize cellular stress. Resistance exercise (RE) stimulates protein synthesis and the accumulation of unfolded proteins may activate the UPR. Aging may impair protein folding, altering the post-exercise UPR that could partially contribute to anabolic resistance and muscle wasting in elderly muscle. 19 young (n=10; 21±1.7 yrs) and old (n=9; 70±4 yrs) males were recruited to determine if an acute RE bout influences the UPR. Participants completed unilateral RE for the knee extensors (4 sets of 10 reps at 80% 1RM) and muscle biopsies were taken from the non-dominant vastus lateralis at 3, 24 and 48 hours post-exercise. Protein levels of the 3 UPR effectors increased following exercise. GRP78 and PERK increased at 48hrs post-exercise (458±117%, p<0.001 and 138±23%, p<0.01 respectively) while IRE1α was elevated at 24hrs (192±37%, p<0.05) and 248±18%, p<0.001 respectively. Despite elevated protein, GRP78 and PERK mRNA were unchanged however IRE1α mRNA increased at 24hrs (151±128%, p<0.05). ATF6 mRNA increased at 24 and 48hrs (142±13%, p<0.05 and 145±13%, p<0.01 respectively), while ATF4 and CHOP were unchanged. In conclusion, acute RE results in UPR activation irrespective of age. Further work is required to clarify whether downstream components of the UPR pathway are stimulated by resistance exercise. Supported by NSERC and CIHR. 23.12 EFFECTS OF UNLOADING ON MYOSIN HEAVY CHAIN FUNCTION AND HSP25 AND 70 EXPRESSION IN MICE. Kimberly Huey1, Brent Moodie1 Pharmacy and Hlth. Sci., Drake Univ., 2507 University Ave., Des Moines, IA, 50311. AMPK agonists, such as AICAR, can be used in the treatment of diabetes since they influence the UPR. Increased protein, GRP78 and PERK mRNA were unchanged however IRE1α in exercised mice was increased at 24hrs (192±37%, p<0.05) and 248±18%, p<0.001 respectively. Despite elevated protein, GRP78 and PERK mRNA were unchanged however IRE1α mRNA increased at 24hrs (151±128%, p<0.05). ATF6 mRNA increased at 24 and 48hrs (142±13%, p<0.05 and 145±13%, p<0.01 respectively), while ATF4 and CHOP were unchanged. In conclusion, acute RE results in UPR activation irrespective of age. Further work is required to clarify whether downstream components of the UPR pathway are stimulated by resistance exercise. Supported by NSERC and CIHR.
24.0: EXTRACELLULAR MATRIX AND CONNECTIVE TISSUE

24.1 LOW-INTENSITY INTERVAL TRAINING ATTENUATES INCREASED MRNA EXPRESSION OF EXTRACELLULAR MATRIX REGULATING BIOMARKERS IN MINI-SWINE WITH COMPENSATED HEART FAILURE

Brittany Muller, Kurt Marshall, Corry Weissman, Craig Caggia
Left ventricular (LV) hypertrophy caused by pressure overload is correlated with extracellular matrix (ECM) remodeling, characterized in part by increased fibrosis, and plays a significant role in the development of diastolic dysfunction in heart failure (HF). Our laboratory has previously shown that low-intensity interval treadmill training attenuates increased fibrosis following aortic-banding in miniature swine. The purpose of this study was to measure the expression of several regulatory biomarkers (matrix metalloproteinases and their tissue inhibitors; MMP/TIMP’s) and ECM components in aortic-banded (AB) sedentary (AB, n=8), AB exercise trained (AB-TR, n=8) and sedentary control (CON, n=8) male Yucatan miniature swine. Increased LV fibrosis was associated with augmented mRNA expression of MMP-2, MMP-9, TIMP-1, and TIMP-4 in AB-S compared to CON animals. Enhanced expression of these biomarkers was attenuated by exercise. There were no group differences in total LV collagen content. However, analysis of collagen isoforms demonstrated a training-induced increase in Type III mRNA expression and a concurrent increase in fibronectin. In conclusion, our results suggest exercise attenuates fibrotic LV remodeling via two potential mechanisms: 1) maintenance of normal MMP/TIMP expression; and 2) altering collagen isoform composition. Exercise may attenuate diastolic impairment in HF by promoting more compliant ECM fibrotic components and preserving ECM regulatory mechanisms.

24.2 MECHANICAL LOADING AND TGF-B REGULATE THE EXPRESSION OF MULTIPLE miRNAs IN TENDON FIBROBLASTS

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Tendons link skeletal muscles to bones and are important components of the musculoskeletal system. There has been much interest in the role of miRNA in the regulation of musculoskeletal tissue to mechanical loading, inactivity and disease, but it was unknown whether miRNA is involved in the adaptation of tendons to mechanical loading. We hypothesized that mechanical loading and TGF-β treatment would regulate the expression of several mRNA molecules with known roles in cell proliferation and extracellular matrix synthesis. To test our hypothesis, we subjected untrained adult rats to a single session of mechanical loading and measured the expression of several miRNA transcripts in Achilles tendons. Additionally, as TGF-β is known to be a central regulator of tendon growth and adaptation, we treated primary tendon fibroblasts with TGF-β and measured miRNA expression. Both mechanical loading and TGF-β treatment modulated the expression of several miRNA’s that regulate collagen synthesis and extracellular matrix synthesis. We also identified mechanosensitive miRNAs, miR-338 and miR-381, that may bind to the 3’UTR of the H1FL1 transcription factor scleraxis, which is a master regulator of tendinopathy development. The results from this study provide novel insight into the mechanobiology of tendons, and indicate that miRNA could play an important role in the adaptation of tendons to growth stimuli.

25.0: FATIGUE

25.1 BEHAVIOR OF THE TIBIALIS ANTERIOR MUSCLE-TENDON COMPLEX DURING REPEATED MAXIMUM ISOMETRIC DORSIFLEXION

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The present study was designed to examine how behavior of the tibialis anterior (TA) muscle-tendon complex is influenced by repeated isometric voluntary dorsiflexion contractions (MVC). Subjects were 20 males seated on a dynamometer chair with the knee joint fully extended and the tibio-tarsal joint angle fixed on the platform at 90 degrees. A task consisting of 5 x MVC followed by 5 s relaxation was repeated 50 times (8 min 20 s), without giving feedback on the number of repetitions to the subjects. Average electromyography (EMG) and frequency power spectrum were calculated from EMG signals. Length (LT) and elongation (ET) of the tendon structures, as well as the pennation angle (PA) at the point where a fascicle arose from the deep aponeurosis, were measured by ultrasonography. Stiffness of the tendon (ST) was also calculated. After the task, blood lactate concentration was significantly increased, and MVC force, ET, and LT were decreased. PA and ST remained unchanged. Similar changes were observed during the test. The MVC per average EMG increased significantly, while mean power frequency decreased. Interestingly, the plantar flexion force increased during TA relaxation with the progress of the task as if it stretched TA that got into the dull movement. These findings imply that fatigue induced by repeated MVC influences muscle function but not tendon structure. In conclusion, fatigue lengthened muscle fibers with incomplete shortening but without changes in PA.

25.2 WHAT DETERMINES THE TIME-COURSE OF PERFORMANCE LOSS AND MUSCLE FATIGUE IN DIFFERENT MODES OF DYNAMIC EXERCISE?

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For nearly a century, investigators have noted the exponential loss in performance that occurs as the duration of an all-out effort increases from seconds to minutes. Our lab has previously found that the exponents describing the decrements in performance for sprint cycling and sprint running are similar between individuals, but differ between modes of exercise. Here, we tested the hypothesis that these different rates of loss are set by the relative duration of muscle activity in the specific modes. We used a custom ergometer and all-out knee-extension exercise to maintain constant muscle contraction durations, and altered the portion of inactivity; resulting in cycles with muscle activity that were either 25 or 75% of the total. Subjects completed a minimum of 10 all-out trials in each condition at force requirements selected to elicit failure between 3 and 300 s. In support of our hypothesis, the exponential rate of force loss was greatest at the 75% duty cycle (k25 = 0.018 ±0.001s-1) vs k75 = 0.009 ±0.001s-1, p<0.001). When we accounted for the different contraction frequencies necessitated by our experimental manipulation, by evaluating rates of fatigue as a function of the cumulative duration of muscle activity (trial duration • duty cycle), the between condition differences disappeared. We conclude that during brief all-out exercise, rates of performance loss are determined by the cumulative duration of muscle activity.

25.3 THE EFFECT OF METABOLIC ALKALOSIS ON LOCALISED NEUROMUSCULAR FATIGUE DURING INTERMITTENT, HIGH-INTENSITY INTERVAL CYCLING AT A FIXED CADENCE

Jason Siegel, Paul Marshall, Sean Rafferty, Cristy Brooks, Benjamin Dowswell, Rick Romans, Karen Mathews, Michael Knox
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Nine recreationally active participants completed four intermittent, high-intensity (30x work: 30s recovery at 120% peak power output) cycling conditions (Placebo 60 rpm (P60), Alkalosis 60 rpm (A60), Placebo 90 rpm (P90) and Alkalosis 90 rpm (A90)) implemented in a randomized manner separated by 1 week. Alkalosis was induced through ingestion of 0.3g·kg-1 sodium bicarbonate over a 90 min period. Peak force (maximal voluntary contraction (MVC)) was measured following each 30s work period, while neuromuscular activity was assessed via surface electromyography (sEMG). Neither the influence of cadence (60 or 90 rpm) nor alkalosis had an independent effect on the MVC fatigue profile, however a main effect for condition was evident with P90 exhibiting a greater decline in force production when compared to all other conditions (p<0.02). Neural recruitment of the gluteus maximus (GM), vastus lateralis (VL) and medialis (VM) initially increased in all conditions but by task failure had also declined similarly across all conditions, and with the exception of GM, remained impaired 10 min post. Conduction velocity (CV) and rate of force development (RFD) declined in all conditions, however only CV remained inhibited 10 min post (p<0.05). The fatigue associated with repeated, high-intensity intermittent cycling is independent of pre-exercise acid-base manipulation or cadence.

