IPS The Iowa Physiological Society

Chapter of The American Physiological Society

20th Annual Iowa Physiological Society Meeting

April 25, 2015

9 am – 5 pm

Des Moines University

Olsen Center

3200 Grand Avenue

Des Moines, IA 50312

Agenda

Time	Presentation and Speaker	
8 am	**Registration, Breakfast, and Poster Set-Up**	
9 am	**Opening Remarks**	
9:05 am	**Research Presentation: Contribution of Cyclooxygenase and Reactive Oxygen Species to Cerebral Dilation in Human Metabolic Syndrome** *John Harrell, PhD, Drake University, Des Moines, IA*	
9:40 am	**Keynote Research Address: The Baroreceptor Reflex: From Sensors to Sympathetic Neurons, and Beyond** *Mark Chapleau, PhD, University of Iowa, Iowa City, IA*	
10:40 am	**Break and Poster Viewing**	
11:30 am	**Keynote Education Address: Case-Based and Problem-Based Learning in Physiology** *Barb Goodman, PhD, University of South Dakota, Vermillion, SD*	
12:30 pm	**Lunch and Poster Viewing**	
1:30 pm	**Faculty and Graduate Student Workshop** How to Contribute Scholarly Activity in Education *Barb Goodman, PhD, University of South Dakota, Vermillion, SD*	**Undergraduate Student Workshop** Summer Research Undergraduate Experiences and How to Apply *Sriram Sundararajan, PhD, Iowa State University, Ames, IA*
2:15 pm	**Highlights from Group Discussions**	
2:30 pm	**Graduate Research Abstract Presentation: Effects of Chronic Pain on Activation of Inflammatory Brain Mechanisms and Development of Depressive-Like Behaviors** *Misty Carder, MBS'18, Des Moines University, Des Moines, IA*	
3 pm	**Undergraduate Research Abstract Presentation: The Effect of Celiac and Renal Denervation in Angiotensin-Induced Hypertension** *Anne Turco, Luther College, Decorah, IA*	
3:30 pm	**Break and Poster Viewing**	
4:15 pm	**A Novel Approach to Incorporating Research into an Anatomy and Physiology Course Using Culturally Competent Strategies** *Juanita Limas, MS, Kirkwood Community College, Cedar Rapids, IA*	
4:45 pm	**Poster Award Presentations and Closing Remarks**	
5 pm	**Adjourn**	
5:15 - 6 pm	**IPS Board Meeting** All members of the IPS are invited to attend.	

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Guest Speakers

Mark Chapleau, PhD
Professor, Internal Medicine, Physiology, Biophysics, Cardiology, University of Iowa

Barb Goodman, PhD
Professor of Physiology, Division of Basic Biomedical Sciences, Sanford School of Medicine of The University of South Dakota

John Harrell, PhD
Assistant Professor of Health Sciences, Pharmaceutical, Biomedical, and Administrative Sciences, Drake University

Juanita Limas, MS
Anatomy and Physiology/Nutrition, LSAMP-IINSPIRE Director, Kirkwood Community College

Sriram Sundararajan, PhD
Professor, Department of Mechanical Engineering, Equity Advisor for the College of Engineering, Iowa State University

Research Presentation: Contribution of Cyclooxygenase and Reactive Oxygen Species to Cerebral Dilation in Human Metabolic Syndrome

John Harrell, PhD, Drake University, Des Moines, IA

The Baroreceptor Reflex: From Sensors to Sympathetic Neurons, and Beyond

Mark Chapleau, PhD, University of Iowa, Iowa City, IA

Case-based and Problem-based Learning in Physiology

Barbara E. Goodman, Ph.D.
Professor of Physiology

UNIVERSITY OF
SOUTH DAKOTA
SANFORD SCHOOL OF MEDICINE

The Case of the Frustrated Professor

Before the semester started, I worked really hard to set goals for the course. During the semester, I have been covering the content in clear, efficient lectures that I think are really well-organized, but the students don't seem to be learning the material. In fact, 40% of students failed the first exam. Students these days don't know how to take notes and study. They just don't get it.