25.4 INFLUENCE OF ALTERED DUTY CYCLE ON CRITICAL POWER DURING HANDGRIP EXERCISE

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Two subjects were used to study the effect of duty cycle on fatigue during handgrip exercise using the power-duration relationship. Handgrip testing was conducted at 20 contractions/min using duty cycles of either 20% or 50% time-under-tension (TUT), while concentric contraction duration was held constant. To date, 2 subjects have completed maximal incremental tests for the determination of peak power (Ppeak) and at least 3 constant power tests for the determination of critical power (CP) and W’ for both 20% TUT and 50% TUT. Each subject also completed six one-handed MVCs (three per arm) which were summed together and averaged to provide a two-handed MVC. The average two-handed MVC was 809 N. Ppeak from the incremental tests were 6.25 W for 20% TUT and 5.00 W for 50% TUT. For 20% TUT, CP was 3.5 W which equated to 60% Ppeak and 27.9% MVC. W’ was 620 J and 412 J for 20% TUT and 50% TUT, respectively. CP remained inhibited 10 min post. Conduction velocity (CV) and rate of force development (RFD) declined in all conditions, however only CV remained inhibited 10 min post (p<0.05). The fatigue associated with repeated, high-intensity intermittent cycling is independent of pre-exercise acid-base manipulation or cadence.
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ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS

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Epidemiological data indicates that habitual physical activity is protective against age-related cognitive decline. Interventional studies in animals support this view and the limited longitudinal data in humans is also supportive. In this context, traditional vascular risk factors (hypertension, altered blood lipids, and diabetes) are also risk factors for age-related cognitive decline. Together these findings raise the possibility that at least some of the protective effects of physical activity in maintaining cognitive function might be due at least in part to positive effects on the cerebral microcirculation. In this talk we will review what is known about aging and cerebral vasodilator function and how it is altered by physical activity. We will also compare and contrast what is known about physical activity and the cerebral circulation with data from other more thoroughly studied vascular beds. The main questions flowing from our analysis and the ideas outlined above are: 1) To what extent is age related cognitive decline linked to microvascular dysfunction in the cerebral circulation? 2) Could this be the triggering event? or 3) Is cognitive decline an epiphenomenon that follows other pathological changes in the brain? In either case we argue that the role of microvascular dysfunction in the cerebral circulation is underappreciated as either a primary cause or amplifier of age related cognitive decline.

26.4 POTENTIAL NEUROBIOLOGICAL MECHANISMS BETWEEN PHYSICAL ACTIVITY AND COGNITIVE FUNCTION

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Physical activity is an essential product of evolution. Our ancestors must face both physical and mental challenges for survival. The modern age may have tilted the balance of natural selection more towards mental capability. Long-term consequences of these changes are not known. However, for the time being, the price of physical inactivity may have to be paid. Recent studies suggest that physical activity influences brain structure and function across the lifespan of human beings. Physical activity appears to modulate the fundamental biological processes of the brain from gene expression to neural circuit plasticity. Not surprisingly, physical inactivity has been identified as an important risk factor for brain diseases such as the Alzheimer’s type of dementia. However, significant knowledge gaps exist in our understanding a potential causal relationship between physical activity and brain structure and function. For example, at present we do not know the specific biological signal(s) or the signaling pathways which brain may use to sense changes in physical activity, they are either neural and/or hormonal, regional inside the brain or from the systemic circulation. Practically, questions such as types of physical activity, influences of individual genotype, as well as a potential “dose-response” relationship need to be addressed to capitalize the salutary effects of physical activity on cognitive function. The revolution of contemporary molecular biology and neuroimaging technology provide us with an unprecedented opportunity to understand the fundamental relationship between physical activity and cognitive function. (NIHR1-AG033106)

26.5 HOW DOES AEROBIC EXERCISE PROTECT AGAINST DEMENTIA

Neill Grafaf-Radford


Auger. It is well established that Alzheimer’s disease (AD), which is the 6th leading cause of death, is the only one in the top 10 that can’t be prevented. A recent 1 year prospective, controlled study by Engedal et al. reported aerobic exercise (contrasted to toning and stretching) in persons age 55-80 (mean:67), resulted in increased hippocampus volume correlated with improved fitness, better visual memory and increased plasma Brain Derived Neurotrophic Factor (BDNF). This study has provided evidence that aerobic exercise and mouse experiments support. However, it does not address a crucial question, that is, will aerobic exercise protect the brain in the setting of asymptomatic pre-Alzheimer disease, recently defined by Sperling and colleagues. From postmortem and brain amyloid (Aβ) imaging studies we know that more than 80% of persons age ≥85 have significant Aβ deposits. These deposits occur 10-15 years prior to AD diagnosis and provide a window of opportunity for intervention. Would exercise protect at mean age 75, when more than 40% of cognitively normal persons have Aβ deposits? This paper addresses the animal and human evidence supporting that exercise may be a broad spectrum intervention against the three commonest causes of dementia, AD, vascular dementia, and Alzheimer’s related dementia. Graf-Radford NR. Can exercise protect against dementia? Alzheimers Res. Ther. 2011 Feb 28;3(1):6.

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

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Aging, insulin resistance, and type 2 diabetes are associated with a diminished heat stress response. The highly conserved family of proteins known as heat shock proteins (HSPs) serves as one of the body’s major endogenous defense systems against oxidative stress. Although limited clinical data exist on HSPs and insulin resistance, patients with type 2 diabetes demonstrate reduced gene expression of heat shock protein 72 (HSP72), which correlates with reduced insulin sensitivity. Previous studies have demonstrated that an increase in HSP72 via heat treatment, transgenic overexpression, or pharmacologic means results in protection against diet- or obesity-induced glucose intolerance and insulin resistance. Increased understanding of HSPs indicates they are involved in a number of adaptive responses in skeletal muscle including mitochondrial biosynthesis, regulation of apoptotic pathways, cytoprotection, and improvements in insulin sensitivity. Enhancing the body’s endogenous defense system of HSPs through a variety of treatment approaches including exercise and heat, could have a profound impact on future approaches to disease prevention and treatment.

29.0 INTEGRATED EXERCISE RESPONSE

29.1 JUMPING ABILITY OF LONG-DISTANCE RUNNERS

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This study was designed to investigate the jumping ability of long-distance (LD) runners in comparison with athletes of other sports. A total of 46 LD runners, 34 other event athletes, 7 ball players, and 13 healthy untrained males volunteered to participate in this study. LD runners were divided into two groups (good and poor) based on their running performance. They performed 3 vertical jumps (VJ), 3 drop jumps (DJ), and 1 exercise of 10-consecutive jumps (RJ), which were filmed at 300 Hz. Jumping height, DJ and RJ indexes were lower in LD runners than in other subjects. In particular, VI height was less than that of healthy untrained males. Good LD runners achieved better height in VJ, DJ, and RJ and showed better indexes for these exercises than poor LD runners. The jumping movement of LD runners was characterized by smaller joint and extension at the ankle and larger extension at the hip on take-off. In the first half of the ground contact phase, angular displacement of the lower limb joints was smaller in LD runners than in other event athletes and healthy untrained males during VI, whereas it was larger during DJ and RJ. Similar differences were observed between good and poor LD runners. The results suggest that the jumping ability of the LD runners was less than that of the other sport athletes because of lower leg power and insufficient stretch-shortening cycle behavior. The characteristics observed in LD runners are likely influenced by duration and type of training method.

29.2 PEAK HEART RATE AND PERFORMANCE IN SEVERE HYPOXIA: DIFFERENCES BETWEEN TIBETANS AND HAN CHINESE

Bengt Kjaer1, Jui-Lin Fan2, Tian-Yi Wu3


The potential changes after the treatment; six subjects (3 men and 3 women) received placebo treatment as controls. Measurements of the VO2max showed better indexes for these exercises than poor LD runners. The jumping movement of LD runners was characterized by smaller joint and extension at the ankle and larger extension at the hip on take-off. In the first half of the ground contact phase, angular displacement of the lower limb joints was smaller in LD runners than in other event athletes and healthy untrained males during VI, whereas it was larger during DJ and RJ. Similar differences were observed between good and poor LD runners. The results suggest that the jumping ability of the LD runners was less than that of the other sport athletes because of lower leg power and insufficient stretch-shortening cycle behavior. The characteristics observed in LD runners are likely influenced by duration and type of training method.

29.3 SHORT-TERM EFFECTS OF INTENTIONAL BIODYNAMIC CRANIOSACRAL THERAPY ON VO2MAX AND HEART RATE RECOVERY: A PILOT STUDY

Massimo Armeni2,3, Rosario D’Onofrio4, Paola Sommaggio5,6, Greger Giannini1


 PURPOSE: To investigate the short-term effects of biodynamic craniosacral therapy on haemodynamic and cardiopulmonary parameters during the Rockport Fitness Walking Test (RFWT), a field aerobic test. METHODS: Nine subjects (4 women and 5 men) underwent 3 sessions of craniosacral therapy and the RFWT. In order to assess the potential changes after the treatment, six subjects (3 men and 3 women) received placebo treatment as controls. Measurements of the VO2max and haemodynamics parameters were recorded at rest, before the treatments, during and after the RFWT. The results were compared by using XLSSTAT 2008 software. RESULTS: The VO2max showed a significant difference (P = 0.04) but the Heart Rate Recovery was almost unchanged after the treatment. CONCLUSIONS: Biodynamic craniosacral therapy seems to have a direct influence only on the VO2max.
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29.4 THE EFFECTS OF DIFFERENT MODES OF EXERCISE ON THE ASSOCIATIONS BETWEEN APPETITE AND APPETITE-RELATED GUT HORMONES

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The purpose of this study was to determine the effects of different modes of exercise (i.e. weight bearing exercise versus non-weight bearing exercise) on the associations between appetite and appetite-related gut hormones. Fifteen healthy young men (age, 24.4±3.4 yrs; maximal oxygen uptake, 47.0±6.1 mL/kg/min) participated in this study. After 12-h fasting, all subjects undertook two trials, rope skipping exercise (64.8±1.9% of VO2max (52.0±7.6%) of VO2max), 3 sets x 10 min with 5 min interval) and bicycle ergometer exercise (63.9±3.3% of VO2max (52.2±7.4%) of VO2max), 3 sets x 10 min with 5 min interval). Plasma concentrations of acetylated ghrelin and peptide YY, and hunger evaluated by visual-analog scale were measured. Both rope skipping and bicycle ergometer exercises significantly suppressed appetite and acetylated ghrelin concentrations, and increased peptide YY concentrations. In the bicycle ergometer exercise trial, exercise intensity (%VO2max) was significantly associated with delta changes in appetite and acetylated ghrelin and peptide YY concentrations, but these relationships were not observed in the rope skipping exercise trial. In addition, there was a significant association between delta changes in appetite and acetylated ghrelin concentrations in the bicycle ergometer exercise trial, but not in the rope skipping exercise trial. In conclusion, exercise intensity-associated changes in appetite and appetite-related gut hormones may disappear in weight bearing exercise.