Enhancing Learning with Student-centered Activities

- Learning by experimentation
- Team-based learning with Readiness Assessment Tests
- Problem-based learning
- Case-based learning
- Project-based learning

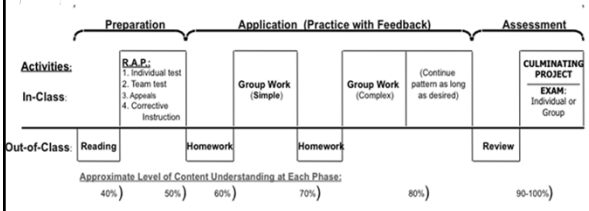
Learning by Experimentation

- Physiology labs offer numerous opportunities for human experimentation (both learning skills and inquiry-based)
- Biopac and ADI LabTutor experiments and cases

Team-based Learning

- Teams of 5-7 students throughout the semester
- Assignments outside of class assured by readiness assessment tests
- Individual RATs and team RATs
- Team rapport and evaluation

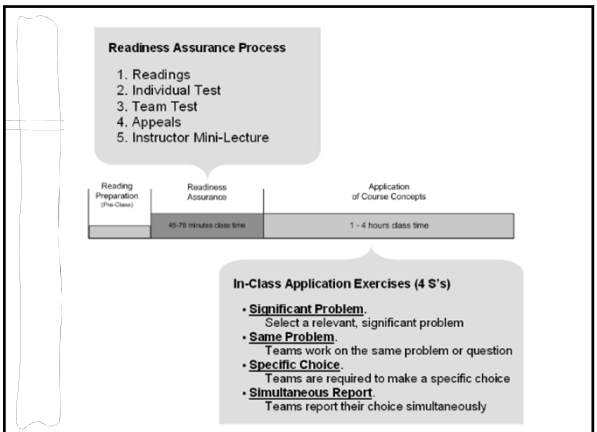
Three Phases of Team Learning



Michaelsen, Larry K., A.B. Knight, and L.D. Fink, Team-based Learning: A Transformative Use of Small Groups in College Teaching, 2004.

Application of TBL (4 S's)

- Significant simple or complex problem
- Same problem – groups work on same problem, case, question
- Specific choice – groups use course concepts to make specific choices
- Simultaneous reporting – groups report choices simultaneously not sequentially



Problem-based Learning

- Specific question or puzzle to be solved to reach a goal
- Encourage self-evaluation and research with factual recall and application
- Resources available (Physiology Cases and Problems by Costanzo, Case Studies in Physiology by Berne and Levy, Problem Solving in Physiology by Michael and Rovick)

Problem-based Learning

- With your team of 3-4 individuals, work through Problem 4 from Michael and Rovick Problem Solving in Physiology

Problem-based Learning Report

- Prediction for activity of enterocyte Na^+/K^+ ATPase pumps

Green card = Increase
Yellow card = No change
Red card = Decrease

Problem-based Learning Report

- Lumen to enterocyte Na^+ concentration gradient

Green card = Increase
Yellow card = No change
Red card = Decrease

Problem-based Learning Report

- Glucose absorption from intestinal lumen

Green card = Increase
Yellow card = No change
Red card = Decrease

Problem-based Learning Report

- Water absorption from intestinal lumen

Green card = Increase
Yellow card = No change
Red card = Decrease

Case-based Learning

- Case-based situations and questions are open-ended without single correct answer
- Additional resources (Human Physiology: An Integrated Approach by Silverthorn, National Center for Case Study Teaching in Science http://sciencecases.lib.buffalo.edu/cs/, APS Life Science Teaching Resource Community http://lifescitrc.org/, ADInstruments LabTutor cases

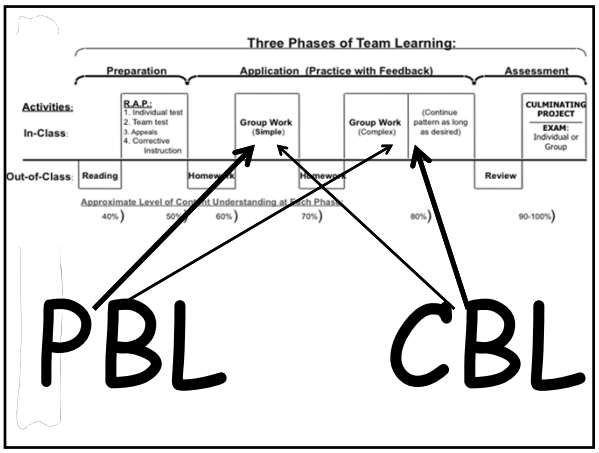
Case-based Learning

- With your team of 3-4 individuals, work through the Case Study for Bathsheba from Goodman in the APS Life Science Teaching Resource Community.

Case-based Learning Report

Each group will be asked to share their answer for a different question.

	TBL	PBL	CBL
Group Size	5-7	2-4 (?)	2-4 (?)
Group Duration	Entire semester/block	length of problem	length of case
RAT	Yes	No	No
'Patient' information	No	No	Yes
Perceived Student workload	++++	++	++
Requires : • Group skills • Problem solving skills • Application of content knowledge	Yes	Yes	Yes



Project-based Learning

- Conduct PhUn week activities at local school
- Prepare introduction to renal physiology for high school A&P students
- Prepare presentation/brochure on why diabetes changes kidney function for patient group
- Write case-study for physiology

Barbara E. Goodman, Ph.D.
Professor of Physiology

Barb.Goodman@usd.edu

Any questions?

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A Novel Approach to Incorporating Research into an Anatomy and Physiology Course Using Culturally Competent Strategies

Juanita Limas, MS, Kirkwood Community College, Cedar Rapids, IA

How to Contribute Scholarly Activity in Education

Barbara E. Goodman, Ph.D.
Division of Basic Biomedical Sciences
Sanford School of Medicine
University of South Dakota

Think, Pair, Share: What Kinds of Educational Scholarship Do You Do?

- Think about what you do to be creative in your teaching and how you enhance learning for your students. Discuss these innovations with someone seated nearby. Be prepared to share some of your ideas with the whole group.

Types of Educational Scholarship

- Publishing in peer-reviewed journals or books
- Publishing online resources
- Participating in faculty development activities to enhance one's skills as an educational researcher
- Serving on journal editorial board
- Organizing a teaching workshop or conference

Physiology of Exercise for Middle School Students by Barbara E. Goodman and Sally Stoll

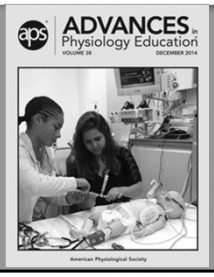
- This unit is adapted from the high school Physiology of Fitness unit, but with activities and content appropriate for middle school students. It includes a lifestyles inventory, exploration of biological variability and experimental variation using heart and respiratory rates, a role play of oxygen supply and demand during rest and exercise and inquiry-based explorations of the baroreflex and responses to exercise.
- http://www.lifescitrc.org/resource.cfm?submissionID=4270

APS Online Teaching Resources

Material Featured in LifeSciTRC

- Case studies or other PBL
- Simulations or other animations/videos
- Laboratory exercises
- Course syllabi; lecture outlines or notes
- Powerpoint presentations and images
- Figures, graphs (either single items or units)
- Web sites with teaching material available
- Pedagogy or teaching strategies

Advances in Physiology Education



Advances in Physiology Education – Types of peer-reviewed articles

- How We Teach: Generalizable Education Research
- How We Teach: Classroom and Laboratory Research Projects
- Laboratory Sourcebook
- Historical Perspectives
- Personal Views
- Staying Current
- Illuminations (short teaching ideas)
- Editorials, Letters to the Editor, Meeting Reports

Advances in Physiology Education: Staying Current

- Barbara E. Goodman and William H. Percy. CFTR in cystic fibrosis and cholera: from membrane transport to clinical practice. Advan Physiol Educ, June 2005; 29:75-82.

Advances in Physiology Education: Staying Current

- BEG. Insights into digestion and absorption of major nutrients in humans. APE, June 2010; 34:44-53.
- BEG. Channels active in the excitability of nerves and skeletal muscles across the neuromuscular junction: basic function and pathophysiology. APE, June 2008; 32:127-135.
- BEG. Transport of small molecules across cell membranes: Water channels and urea transporters. APE, Sep 2002; 26:146-157.

Advances in Physiology Education: How We Teach

- Barbara E. Goodman, Elizabeth M. Freeburg, Katherine Rasmussen, and Di Meng. Elementary education majors experience hands-on learning in introductory biology. Advan Physiol Educ, December 2006; 30: 95-203.

Advances in Physiology Education: How We Learn

- Barbara E. Goodman, Karen L. Koster, and Patrick L. Redinius. Comparing biology majors from large lecture classes with TA-facilitated laboratories to those from small lecture classes with faculty-facilitated laboratories. Advan Physiol Educ, June 2005; 29:112-117.

Advances in Physiology Education: A Personal View

- Barbara E. Goodman. Evolution of a partnership to improve K-16 science education. Advan Physiol Educ, Sep 2002; 26:168-173.

Advances in Physiology Education: Teaching in the Laboratory

- Barbara E. Goodman, Douglas S. Martin, and John L. Williams. Teaching human cardiovascular and respiratory physiology with the station method. Advan Physiol Educ, Mar 2002; 26:50-56.