29.5 VOLUNTARY WHEEL RUNNING THAT ENHANCES NEUROGENESIS DOES NOT ACTIVATE MICROGLIA IN THE MICE HIPPOCampUS.

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Research has shown that exercise improves neuronal plasticity, including neurogenesis, in the hippocampus of rodents. However, little is known about how exercise affects neuronal cells in the brain. Microglia, the brain-resident macrophages, plays a pivotal role in mediating neuroinflammatory responses in the CNS through producing pro-inflammatory cytokines. When microglia is activated by multiple types of stimuli, morphological transition from a ramified-resting state to an activated (hyper-ramified; reactive; or phagocytic) state occurs. Microglia is also known to proliferate with activation. In this study, we investigated whether voluntary wheel running which can enhance neurogenesis changes activation status of microglia in the mice hippocampus. Male C57BL/6 mice were housed with or without running wheel for 4 weeks. The brains were processed for immuno-labeling of Iba-1 (ionized calcium-binding adaptor protein-1, a marker of microglia) and DCX (doublecortin, a marker of immature neuron). Voluntary running significantly increased DCX-positive neurons in the dentate gyrus, demonstrating that the voluntary running significantly increased DCX-positive neurons in the dentate gyrus, demonstrating that the voluntary running significantly increased DCX-positive neurons in the dentate gyrus, demonstrating that the voluntary running significantly increased DCX-positive neurons in the dentate gyrus, demonstrating that the voluntary running significantly increased DCX-positive neurons in the dentate gyrus, demonstrating that the voluntary running significantly increased DCX-positive neurons in the dentate gyrus.

29.6 BLOOD PRESSURE RESPONSE TO EXERCISE IS NOT RELATED TO VASCULAR ENDOTHELIAL FUNCTION IN OVERWEIGHT/OBESE ADULTS

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Obesity and obesity are associated with endothelial vasodilator and fibrinolytic dysfunction. Recent data, from the Framingham Heart Study has suggested that vascular dysfunction may contribute to exaggerated blood pressure (BP) responses during exercise. Accordingly, we determined if BP response to exercise is related to endothelial vasodilator and fibrinolytic function among overweight/obese (OW/Ob) adults. 92, sedentary OW/Ob adults, were studied. All subjects were free of cardiovascular disease and completed a Ballex exercise treadmill test to volitional exhaustion. Blood pressure was measured at rest, stage 1, stage 2, peak exercise and 3 minutes after exercise. In 50 subjects (64.1% female; age: 55.6±11.3 yrs; BMI: 29.7±5.3 kg/m2, forearm blood flow (FMD) and blood flow response to acetylcholine (4.0-16.0 µg/mL) were measured in rest and during handgrip exercise with a 20% duty cycle, the deoxy-(Hb-Mb) signal (and oxy-Hb signal) was measured during 0-, 15-, and 30-s exercise periods. There were no significant changes in baseline FMD and blood flow response to acetylcholine (4.0-16.0 µg/mL) between rest and exercise. These findings suggest that during handgrip exercise with a 20% duty cycle, the FMD and blood flow response to acetylcholine were not affected by exercise, indicating a lack of vascular dysfunction in overweight/obese adults. No changes was observed in blood glucose levels during exercise and fasting, but no hepatic gluconeogenesis concentrations were progressively depleted with both longer exercise and fasting periods. Saturation curve analysis indicated a progressively higher GR density response to bradykinin (12.5-50.0 ng/100mL tissue/min). There were no significant correlations between the peak FBF response to acetylcholine or total FA release and BP at rest (r=0.05; 0.07, respectively), stage 1 (r=0.01; 0.10), stage 2 (r=0.09; 0.05), peak exercise (r=0.07; 0.14), or recovery (r=0.05; 0.15). These results suggest that vascular endothelial function is well preserved in overweight/obese adults during exercise.
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29.10 THE METABOLIC RESPONSES TO EXERCISE MODE IN OVERWEIGHT/OBESE ASTHMATICS
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Asthma and obesity/obesity (OWOB) progress concurrently and are poorly understood. This study characterized the interactions of asthma & OWOB using VO2max testing. METHODS: Stable asthmatics (n=10) and normal-lung indi
guals (n=15) were studied. Groups were similar (p>0.05; ANOVA) on age (AS=22.4 ± 2.0 vs. NL=22.2 ± 1.7;VE=37.4 ± 7.3 L/min; 89.5 ± 6.9 min; 27.8 ± 5.6 kg/m²; 87.9 ± 7.6 kg; 73 ± 5.3 yrs). There were three VO2max trials: 1) treadmill (TM): 2) cycle
cycle-ergometer (Sit-Cel); and 3. stand up when RER>1.0 (Stand-CE). RESULTS: ANCOVA (Sit,davit, covariate) showed differences (p<0.05) by group & trial, but no interac
tions, on VO2max. CONCLUSIONS: These results demonstrated that, per exercise mode, metabolic responses between groups were generally parallel. The lower AS VO2max and VO2max-related values were due to poor physical fitness, not OWOB or cardiopulmonary limits. The study was funded by Southern Arkansas University.

29.11 EFFECT OF INTERVAL TRAINING ON CHANGES IN VO2MAX:
A META-ANALYSIS
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The HERITAGE study showed 0.4 L/min changes and marked variability in the VO2max responses to continuous training (CT; <75% of VO2max for 20 ks Bouchard et al. 2011). Smaller studies using interval training (IT) or combined IT/CT have shown much larger increases in VO2max (<1.0 L/min, Hickson et al. 1977). This raises questions about the role of exercise intensity for both mean and individual VO2max responses to training. We analyzed IT and CT/IT studies published in English from 1965-2012. Inclusion criteria were: 1) ≥3 healthy sedentary/recreationally active humans <45 yrs old, 2) training du
tions 6-12 weeks, 3) ≥3 days of training per week, 4) ≥20 min of high intensity training, and 6) results reported as mean ±SD or SE. 28 studies with 308 subjects were identified. Statistical analysis used a fixed effects model with difference in means calculated with a 95% confidence interval (mean 0.43 L/min). Due to mild heterogeneity (I² = 13.4), a random effects model was used (mean 0.45 L/min). An estimated distribution for number of subjects vs. change in VO2max was compared to Bouchard et al. We estimate all IT subjects improved VO2max >0.1L/min, and 26% of the subjects improved >0.7 L/min; whereas Bouchard et al. showed 7% of subjects had VO2max increases >0.5 L/min, and 8% of subjects improved by >0.7 L/min. These results suggest that ideas about the trainability of VO2max should be further evaluated with standardized IT or IT/CT training programs.

29.12 AN ALTERNATIVE APPROACH TO MATCHING RELATIVE WORK AND INTENSITY DOMAINS DURING INTERVAL AND CONTINUOUS EXERCISE
Emma Harron1, Amy Weeks2, Ali Khalil3, Gurpreet Birik4, Carrie Ferguson5, Karen Birch6


Superior health benefits have been reported following interval (IE) compared to continuous exercise (CE). However, due to the methods used to match IE and CE for work and intensity, it is unclear whether work rate (WR) oscillations or the intensity domain of IE drives these benefits. PURPOSE: To determine a between-subject protocol in which both the intensity domain and work (kL) for CE and IE are matched, highlighting the in-appropriateness of previous methods. METHODS: 7 women (age 38.6±8.6y; BMI 29.3±6.0 kg/m²) completed a maximal ramp- incremental cycle ergometer test (VO2max and lactate threshold: LT) and either an IE (n=4) or CE (n=3) session. IE WR alternated between 40% ± 10% i.e. 3.8±1.0 W/kg with 40% ± 10% 4.0±2.0 W/kg lasting 30 min. CE was set at 20%±10% for the duration required to achieve the same total work that each individual would have accomplished in an IE session. VO2 was measured throughout and blood was drawn at ~30s intervals. RESULTS: VO2max was determined to be 3.5±1.2 L/min, and 2.9±1.0 L/min for IE and CE, respectively. CONCLUSIONS: These findings demonstrated that, per exercise mode, metabolic responses between groups were generally parallel. The lower AS VO2max and VO2max-related values were due to poor physical fitness, not OWOB or cardiopulmonary limits. The study was funded by Southern Arkansas University.

29.13 INFLUENCE OF EXERCISE MODALITY ON PHYSIOLOGICAL ADAPTATIONS TO SHORT-TERM SPINT INTERVAL TRAINING
Rebecca Scaife1, Garrett Peltonen1, Scott Bram1, Gregory Grodzens1, Anna Klocka1, Hjalmar Pra1, Melanie Schwedel1, Kyle Sevitt1, Steve Szallar1, Lacey Wood1, Raoul Reiser2, Christopher Bell3

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Short-term sprint interval training (SIT) has been shown to elicit physiological adaptations similar to long-term endurance exercise. Most SIT studies have focused on cycle ergometer or non-motorized treadmill exercise, but the influence of exercise modality has not been directly addressed. Hypothesis: improvement in end
durance exercise performance following SIT will be similar between stationary cycle ergometer (Cyc), non-motorized treadmill running (RUN), and a novel exercise modality incorporating repetitive vertical jumping on a pneumatic platform (RJV). Ex
perimenal procedures conformed to the Declaration of Helsinki. 20 seden
tary/recreationally-active adults (age: 22.1 ± 1.9 yrs; body mass index: 25.1±1.0 kg/m²; mean/SE) were randomly assigned to RUN (n=8); CYC (n=4) or RJV (n=8). Following 3 weeks of SIT (9 sessions of 4-8 reps of 30-second “all-out” maximal exertions sepa
rated by 4 minutes of recovery), time to exhaustion while cycling (Cyc) or running (RUN & RJV) at 80% maximal oxygen uptake (VO2max) was increased (P<0.009) with RUN (44.5±4.5 vs. 57.1±0.4 min) and increased to a greater extent in CYC (48.6±7.4 vs. 88.1±18.2 min) but was unchanged in RJV (32.2±5.2 vs. 32.7±4.9 min). VO2max was unaffected by SIT (P>0.55), regardless of exercise modality. These preliminary data sug
gest the SIT-induced improvements in endurance performance are influenced by exercise modality.

29.14 A SINGLE SESSION OF SPRINT INTERVAL TRAINING INCREASES TOTAL DAILY ENERGY EXPENDITURE
Kyle Sevitt1, Edward Melanson1, Tracy Swingle1, Garrett Peltonen1, Rebecca Scaife1, Scott Bram1, Anna Klocka1, Christopher Melot1, Christopher Bell2

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High intensity sprint interval training (SIT) is known to elicit favorable physiological adaptations, including improved insulin sensitivity and glucose tolerance. However, its utility for weight loss is questionable. The objective of this ongoing study is to determine the effects of a single bout of SIT on total daily energy expenditure. 24-hour energy ex
dpenditure was determined in 5 healthy men (age: 28.3±1.9 yrs; body mass index: 23.4±0.8 kg/m²; mean/SE). After three days of controlled diet and maintenance of energy balance, subjects were studied in a whole-room indirect calorimeter for two consecutive days. One of these days (random order) began with a single bout of SIT (5 x 30 second “all-
out” exertions on a cycle ergometer against a resistance equivalent to 7.5% body mass, separated by 4 minutes of loadless cycling). A single bout of SIT increased 24-hour energy expenditure in all subjects during an otherwise sedentary day (2463±226 vs. 2221±175 kcal/day; P<0.001). Our preliminary data provide support for SIT as a time
efficient alternative to endurance exercise and as a strategy for weight maintenance. Sup
ture: University of Colorado Clinical and Translational Science Award (I1UL1 RR025780).

29.15 A SINGLE BOUT OF SPRINT-INTERVAL TRAINING IN NORMOXIA DOES NOT IMPROVE ENDURANCE EXERCISE PERFORMANCE IN HYPOXIA
Garrett Peltonen1, Rebecca Scaife1, Scott Bram1, Anna Klocka1, Steve Szallar1, Lacey Wood1, David Freivogel2, Thomas Schroeder2, Karen Hamilton1, Christopher Bell3

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A single bout of sprint-interval training (SIT) produces very rapid favorable adaptions but does not affect subsequent endurance performance in a low oxygen environment.

C-75
Hypoxic Exercise Performance Following Intravenous Glucose Administration: Influence of Sympathetic Inhibition

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Endurance exercise performance (time to exhaustion) is positively associated with basal muscle glycogen content. Sympathetic inhibition promotes insulin sensitivity and glucose clearance in hypoxia, but may impair subsequent hypoxic exercise performance, in part due to suppression of cardiac output. Hypothesis: hypoxic exercise performance following intravenous glucose feeding in a low oxygen environment will be attenuated when feeding occurs during sympathetic inhibition. Experimental procedures conformed to the Declaration of Helsinki. On two separate occasions (random order) glucose (20% glucose solution in saline; 75g) was intravenously administered over 1 hr to 10 healthy men while breathing a hypoxic gas mixture (15% O2), with and without prior sympathetic inhibition (48-hr transdermal clonidine; 0.2 mg/d). On initiation of glucose administration the clonidine patch was removed. 3 hr after completion of glucose infusion, subjects completed a hypoxic time to exhaustion trial (stationary cycle ergometer, ~65% mean±SE; 23.5±5.1 min; mean±SE; P<0.73). Sympathetic inhibition protects against hypoxia-mediated insulin resistance without influencing subsequent hypoxic endurance performance.

Short-term Training Improves Glucose Tolerance in Elderly Men

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The aim was to elucidate the molecular mechanisms behind training-induced improved glucose tolerance in elderly subjects. Healthy men (n=12) aged 62 to 72 years completed 5 weeks of exercise training consisting of cycling and cross fit exercise. All subjects performed baseline testing before and after the training period an incremental bicycle VO2max test and time to exhaustion during one legged knee-extensor exercise. In addition, an oral glucose tolerance test (OGTT; 1g/kg bw) with blood sampling up to 2hr after and vastus lateralis muscle biopsies obtained before and 45 min after glucose intake was performed. VO2max increased 19% and time to exhaustion increased 22% with training. While the plasma glucose response during the OGTT was unchanged, the area under the curve for plasma insulin and c-peptide was reduced following the training period. Glucose intake elicited a 2.5-3 fold increase in Akt Thr308 phosphorylation in skeletal muscle with no difference before and after training. However, basal GLUT4, cytochrome c and cytochrome oxidase 1 protein content in skeletal muscle was 1.2-fold higher after training. In conclusion, these findings suggest that short term high-intensity training may improve glucose tolerance in elderly men in part due to increased total capacity for glucose transport and substrate oxidation.

The Advantages/Disadvantages to Using Cultured Single Muscle Fibers as an In Vitro Model to Mechanistically Research Skeletal Muscle