Advances in Physiology Education: Special Communications

- Barbara E. Goodman. Pulmonary and renal pressure-flow relationships: What should be taught? Advan Physiol Educ, June 2001; 25:15-28.

Advances in Physiology Education: Call for Papers on Pre-Professional Education in Transition

- Barbara E. Goodman, Karen L. Koster, and David L. Swanson. The development and implementation of a new medical biology major including physiology. Advan Physiol Educ, June 2015; in press.

APS Institute on Teaching and Learning

- 2014 Institute in Bar Harbor, ME June 23-27, 2014 led to founding a Physiology Education Community of Practice (PECOP) with an education blog open to everyone at http://blog.lifescitrc.org/pecop/.
- 2016 Institute planned for June 20-24, 2016 at Beloit College in Beloit, WI with exciting program for both undergraduate physiology educators and professional school physiology educators.
- APS conference organized by volunteers from the APS Teaching Section.

Think, Pair, Share

- Which of these types of scholarship have you or would you like to write? Describe your desire to a partner or people nearby. When do you plan to complete this scholarly activity? Some individuals will be asked to discuss their interests with the whole group.

Any questions?

Barb Goodman
Barb.Goodman@usd.edu
605-658-6337

Summer Research Undergraduate Experiences and How to Apply

Sriram Sundararajan, PhD, Iowa State University, Ames, IA

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1 UG

Adrenergic Stimulation of Dorsal Crest Erection in Male Anolis Lizards

Besim Ademi, John Ficklin, Morgan Gerace, Matthew Rand

Department of Biology, Carleton College, Northfield, MN

Males in the lizard genus *Anolis* erect a ridge of tissue along the dorsum, which increases their lateral profile during escalated aggressive encounters with other males. Though noted in behavioral studies, little attention has focused on the physiological regulation of these crests. Suspecting that the tissue erection involved vascular dynamics, we hypothesized that adrenergic receptor stimulation played a major role in crest development. We found that moderate doses of epinephrine (1.0 µg/lizard) induced full crest erections, but that lower and higher doses appeared to inhibit crest formation. Similar to mammalian vascular systems, we hypothesized that lizards have α and β adrenergic receptors that ultimately lead to vasoconstriction and vasodilation, respectively. The present study focused on the possible interplay between the two receptor subtypes using a pharmacological approach. We found that the general β adrenergic agonist isoproterenol induced crest formation in a dose-dependent manner that mimicked natural, behaviorally induced crest formation. We then used specific β_2 agonists—salbutamol and terbutaline—to induce crest formation while using the α_1 agonists, phenylphrine and methoxamine, to inhibit the effects of the β_2 agonists. Although salbutamol and terbutaline are isomers, only salbutamol consistently produced a full crest with an optimal dose concentration of between 1.0 and 5.0 µg. Methoxamine was the only α_1 agonist that showed some level of inhibition, although not fully. Phenylphrine was not effective as an inhibitor at any level. Our results suggest that β_2 receptor binding initiates the mechanism leading to crest erection while α_1 receptor binding inhibits the process.

2 G

Longitudinal Effects of Chronic Stress on the Murine Gut Microbiota

Aaron Shoskes[1*], Alexandra Proctor[2*], Kathryn Battani[1], Vanja Duric[1], Gregory Phillips[2], LiLian Yuan[1]

[1]*Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA*
[2]*Department of Veterinary Microbiology, Iowa State University, Ames, IA*
** Equal contribution*

Background and Aims: Emerging literature supports a bidirectional communication axis between the brain, the gastrointestinal tract, and the microbiota colonizing the gut. Various physical and psychological stressors have been shown to influence the function of the GI tract and its resident microbiota. Furthermore, dysbiosis of GI tract colonization has been associated with different diseases, including depression. We investigated the relationship between chronic stress and the murine gut microbiota by comparing the taxonomic composition before and after chronic stress.

Methods: Mice were subjected to chronic unpredictable stress (CUS) for six weeks. Fecal samples were collected at different time points before and after CUS. Bacterial genomic DNA was extracted and amplicons representing the V4 region of 16s rRNA genes were sequenced on the Illumina MiSeq platform and analyzed using the QIIME pipeline.

Results: Phylum level differences were observed at a trend level between the two time-points: mean abundance of *Bacteroidetes* increased and *Firmicutes* decreased over the chronic stress period. At the class level, *Bacilli* were observed to decrease between time points. No significant difference in alpha diversity was noted.