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Muscle cell cultures have served as an important experimental approach for many seminal discoveries in skeletal muscle. Currently, immortalized skeletal muscle rodent lines, MDA-MB-231 and MCF-7, using two model systems of acute exercise. 1) In vitro, the cancer cells was incubated with human serum, obtained during an acute exercise trial in healthy young women, cycling for 2 hours at 60% Vo2max, and subsequently resting for 3 hours. 2) In vivo, tumor-bearing mice was subjected to 1 hour of swimming, after which the tumor was dissected and analysed for AMPK activation. Results: Acute exercise induces AMPK phosphorylation at the Thr 172 activation site in both cancer cells stimulated with exercise-conditioned serum and in tumors in vivo. In the in vitro system, phosphorylation at the Thr 172 site was associated the decreased viability of the MCF-7 cells. Conclusion: Acute exercise activates AMPK in breast cancer cells, and this activation might link exercise-induced alterations in breast cancer cell metabolism with the protective effect of exercise on cancer.
29.22 COUNTERINTUITIVE INCREASE IN PLASMA MYOSTATIN AFTER RESISTANCE TRAINING WITH HIGH PROTEIN DIET IN YOUNG HEALTHY SUBJECTS
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INTRODUCTION: Myostatin (MSTN) regulates muscle body fat amount, training status and nutrition has been widely investigated but with conflicting results. Although MSTN inhibits the Akt/mTOR pathway and reduces IGF-1 some studies have shown a “paradoxical” positive correlation between MSTN and muscle mass. We investigated the influence of two months of resistance training (RT) and high protein diet on plasma myostatin, IL1, IL6 and MSTN-α and MSTN-β were analyzed.
RESULTS: MSTN showed a significant increase after the last training in the HP compared to NP. There were no significant differences in IGF-1, IL1, IL6 and MSTN-α were analyzed before and after the first and last training session. Lean body mass, muscle mass, arm muscle area and IRM test were analyzed. RESULTS: MSTN showed a significant increase after the last training in the HP compared to NP. There were no significant differences in IGF-1, IL1, IL6 and MSTN-α showed a positive correlation with MSTN in HP after the last training (r=0.6456; p=0.0295). No correlations were found with other blood parameters nor with muscle mass. CONCLUSIONS: We found a “paradoxical” response of plasma MSTN to HP diet after RT. The double increase of IGF-1 and MSTN could explain the overlapping of muscle mass increases in both groups and let us to argue that HP diet influence metabolic regulations of IGF-1 and MSTN upstream the same pathway. This conflicting results could reflect the complexity of MSNT release mechanism.
29.23 THE EFFECT OF MUSCLE CONTRACTION ON CACHECTIC MUSCLE MTOR SIGNALING AND PROTEIN SYNTHESIS IN ACPM1+/+ MICE
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Cachexia is characterized by muscle mass loss regulated by disrupted protein turnover, which includes the suppression of muscle mTOR signaling and myofibrillar protein synthesis (MPS). Eccentric muscle contraction (EC) stimulates MPS and muscle mass accretion. The purpose of this study was to determine if cachectic TA muscle maintains anabolic plasticity related to EC stimulation of MPS through mTOR signaling during the progression of cachexia. Female C57BL6/J (WT) and Acpm1 mutant (Min) mice performed a well-described EC protocol by stimulating the sciatic nerve (10 sets of 6 repetitions, ~22 minutes). The tibialis anterior (TA) muscle from one leg was stimulated, while the contralateral leg was the control. The TA muscle was harvested at 3, 14, or 24h after an acute novel bout of EC. Repeated bouts of contraction were performed over 2 wks. TA muscle mass and type IIA and IIB mean fiber cross-sectional area (CSA) were reduced by cachexia. Repeated EC increased TA mass by 5% and the type IIA and IIB mean CSA by 32% and 14%, respectively. Acute EC increased 4E-BP1 and p70S6K phosphorylation, but this induction was attenuated by cachexia. MPS was induced by EC but remained suppressed below WT control levels in Min mice. Acute EC also attenuated AMPK phosphorylation, which was induced by cachexia, at 3h and 14h post EC. These data suggest repeated EC can reverse muscle wasting, but the acute induction by EC is attenuated in cachetic muscle. Funded by NIH Grant RO1CA121249-01.
29.24 EXERCISE TRAINING IMPROVES EXERCISE CAPACITY DESPITE PERSISTENT MUSCLE MITOCHONDRIAL DYSFUNCTION IN THE TAZ SHRNA MOUSE MODEL OF HUMAN BARTH SYNDROME
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Barth Syndrome is a mitochondrial disease associated with exercise intolerance and cardiorespiratory myopathy resulting from mutations in the tafazzin (taz) gene. The present study characterized skeletal muscle mitochondrial function and exercise capacity of a taz shRNA mouse model of Barth Syndrome (90% taz-deficient), and examined the effect of exercise training on these parameters. Mitochondrial respiratory function was assessed in mitochondria freshly isolated from hindlimb muscles using an Oroboros O2K respirometer. At day 5 post-MI (p<0.05) than both the MIEX (940±82/mm) and Sham (827±78/mm) groups did not differ from each other, but both of the groups were higher (p<0.05) than the Sham group (512±78/mm). These results suggest that post-MI exercise training significantly induces angiogenesis in both the viable myocardium of LV and septum. Such training effect is not observed in the RV. Supported by a grant from the NIH (RO1-HL74273).
29.25 EFFECTS OF THE MENSTRUAL CYCLE PHASE ON OXIDATIVE DNA DAMAGE FOLLOWING SUBMAXIMAL CYCLING EXERCISE
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PURPOSE: The purpose of this study was to determine effects of the menstrual cycle phase on oxidative DNA damage following 2 hours of prolonged cycling exercise in women. METHODS: Twelve recreationally active eumenorrheic women served as the subjects (n=6 Age: 20±0.3 year; Height: 160±1.5 cm; Body weight: 54±7.5 kg; Body fat: 21.9±3.1 %; Peak oxygen uptake (VO2-peak): 44±5.0 ml/kg/min (means±SD)). Before (Pre) and after (immediately Post and Post 24 hours) 2 hours of cycling exercise at 60%VO2-peak, spot urine was collected for later analysis of 8-hydroxy-2'-deoxyguanosine (8-OHdG; a marker of whole body DNA damage and repair) determined with high performance liquid chromatography. All subjects performed the same exercise protocol during the follicular (F: 5–8 days after the onset of the menses) and luteal (L: 22–25 days after the onset of the menses) phase. RESULTS: With regard to 8-OHdG level (ng/mg Creatinine), two-way (time x phase) analysis of variances (ANOVA) showed no significant main effects for time and phase or interaction (Pre: 3.2±1.2, Post: 3.3±1.1, 24h: 3.2±0.8 for F; Pre: 3.0±1.1, Post: 3.1±0.7, 24h: 3.3±0.9 for L). CONCLUSIONS: The findings of the present study indicate that the menstrual cycle phase appears not to influence oxidative DNA damage following 2 hours of cycling exercise at 60%VO2-peak. Supported partly by funds from the Grant-in-Aid for Scientific Research (C) in Applied Health Sciences (Grant No.23508067) of Japan Society for the Promotion of Science.
29.26 IMPAIRED EXERCISE CAPACITY IN LIFE-LONG SKELETAL MUSCLE SPECIFIC VEGF GENE DELETED MICE
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1Medicine, Univ. of California, San Diego, 9500 Gilman Dr., La Jolla, CA, 92039-0623. Exercise capacity is dependent on adequate oxygen for mitochondrial respiration in muscle. To determine whether skeletal muscle VEGF is critical for regulating exercise capacity, adult skeletal muscle VEGF null mice (skmVEGF/-) and control, littermates (WT), were speed and endurance tested on a treadmill. Changes in locomotor skeletal muscle capillarity, muscle mass, and type IIA and IIB mean fiber cross-sectional area were reduced by cachexia. When VEGF was expressed in skeletal myofibers during development is essential for maximal exercise capacity. This limitation is not due to a deficit in cardiac or locomotor muscle contractile function but may be affected by fewer capillaries.
29.27 EFFECT OF POST-MYOCARDIAL INFARCTION EXERCISE TRAINING ON ANGIGENESIS
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After a myocardial infarction (MI), adequate growth of new capillaries plays a crucial role in the surviving portion of myocardium. Evidence has shown that angiogenesis is inadequate in the post-MI hearts. PURPOSE: To investigate the effect of post-MI exercise training on myocardial angiogenesis. METHODS: Left ventricular (LV) MI was surgically induced on 7-wk-old rats by ligation of the left coronary artery (~35% infarction) with sham-operated animals serving as control. The survivors were assigned to three groups (n=4/group): Sham (no MI, no exercise), MIEX (MI-exercise), and MISd (MI-exercise). Treadmill exercise training (16m/min, 5°incline, 40min/d, 5d/wk) began at 2 wk post-MI and lasted for 8 wk. Upon completion of the exercise training, hearts were harvested. Transverse cross-sections of the myocardium were stained with CD31 (an antibody against endothelial cells of capillaries). Capillary densities of the LV, septum, and right ventricle were measured under a light-microscope. Results: The capillary densities of LV in the Sham group (1292±215/mm²) was higher (p<0.05) than both the MIEX (949±225/mm²) and MISd (605±80/mm²) groups. The MIEX group had higher (p<0.05) LV capillary densities than the MISd group. The capillary densities of septum in the Sham (1523±70/mm²) and MISd (1247±130/mm²) groups did not differ from each other, but both of the groups were higher (p<0.05) than the MISd (906±24/mm²) group. There were no significant differences (p>0.05) in the capillary densities of RV among the three groups. These results sug-
29.28 INCREASED BASELINE BUT REDUCED ENDOTHelial PROGENITOR CELLS AFTER AEROBIC EXERCISE IN SUBJECTS AT CARDIOMETABOLIC RISK
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Acute exercise is able to improve the function of circulating endothelial progenitor cells (EPC) contributing for the reparative process in healthy subjects, but it is unknown if this mechanism is presented in subjects with cardiometabolic risk (RC). This study aimed to isolate and quantify the EPC after a single bout exercise in subjects at increased CR. Five healthy subjects (7; CT group: 28±9 years) and four subjects at increased CR (CR group: 55±9 years) were enrolled. The CR group presented at least three of five criteria for the metabolic syndrome diagnosis, while the CT group presented none of them. Blood samples were collected before and 15 min after 40-min exercise or control session to isolate and isolate mononuclear cells (MNC). After seven days of MNC culture in EGM-2, the adherent cells were labeled with Dil-acLDL and FITC-UEA-1 lectin by immunofluorescence. The protocol was approved by the ethics committee and performed in accordance with the Declaration of Helsinki. The CT group presented lower percentage of EPC at baseline (CT: 30.8±5% vs. RC: 59.6±5%; p<0.02). After exercise, the EPC increased in CT group (pre: 30.8±5% vs. post: 45.7±7%, p<0.04) whereas they were reduced in CR group (pre: 59.5±5% vs. post: 51.6±6%, p<0.03). There were no differences between the groups or moments in the control session (p>0.05). These results suggest that subjects at CR present an increased percentage of EPC at baseline and that a single bout of exercise decreases EPC in these subjects. Support: CAPES, CNPq, FAPERJ and Labs D’Or.

29.29 EXERCISE DECREASES THE LIPOGENIC CAPACITY OF ADIPOSE TISSUE DURING WEIGHT REGAIN
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OBJECTIVE: To assess the effect of exercise on adipose tissue metabolic gene expression during weight maintenance and the relapse to obesity. METHODS: Mature, obese rats were weight-reduced for 5wk with or without daily treadmill exercise. Rats were then fed a weight maintenance provision, ad libitum (relapse), or a provision that matched the energy imbalance of exercised, relapsing animals for 1d. Gene expression was measured by qPCR. 24h, 14day dietary intake and de novo derived fat were assessed with nutrient tracers. RESULTS: Exercise attenuated the expression of genes involved in lipid uptake (CD36 & LPL), de novo lipogenesis (FAS, ACC1), and triacylglycerol synthesis (MGAT & DGAT) during weight regain. Most of these effects remained significant after controlling for the reduced energy balance. These observations were consistent with the metabolic data, whereby exercise reduced retention of de novo derived fat by 49% (p<0.01) even when controlling for the positive energy imbalance (by 34%, p<0.05). Reflective of CD36 expression, the effect of exercise on the trafficking of dietary fat to adipose tissue was explained by its attenuation of the energy imbalance. CONCLUSION: Exercise decreased the lipogenic capacity of adipose tissue during weight maintenance, both attenuating the positive energy imbalance and by directly suppressing lipogenic gene expression. These concerted effects may explain the beneficial effects of exercise on weight regain prevention.

29.30 EFFECT OF DAILY EXERCISE ON THERMAL PREFERENCE AND HEAT-ESCAPE COLD-SEEKING BEHAVIOR IN MICE
Kai Li1,2, Chien-Chung Li1,2  

The aim of the present study was to assess the effect of exercise training on behavioral thermoregulation and thermal preference in heat with dehyrdation, i.e. hyperosmotic condition. We used mice with/without access to a running wheel for 8 wks (WR and NWR groups, n=40 each). In “a”, the WR group showed higher Tb than NS subgroup, but the WR group didn’t. Thermal preference was lower in the WR than NWR group without any differences between the subgroups (e.g. 33.4±0.3°C and 34.7±0.1°C in the IS groups). Exercise training may alter behavioral thermoregulation and themai preference, and restores the meoregulation in dehydrated.
2012 APS Intersociety Meeting: The Integrative Biology of Exercise-VI

ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS

Cheong Hwa Ooi,1,2 Martin Thompson,3 Patricia Roux,4 Kieron Roseney,3,4 Ross Bradleid

The presence of the cell necrosis provides cytotoxic protection against stress-induced cellular damage and has a cross-tolerance effect to a range of stressors including exercise. Treating mice with 17AAG has been shown to increase HSP70 synthesis in skeletal muscle and enhance recovery from exercise-induced muscle damage. However, it is not clear if this is a specific neurotrophic phenomenon. We hypothesized that 17AAG would increase skeletal muscle HSP70 in rats, thereby protecting against myofibrillar damage following prolonged downhill treadmill running. Rats were randomly treated with 17AAG (40 mg/kg body wt) or DMSO 24 h prior to undertaking exercise for 90 min at 16 mm/min and 16° grade. Red vastus was harvested at 24 h (EX+24h) and 48 h (EX+48h) post exercise, as well as 24 h post treatment in non-exercising groups (Non-EX). Grip strength and serum CK were measured in vivo prior to muscle sampling. Downhill running increased post-exercise HSP70 of both 17AAG and DMSO treated animals (p < 0.001) but the rise in HSP70 expression was precluded by 17AAG in EX+24h rats (p = 0.023). Electrophoresis microscopy showed signs of ultrastructural abnormalities only in DMSO treated EX+24h rats. Muscle capalin and SERCA activity, grip strength and serum CK were not affected. Our data suggest that 17AAG treated rats may have experienced less eccentric contractile strain following downhill running. This study was financially supported in part by the Faculty of Health Sciences under the auspice of the University of Sydney.

30.0: SIGNALLING

30.1 GLUCOSE METABOLISM AND EFFECTS OF CONTRACTILE ACTIVITY ON SKELETAL MUSCLE GLUCOSE UPTAKE SIGNALING IN SPINAL CORD-INJURED VS. ABLE-BODIED INDIVIDUALS

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Evidence suggests that neuromuscular electrical stimulation (NMES)-induced resistance exercise (RE) in individuals with SCI can improve glucose tolerance; however the mechanisms by which these improvements occur remain unclear. Our purpose is to determine whether muscle glucose uptake signaling responds similarly to NMES resistance exercise in SCI vs. able-bodied (AB) individuals and whether glucose tolerance and whole body insulin sensitivity (WHS) are impaired in SCI individuals.13 individuals with SCI (AISA, A; E; 50.11 y), and 13 AB (ASA, A; E; 42/11 y) participated in 84 NMSE training sessions consisting of 60-min, 5 days/week for 8 weeks, with the mice supporting an overload of 5% b.w. PT beyond have an 8 week aerobic interval training program. Isolated ventricular myocytes from these Ex+24h rats were treated with Resveretrol (RSV), a heat shock protein (HSP) inducer and -16° exercise (shortening and Ca

30.2 TSC2/RHEB SIGNALING MEDIATES ERK-DEPENDENT REGULATION OF MTORC1 ACTIVITY IN SKELETAL MUSCLE CELLS

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Previous work from our laboratory demonstrates that heat treatment (HT) protects skeletal muscle from insulin resistance. The exact molecular mechanisms for the protective effects of HT on skeletal muscle are not known, but modifications of insulin signaling and mitochondrial biogenesis are two possibilities. The purpose of the present study was to identify metabolic signaling pathways modified by HT in L6 muscle cells. L6 cells were also treated with Resveretrol (RSV), a heat shock protein (HSP) inducer known to affect insulin sensitivity. L6 cells were subjected to 20 min shrun (37°C) or HT (48 h), returned to 37°C for 24 hours later for Western analysis. A subset of cells were treated with RSV for 3 h, sham or HT for 24 h, and returned to RSV at 37°C. Cells were incubated with or without insulin for 10 minutes prior to harvest. HT increased HSP72 expression in L6 cells, and this effect was enhanced when combined with RSV. HT combined with insulin resulted in an increase in HSP72 above levels seen with HT alone. HT resulted in an increase in phosphor-Akt, however this effect was mitigated in the presence of insulin. RSV treatment resulted in a significant increase in phosphor-AMPK and expression of PGC-1α, while HT had no effect on these proteins. Our findings indicate that HT could increase glucose uptake by increasing insulin signaling intermediates, with little to no effect on insulin-independent pathways of glucose uptake. NIH AG031575.

30.3 METABOLIC SIGNALING IN L6 MUSCLE CELLS IN RESPONSE TO HEAT TREATMENT AND RESVERETROL

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...signaling pathways modified by HT in L6 muscle cells. L6 cells were also treated with Resveretrol (RSV), a heat shock protein (HSP) inducer known to affect insulin sensitivity. L6 cells were subjected to 20 min shrun (37°C) or HT (48 h), returned to 37°C for 24 hours later for Western analysis. A subset of cells were treated with RSV for 3 h, sham or HT for 24 h, and returned to RSV at 37°C. Cells were incubated with or without insulin for 10 minutes prior to harvest. HT increased HSP72 expression in L6 cells, and this effect was enhanced when combined with RSV. HT combined with insulin resulted in an increase in HSP72 above levels seen with HT alone. HT resulted in an increase in phosphor-Akt, however this effect was mitigated in the presence of insulin. RSV treatment resulted in a significant increase in phosphor-AMPK and expression of PGC-1α, while HT had no effect on these proteins. Our findings indicate that HT could increase glucose uptake by increasing insulin signaling intermediates, with little to no effect on insulin-independent pathways of glucose uptake. NIH AG031575.
30.6 SMAD3 IS SUFFICIENT TO INHIBIT PROTEIN SYNTHESIS AND INCREASE MUSCLE FIBER ATROPHY IN VIVO
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Myostatin is a negative regulator of skeletal muscle mass and previous studies have shown that myostatin-induced atrophy is associated with an increase in the expression of atrogin-1. Furthermore, both myostatin, and increased levels of atrogin-1, have been shown to inhibit protein synthesis. It has also been reported that signaling through the transcription factor Smad3 is necessary for myostatin-induced atrogin-1 expression and muscle atrophy; however, it remains to be determined whether Smad3 is sufficient to induce these changes, or whether Smad3 simply plays a permissive role. Thus, the aim of this study was to determine if Smad3 is sufficient to stimulate atrogin-1 promoter activity, inhibit protein synthesis and induce muscle fiber atrophy in vivo. To accomplish this, mouse tibialis anterior muscles were transfected via electroporation with plasmid DNA encoding LacZ (control) or Smad3 alone, or in combination with a luciferase reporter for atrogin-1 promoter activity. Muscles were collected at 3 or 7 days post electroporation and analysed for rates of protein synthesis, fiber size and luciferase activity. Our results demonstrate that overexpression of Smad3 induces an increase in atrogin-1 promoter activity and a decrease in protein synthesis and fiber size. Combined, these results provide the first evidence that Smad3 is not only necessary, but also sufficient to inhibit protein synthesis and induce atrophy in vivo. This work was supported by NIH grant R057347 to TAH.

30.7 ROLE OF LKB1 IN THE REGULATION OF GENE EXPRESSION AFTER SKELETAL MUSCLE CONTRACTION
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Exercise training-induced skeletal muscle adaptations result in part from altered gene expression. The necessity of liver kinase B1 (LKB1) for this increase in gene expression is unknown. Our purpose was to determine whether LKB1 is required for contraction-induced changes in gene expression. To test this, two groups of skeletal muscle-specific LKB1 knockout (KO) and control (C) mice (n=8) underwent an electrical stimulation bout of the left sciatic nerve (1 pulse/2 seconds, 5 ms/pulse for 15 minutes). The right leg served as a control. Mitochondrial function was characterized by a decreased expression of complex I and II-III enzymes and a reduced activity of AMP-activated protein kinase (AMPK), but increased p70S6k and increased oxygen consumption in the LKB1 KO compared to the control group. Vastus lateralis samples were obtained at rest and analysed for mitochondrial enzyme expression measures via RT-PCR. AMP-activated protein kinase (AMPK) and p70S6K phosphospecific antibodies were quantified by Western Blot. LKB1 KO mice showed an increased expression of p70S6K after contraction. Pearson correlation was used to determine if p70S6K expression was related to increased p-p70S6K in the LKB1 KO mice. Our results demonstrated that LKB1 is required for contraction-induced increases in AMPK activity and p70S6K after muscle contraction.
exercise. These results provide new insights into the mechanisms by which exercise re-attenuated insulin signaling in the muscle of rats, a phenomenon that was reversed by exercise in the skeletal muscle, in parallel with a reduction in pJNK and IkBalfa de-

3.1.4 FRACtalkine-INDUCED IN EXERCISED HUMAN SKELE- TAL MUSCLE AND STIMULATES MYOBLAST PRO- LIFERATION

3.1.5 INFLAMMATION AND THE HYPERTRIGLYCERIDEMIC WAIST PHENOTYPE

3.1.6 INFLUENCE OF FITNESS AND ADIPOSITY ON WHOLE BLOOD RESPONSE TO Α

3.1.7 EFFECT OF EXERCISE ON T CELLS IN CANCER SURVIVORS

3.1.8 EFFECT OF EXERCISE ON T CELLS IN CANCER SURVIVORS

3.2.1 THE INFLUENCE OF FITNESS AND ADIPOSITY ON MELANOCORTIN-1 AND MELANOCORTIN-3 RECEPTORS ON MONOCYTES

3.2.2 PHYSICAL EDUCATION, Texas Christian Univ., Fort Worth, TX, 76120-2012 APS Intersociety Meeting: The Integrative Biology of Exercise-VI
The influence of estrogen (E2) status on IL-6 response to prolonged endurance exercise was examined in 16 eumenorrheic women. Treadmill runs were performed at ~65% VO2max for 60-90 min (X:71.3±3.8 min) in the mid-follicular (Low E2) and mid-luteal (High E2) phases of the menstrual cycle. Blood samples were taken at Rest, immediately post exercise (IE), and 30 min, 24 and 72 h into recovery (R) from exercise trials. Trials were randomized and controlled for prior exercise, environmental conditions, diet, and hydration status. Blood was analyzed for E2 (Rest only) and IL-6 using ELISA assays and examined via an ANOVA. All subjects exhibited a 2x-4x increase in IL-6 from the Low E2 to the High E2 (p<0.05). Heart rate and VO2 increased (p=0.01) as exercise progressed in each trial, but did not differ between the Low and High E2 trials. The IL-6 responses were significantly elevated from Rest at IE and 30 min R in both Low and High E2 trials; however, the magnitude of these increases were greater (25-85%) in the Low E2 than the High E2 trial (p=0.05). At 24 h and 72 R in no differences were noted for IL-6 for the trials. These findings indicated elevations in E2 in women are associated with a lower acute IL-6 response to prolonged endurance exercise.

31.10 EFFECTS OF PRIOR EXERCISE ON THE INFLAMMATORY RESPONSE TO A HIGH-FAIT MEAL IN YOUNG MEN

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The effect of prior exercise on circulating cytokines and markers of systemic inflammation and cardiometabolic risk in overweight/obese adults. We collected a blood sample after an overnight fast, with prior exercise (p<0.05), but no significant increase without prior exercise. No significant effects of the HFM or exercise were observed for TNF-α. We observed an effect of prior exercise on leptin concentrations (+17% at both time points vs. no exercise; P<0.05). The HFM significantly decreased leptin concentrations (-11%, P=0.005 for both trials). As both exercise and consumption of a HFM can independently increase IL-6 and IL-6 concentrations, it is possible that the two stimuli interact to create an inflammatory response that is independent of the exercise-induced reduction in leptin concentrations.