Conclusions: Chronic stress exposure appears to result in an increase in the phylum *Bacteroidetes* along with a decrease in the phylum *Firmicutes*. A decrease in the class *Bacilli* was further observed. The increased ratio of *Bacteroidetes* to *Firmicutes* has been found to be associated with metabolic disease and obesity. Our results support the notion that genera within *Bacilli* may be targets of prebiotic or probiotic therapies to restore a microbiota associated with well-being.

3 G

Combinational Effects of Glutamatergic Agents in a Preclinical Model of Depression

Jessica Kline, Lori Semke, Vanja Duric, LiLian Yuan

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

Accumulating evidence suggests dysregulation of glutamatergic transmission in the brain is linked with depressive disorders. Ketamine, an antagonist of a subtype of glutamate receptors, exhibits fast-acting and long-lasting antidepressant effects in humans and in animal models. However, limitations of ketamine use as a long-term treatment, particularly its dissociative/psychotomimetic effects and abuse potential, highlight the need for alternative glutamatergic agents. D-serine, an endogenous NMDA receptor co-agonist, also targets glutamate transmission and has shown therapeutic potential in preclinical models of depression. Their opposing actions on the shared target (NMDAR) and the highly overlapped molecular signature evoked by ketamine and D-serine raises the possibility that their co-administration may diminishes adverse side effects of ketamine without compromising its antidepressant effectiveness.

Immediately following intraperitoneal injection (< 1 min), ketamine (10 mg/kg) altered *states* of consciousness and induces motor incoordination in mice. Co-administration of D-serine significantly reduced the level of motor incoordination as quantified by the number of falls induced by ketamine. However, the antidepressant effects of ketamine did not appear to be compromised by D-serine as assessed in the forced swim test, 1 hour and 24 hours post drug injection. In parallel with its behavioral influences, D-serine addition did not interfere with ketamine-activated signaling pathways at the 1-hour time point; it actually enhanced ketamine's effects on key synaptic proteins at the 24-hour time point. These results support the notion that ketamine and D-serine may represent a more effective combination therapy than either one alone.

4 G

Effects of Chronic Pain on Activation of Inflammatory Brain Mechanisms and Development of Depressive-Like Behaviors

Misty Carder, Mai Lan Leong, Michelle Lende, Kevin Watson, LiLian Yuan, Vanja Duric

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

Clinical reports indicate that many chronic pain patients also develop symptoms of mood disorders, especially major depressive disorder (MDD); however, the underlying neural mechanisms linking chronic pain conditions and depressive behaviors are still poorly understood. Our previous studies have demonstrated that rodent models of chronic pain mimic some of the stress-like alterations in intracellular signaling and cellular architecture within the hippocampus, a limbic brain region involved in regulation of mood. Furthermore, recent reports suggest that stress-induced activation of interlukin-1-beta (IL-1ß)-mediated inflammatory mechanisms suppress neurogenesis in the adult rat hippocampus and, therefore, may present novel factors contributing to the depressive-like effects observed in chronic stress models of depression. Thus, in this study, we examined the effects of persistent pain on activation of immune-inflammation processes in the limbic brain regions. Male rats

were initially exposed to either injection of complete Freund's adjuvant (CFA; model of chronic inflammatory pain) or spared nerve injury (SNI; model of chronic neuropathic pain). Both pain models produced robust mechanical hypersensitivity over the 21 day period, accompanied by depressive-like phenotype. Exposure to pain also induced changes in expression of proteins involved in microglial pro-inflammatory signaling pathways that resemble previously observed responses to stress and depression. Preliminary results indicate that pain evoked upregulation of specific members of Nod-like receptor (NLR) family of inflammasome multiprotein complex within the hippocampus. The results of this study may ultimately contribute towards the identification of new treatment targets and the development of novel clinical strategies to diminish the mental health consequences of chronic pain.

5 G

Role of MKP-1 in Rapid Antidepressant Responses

Jeremy Kapuscinski, Rachel Firkins, Misty Carder, Jessica Kline, Lilian Yuan, Vanja Duric

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

Major depressive disorder (MDD) is a common psychiatric illness affecting approximately 17% of the world's population. The pathophysiology of MDD is complex, and the exact mechanisms involved are yet to be identified. Depression affects a variety of intracellular pathways, leading to atrophy in limbic brain regions, particularly the hippocampus and prefrontal cortex (PFC). One of the pathways implicated in MDD is the mitogen-activated protein kinase (MAPK) pathway, which plays a significant role in synaptic plasticity. Depressed subjects showed decreased MAPK activity, as indicated by decreased expression of extracellular signal-related kinases 1/2 (ERK1/2), and reduction in volume of both the hippocampus and PFC suggests a loss of function or synaptic connections between regions.