31.11 INFLUENCE OF SHORT TERM SPRINT INTERVAL TRAINING ON SKELETAL MUSCLE INFLAMMATION

Melani Schwedel, Jennifer Richardson, Matthew Hickey, Christopher Bell

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Short-term sprint interval training (SIT) has many health benefits, including improved glucose regulation and insulin sensitivity, however the exact mechanism by which these benefits are bestowed is unclear. Inflammation adversely affects insulin sensitivity, thus we have investigated the hypothesis that short-term SIT decreases skeletal muscle inflammation in adult humans. Experimental procedures conformed to the Declaration of Helsinki. 14 young, healthy sedentary/recreationally-active adults completed 6 sessions of SIT (between 4 and 7 "all-out" maximal 30-second efforts on a cycle ergometer, separated by 4 minutes of light recovery) over 2 weeks. Skeletal muscle (vastus lateralis) was sampled prior to and 96-hours following training. SIT did not affect skeletal muscle inflammation, as represented by the phosphorylation of JNK relative to total JNK a-antigen (P=0.76 ± 0.24; mean ± SE; 0.76 ± 0.24; mean ± SE; P=0.42), and the phosphorylation of IκB-α tended to be lower in active (P<0.05). The HFM significantly decreased leptin concentrations (-11%, P=0.005 for both trials). As both exercise and consumption of a HFM can independently increase IL-6 and IL-6 concentrations, it is possible that the two stimuli interact to create an inflammatory response that is independent of the exercise-induced reduction in leptin concentrations.

31.2: LATE-BREAKING ABSTRACTS

31.2.1 ABSENCE OF MALONYL-CoA DECARBOXYLASE (MCD) IMPACTS ENDURANCE EXERCISE MUSCLE MANNITOL REDUCTIONS OF PEPCk IN ADIPOSE TISSUES FROm CD36 KO MICE

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Exercise induces phosphoenolpyruvate carboxykinase (PEPCK) mRNA expression in adipose tissue, a key enzyme involved in fatty acid (FA) re-esterification. CD36 is a transmembrane protein highly expressed in adipose tissue and plays a key role in FA uptake and lipolysis. The aim of this study was to determine 1) if PEPCK expression is reduced in adipose tissue from CD36 knockout (KO) mice secondary to reductions in lipolysis; and 3) if exercise induced PEPCK mRNA expression is attenuated in adipose tissue from CD36 KO mice. PEPCK mRNA and protein expression in epidydimal white adipose tissue (EAT) were reduced from CD36 KO mice compared to age-matched (16 weeks of age) wild type (WT) mice, and this was associated with increased FFA/glycerol ex vivo in EAT from CD36 KO mice. Basal and norepinephrine (NE) (1μM) stimulated glycerol and FFA release ex vivo in EAT were attenuated from CD36 KO mice compared to WT mice. CAY10499 (2μM), a hormone sensitive lipase (HSL) agonist, reduced basal and NE induced lipolysis, and this was related to reduced basal and NE induced PEPCK mRNA expression in cultured EAT. An acute bout of treadmill running (15 minutes/m, 5% incline, 90 min) induced PEPCK mRNA to a similar extent from WT and CD36 KO mice. In summary, our data demonstrates that CD36 controls the expression of PEPCK in mouse adipose tissue. Our data would suggest that reductions in PEPCK may be secondary to decreased lipolysis. This work was supported by a Bridge Funding Operating Grant from the Canadian Institutes of Health Research, Institute of Nutrition, Metabolism and Diabetes to DCW. DCW is a Tier II Canada Research Chair and Canadian Diabetes Association Scholar.

32.3 INDUCTION OF SIRT1 BY RELOADING ON ATROPHIED SOLEUS MUSCLE IN MICE
Ayumi Goto1, Yoshikata Ohba1, Tatsumi Egawa2, Takao Sagaiura3, Yoshinobu Ohira4, Yoshinada Yoshida1, Katharina Gozur1

Loading is one of hypertrophic stimuli for skeletal muscle. Sirtra 1 (SIRT1) is considered to be implicated in lifespan extension. SIRT1 induction by mechanical stretch plays a role in preventing of oxidative stress. However, SIRT1 expression in response to unloading and reloading on skeletal muscle is still unclear. The purpose of this study was to investigate the effects of unloading and reloading on SIRT1 expression in skeletal muscle. Male mice (C57BL/6J) were subjected to continuous hindlimb suspension for 2 weeks. Immediately after the suspension, ambulation recovery was allowed. Soleus muscles of suspended group were dissected bilaterally before, immediately after, and 2 weeks after the suspension. Immediately after the suspension, expression levels of SIRT1 in soleus muscle showed a trend to increase, then significantly increased during re-loading. Oxidative stress induced by unloading and reloading on skeletal muscle might be different. This study was supported, in part, by KAKENHI (22240071, 24504011, 24680470) from Japan Society for the Promotion of Science and the Science Research Promotion and the Promotion and Mutual Aid Corporation for Private Schools of Japan.

32.4 A PILOT STUDY OF PHYSIOLOGIC CORRELATES TO SUBMAXIMAL AND MAXIMAL EXERCISE IN PATIENTS WITH IPF
Robert M. Jackson1,2, Lawrence P. Caihalm3, Carol F. Ramirez3, Diana D. Clandes3,3, Consellon3, M. Sael1, Meryl I. Cohen3, Ignacio A. Gaurnaud1, Nicole D. Eustis1, Orlando W. Gómez-Martín4,5
1Res. Service, Miami V AHS, Miami, FL 33125 and Depts. of 2Rehabilitation Med., W. Gómez-Marín1,4,5,6 3Res. Service, Miami V AHS, Miami, FL 33125 and Depts. of 4Rehabilitation Med., 5Kinesiology, Recreation, and Sport, and 6Western Kentucky Univ., Bowling Green, Kentucky, USA.

The purpose was to examine lymphocyte subsets (CD4+ and CD8+) apoptosis and migration to an acute session with different rest intervals of RT in accordance with ACSM. 12 untrained young men (N=3) and women (N=9) performed a familiarization, test-rest and acute RT sessions (3 sets of 9 exercises: press chest, press front, press lat pull-down, seated leg extension, up right row, seated leg curl, triceps extension, calf rise and biceps curl) with two different rest intervals between sets and exercises (1 min and 3 min) separated by 5 days in a balanced, randomized order in accordance with Declaration of Helsinki. Lymphocyte subsets (CD4+ and CD8+) were assessed for apoptosis (annexin V+) and cellular migration (CX3CR1). CD4+ and CD8+ cells count displayed no significant changes after 1 min and 3 min rest. CD4+ counterparts of CD4+ positive for annexin V+ and CX3CR1+ cells immediately after and 24 post Hyper-1 (p < 0.05). Percent of CD4+ positive for annexin V+ increased 2h and 24h post Hyper-3, and decrease for CX3CR1 in some time-points (p < 0.05). Increase in CD4+ positive for annexin V+ and CX3CR1+ immediately after, 2h and 24h post Hyper-1 and Hyper-3 (p< 0.05). No differences between Hyper-1 and Hyper-3 in the same time-points analysis (p > 0.05). In conclusion, RT sessions inaccordance to ACSM, increase the apoptosis and migration of CD4+ and CD8+ lymphocytes even 24 h after exercise, with minimal effects of rest interval length. Financial support was provided by the Conselho Nacional de DesenvolvimentoCientífico e Tecnológico (CNPq) and by the Kinesiology, Recreation, and Sport Department from the Western Kentucky University, USA.

32.7 BRONCHODILATION DURING EXERCISE IN PATIENTS WITH CYSTIC FIBROSIS, COMPARISON TO ALBUTEROL ADMINISTRATION
Meghan C. McCue, Courtney M. Wheatley, Sarah E. Baker, Mary A. Morgan, Eric C. Wong, Monika Sattler, and Eric M. Snyder
Moderate intensity exercise causes bronchodilation and can also improve mucociliary clearance. Cystic fibrosis (CF) patients are treated with albuterol to promote bronchodilation and to possibly stimulate mucociliary beat frequency. Fitness has been associated with improved survival in CF patients and attainment of the yearly 2-3% expected decline in pulmonary function. We sought to compare the effects of albuterol and moderate intensity exercise in patients with CF. Sixteen patients with CF and 16 healthy control subjects underwent pulmonary function testing at baseline, 30, and 60 minutes post-albuterol administration. On a separate day subjects performed a maximal expiratory flow-volume maneuver to determine airway function at baseline and at 30% and 50% V_max. Percent change in forced expiratory flow at 25-75% of the forced vital capacity (FEF25-75%) was significantly greater with moderate intensity exercise than at 30 or 60 minutes post-albuterol administration in CF patients, while there was no difference in percent change FEF25-75 between albuterol and exercise in the healthy control subjects (change from baseline: 30min post albuterol=23±5 vs. 9±4%, 60min post albuterol=22±5 vs. 20±4%) with 25-30% greater maximal uncoupled mitochondrial respiration compared with sed patients. In conclusion, these preliminary findings suggest that 4 weeks of exercise increases in hepatic function and metabolism. These findings need to be confirmed in a larger study cohort. Supported by NIH T32 AR 048523-07 (JAF and EMM), NIH DK088940 (JFT), and VHA-CDA 2CH3X001299-01 (RSR).
The aim of this study was to verify the viability on critical load (CL) estimate (acetic acid promoter) using three different mathematical models. Nine male Wistar rats (40 days old) were submitted to exhaustive swimming efforts against 9, 11, 13 and 15% of their body weight (bw), in four consecutive days. Times to exhaustion (TEx) were considered as the moment at which all coordinated movements ceased and the animal could no longer return to the surface. CL was estimated using 3 models: Lin-1 = linear 1 (load vs TEx), Lin-2 = linear 2 (impulse vs TEx) and Hyp = hyperbolic model (load vs TEx). Anova one-way and intraclan correlation coefficients (ICC) was employed (significance at P<0.05). A 2-way ANOVA results that the coefficients for determination for Lin-1, Lin-2 and Hyp models were highly applicable (0.97 to 0.99) and significant differences were found among CL (%bw) estimated from the Hyp (7.8±1.1), Lin-1 (7.8±1.2) and Lin-2 (7.9±1.1) models, with significant relationships (ICC >0.87) between multiple Power models. Our data have been adapted as an interesting alternative (non-invasive method) for estimates of aerobic capacity in biomedical research in laboratory animals. Despite of largely explored in sportive modalities for humans and rodents submitted to treadmill running, scarce information exists regarding CL in swimming. Thus, our results attest the viability of CL estimation for accesses aerobic capacity independently of mathematical model.


32.9 INTERLEUKIN-6, EPINEPHRINE AND THE REGULATION OF SKELETAL MUSCLE LIPOLYSIS

| Tara Macdonald, Zhongxiao Wan, David J. Deck, David C. Wright |
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| 1 Dept. of Agriculture, Food and Nutritional Sci., Univ. of Alberta, Edmonton, AB, Canada |
| SKELETAL MUSCLE LIPOLYSIS |


32.10 HSP70 REGULATES THE SKELETAL MUSCLE INFLAMMATORY RESPONSE FOLLOWING INJURY

Sarah M. Scaf, Sandra Strobel, Aaron R. Judge |
| Dept. of Physical Therapy, Univ. of Florida, Gainesville, FL |


32.11 ROLE OF THE NOVEL TISSUE-SPECIFIC PGC-1 AND ERR-INDUCED REGULATOR PERM1 IN MUSCLE

Yanjun Shi, Surya Kishore, Aaron Russell, Amanda L. Martin |
| The Scripps Res. Inst., Dept. of Chemical Physiology, La Jolla, CA, USA; 3 Ctr. for Physical Activity and Nutrition, Sch. of Exercise and Nutrition Sci., Deakin Univ., Burwood 3125, Australia. |

Mitochondria and oxidative metabolism are critical for maintaining skeletal and cardiac muscle function. The expression of genes important for mitochondrial biogenesis and oxidative metabolism are under the control of transcriptional coactivators of the PGC-1 family and orphan nuclear receptors of the ERR (Estrogen-related receptor) subfamily. Derepression of PGC-1/ERR signaling is associated with decreased muscle performance, muscle wasting and heart failure. The mechanism(s) by which ERRs and PGC-1 regulate muscle-specific pathways are not fully understood. In a search for factors that enable PGC-1/ERR function in muscle, we identified a so far uncharacterized muscle-specific protein that is induced by PGC-1s and ERRs, and is predicted to be nuclear. We have named this novel protein PERM1, for PGC-1 and ERR-induced Regulator in Muscle. Expression of PERM1 in cardiac and skeletal muscle targets for treating muscle and heart diseases.

32.12 INTERLEUKIN-6 AND ADIPOSE TISSUE INFLAMMATION DURING THE RECOVERY FROM EXERCISE

Laura Castellani, Jared Ross-MacDonald, David D. Wright |
| Dept. of Human Health and Nutritional Sci., Univ. of Guelph, Guelph, ON, Canada. Sch. of Kinesiology and Hlth. Sci., York Univ, York, ON, Canada. |

Interleukin-6 (IL-6) expression is increased in adipose tissue after exercise, however, the functional significance of this increase is unknown. The current study aimed to define the relationship between increases in IL-6 signalling and adipose tissue metabolism following a single bout of exercise. Male C57BL/6 mice ran for 2-hours on a motorized treadmill (15 miles/minute, 5% incline). Immediately following exercise IL-6 mRNA expression was increased in epididymal white adipose tissue (eWAT). This was accompanied by a subsequent increase in IL-6 protein content and SOCS-3 mRNA 4-hours after exercise. At this time point circulating IL-6 levels were not elevated. To ascertain a functional association between elevated IL-6 signalling and adipose tissue metabolism, we assessed in vivo insulin signalling. Insulin-stimulated Protein Kinase B (PKB) phosphorylation was blunted in eWAT from mice that had run 4-hours previously compared to sedentary controls and this was associated with an attenuated reduction in plasma glycerol and fatty acid levels following insulin injection. Insulin-stimulated PKB phosphorylation was intact in triceps muscle and liver. Our results demonstrate an association between adipose tissue IL-6 and the metabolic response to insulin resistance during the recovery from exercise. This may be advantageous in the provision of fatty acids to liver and skeletal to be used as a fuel source, while sparing glucose for glycogen synthesis.

32.13 ELUCIDATING THE ROLE OF HISTONE DEACTYLASES IN SKELETAL MUSCLE ATROPHY

Michael E. Walsh, Arunabh Bhattacharya and Holly Van Remmen |

Motor neurons form a specialized synapse with skeletal muscle known as the neuromuscular junction, and degeneration of the NMJ has been implicated in disease and aging. Recently, a role for histone deacetylases (HDACs) in the regulation of the adult neuromuscular system has been established. HDACs are a family of enzymes that remove acetyl groups from the lysines of histone and non-histone proteins. HDACs regulate a number of transcription factors required for the maintenance of the adult neuromuscular system, including Mysl, myogenin and myocyte enhancer factor 2. HDAC2 and HDAC5 knockdown mice are protected against age-related denervation and pharmacological inhibition of histone deacetylation is protective in multiple models of neuromuscular disease. In this study, we examined the effect of sodium butyrate (NaBu), a histone deacetylase inhibitor, on muscle atrophy in a model of sciatic nerve crush and in age-related muscle atrophy (AOM) injury or NaBu treatment to wild type (WT) mice in vivo and protects against the muscle loss induced by nerve crush. The control-fed mice lost 22% of their gastrocnemius mass while the NaBu-fed mice lost only 11% one week after surgery. NaBu protects against the loss of cross sectional area and prevents the induction of atrogin-1, which has been implicated in neuromuscular disease. Our laboratory has reported extensive neuromuscular changes with age. Intriguingly, we have found an increase in HDAC4 protein levels in skeletal muscle from 31 month old C57BL/6 mice. Preliminary results indicate that sodium butyrate protects against age-related muscle atrophy in female mice. Future studies will determine the mechanism by which sodium butyrate protects against neuromuscular atrophy. This work was funded by the UTHSC at San Antonio Biology of Aging Training Grant to Steve N. Austad (MEW T32AG021890-10).

33.0 HOT TOPICS IN EXERCISE PHYSIOLOGY

33.3 MITOCHONDRIA, HYPERGLYCEMIA, REDOX AND CARDIAC DYSFUNCTION IN TYPE 2 DIABETES

Maged A. Annan |
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In type 2 diabetes (T2DM), hyperglycemia (HG) and increased sympathetic drive/ mitochondrial endocrine/redox properties, decreasing the organelle’s functionality. These perturbations may promote or sustain basal low cardiac performance and limited exercise capacity. In T2DM (db/db) mouse hearts, we recently reported that altered energetic/redox balance in mitochondria is associated with the triggering ofmitochondrial oxidizing conditions leading to cardiac mechanical dysfunction under HG and increased sympathetic stimulation (to simulate stress and overload). Dysfunctional mitochondrial and HG act as permanent drivers of redox imbalance impairing excitation-contraction coupling in the T2DM heart. Glutathione (GSH) or the fatty acid palmitate (Palm)
rescued cardiac redox milieu and mechanical function. Metabolomics data indicate that HG elicits an unfavorable intracellular redox/energetic status by propelling a permanent redox imbalance driven by glucose shunt to polyol pathways and apparent blockage of glycolysis. Palm oxidation in the presence of HG appears to alleviate the adverse metabolic remodeling elicited by HG in the T2DM heart. Preliminarily, we conclude that in the presence of poor glycemic control, the diabetic patient's inability to cope with increased cardiac work demand largely stems from mitochondrial and HG-elicited redox/energetic disarrangements that mutually influence each other, leading to myocyte or whole-heart mechanical dysfunction.

34.0: UNIFIED CELLULAR AND MOLECULAR MECHANISM OF MUSCLE HYPERMORPHY

34.2 THE ROLE OF MTOR IN SKELETAL MUSCLE HYPERMORPHY

Troy Hornberger

Mechanical stimuli play a major role in the regulation of skeletal muscle mass and the maintenance of muscle mass contributes significantly to disease prevention and issues associated with the quality of life. Although the link between mechanical signals and the regulation of muscle mass has been recognized for decades, the mechanisms involved in converting mechanical information into the molecular events that control this process remain poorly defined. Nevertheless, our knowledge of these mechanisms is advancing. For example, recent studies indicate that signaling through a protein kinase called the mammalian target of rapamycin (mTOR) plays a central role in this event. Hence, this seminar will begin with a summary of the evidence which implicates mTOR in the mechanical regulation of muscle mass. We will then explore the current knowledge of how mechanical stimuli are thought activate mTOR signaling. In particular, we will focus on studies which indicate that mechanical stimuli activate mTOR signaling through an atypical mechanism that is distinct from the core pathways employed by growth factors and nutrients. Furthermore, we will discuss the evidence which suggests that phosphatidic acid may be a key component of this pathway. Finally, we will present preliminary data which might suggest that mechanical stimuli activate signaling through a unique pool of mTOR that is not associated with the classic mTOR complex 1. Funding provide by NIH grant R01AR057347.

34.3 MYOSTATIN AND THE CONTROL OF MUSCLE SIZE

David Allen

Since its discovery in 1997, MSTN (MSTN) has become recognized as a critical regulator of skeletal muscle growth. Pharmacological or genetic inactivation of MSTN results in significant muscle growth in a wide variety of organisms, including cow, mouse, and human. MSTN influences muscle growth through multiple pathways; specifically, MSTN inhibits proliferation and differentiation of myogenic precursors during muscle development and adult muscle regeneration and inhibits protein accretion of adult muscle fibers through inhibition of muscle protein synthesis and increased muscle protein degradation. The pathways through which MSTN accomplishes these processes include canonical signaling through the activin receptor IIb-SMAD transcriptional pathway as well as cross-talk through the Akt-mTOR, MAP kinase, and Wnt pathways. Expression and activity of MSTN is in turn regulated by a variety of different inputs and changes in MSTN expression/activity appear to be a crucial contributor to changes in muscle size in response to both physiological and pathological alterations in muscle growth. Expression of MSTN is regulated by both transcriptional and post-transcriptional mechanisms; our laboratory has shown that expression of MSTN is transcriptionally under the control of FoxO, SMAD, and CEBP transcription factors and post-transcriptionally regulated by the microRNAs miR-27a and b. Activity of MSTN is also tightly regulated, by members of the follistatin family, expression of which are in turn altered during periods of muscle remodeling and growth. Thus MSTN has been demonstrated to be a critical node in the regulation of muscle growth.

NOTES

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