MAPK phosphatase-1 (MKP-1) is inducible by stress and acts as a negative regulator of the MAPK cascade. Recent whole genome microarray analysis showed increased MKP-1 expression in the depressed human hippocampus, indicating dysregulation of MAPK signaling. However, the potential contribution of MKP-1 activity in treatment of depression, especially in response to fast- acting antidepressants, such as ketamine, is yet to be determined. In this study, we investigated activation of MKP-1 and its main MAPK substrates in response to dose and time-dependent administrations of ketamine. Preliminary results indicate that phosphorylation of MKP-1 protein in the PFC is significantly increased at 1 h and 24 h after ketamine treatment. Currently, studies are ongoing to determine whether the observed increases in MKP-1 activity are correlated to ketamine-mediated activation of MAPK cascades and whether this effect is common to other rapid antidepressant agents.

6 G

Calmodulin: A New Partner for the α1A-Adrenergic Receptor

Briana Gebert-Oberle, Mark VerMeer, Quang-Kim Tran

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

The α_{1A}-adrenergic receptor (α_{1A}-AR) plays an essential role in the vascular adrenergic response and is increasingly recognized as a rescue mechanism under circumstances where β-ARs are insufficient to provide stimulus in the myocardium, such as in heart failure. Calmodulin (CaM) is the ubiquitous transducer of Ca^{2+} signals and is involved in virtually all aspects of cell functions. It is completely not known if CaM plays a role in α_{1A}-AR signaling at the receptor level in the heart. We have observed that in freshly isolated ventricular tissues, α_{1A}-AR forms a complex with calmodulin in unstimulated condition or under α_{1A}-AR agonism. To identify and characterize the precise interaction sites between CaM and α_{1A}-AR, we developed novel biosensors that span fragments of the four sub-membrane

domains (SMDs) of α_{1A}-AR. Responses of these biosensors to Ca^{2+}-saturated CaM reveals that α_{1A}-AR directly interacts with CaM at a number of locations in submembrane domains (SMD) 3 and the juxtamembranous region of SMD4 ($SMD4_{JM}$). CaM interacts with these domains in a strictly Ca^{2+}-dependent fashion, with drastically different affinities and Ca^{2+} sensitivities. Interestingly, the full-length CaM-binding domain in $SMD4_{JM}$ contains in it α_{1A}-AR's nuclear localization signal sequence, which also binds CaM, albeit with a 3-fold lower affinity. These data indicate that CaM is a novel partner for α_{1A}-AR and suggest that CaM may play an important role in the adrenergic response in the cardiovascular system at the receptor level.

7 G

Characterization and Functional Impact of Calmodulin Interactions with the Angiotensin II Receptor Type 1A

Kevin Ehlers, Mark VerMeer, Robert Clements, Quang-Kim Tran

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

The angiotensin II receptor type 1A ($AT_{1A}R$) is responsible for many effects of AngII. Calmodulin is the ubiquitous transducer of Ca^{2+} signals and is increasingly found to play a role in the functions of G protein-coupled receptors. CaM has recently been found to interact with $AT_{1A}R$, yet the identification of interaction sites is incomplete and little is known regarding its functional impact on $AT_{1A}R$ function. We observed that in primary vascular smooth muscle cells, $AT_{1A}R$ associates with CaM upon stimulation by AngII or thapsigargin. To exhaustively identify all CaM-binding domains in AT1R, we generated a series of FRET-based biosensors to scan all four sub-membrane domains (SMDs) of $AT_{1A}R$. Responses of these biosensors confirmed and extended two previously reported binding sites in the third and fourth submembrane domains, and revealed a hitherto unknown binding site in submembrane domain 2 of $AT_{1A}R$. Biosensor characterizations revealed strictly Ca^{2+}-dependent interactions between CaM and these domains, with distinct affinities and Ca^{2+} sensitivities. To investigate the functional impact of these interactions, we generated multiple substitutions in these domains to alter CaM binding affinity. Using biosensor technique, these substitutions were confirmed to have drastically reduced or abolished interactions with CaM. In primary vascular smooth muscle cells, AngII stimulates robust phosphorylation of the extracellular signal-related kinase (ERK1/2), which was virtually abolished by CaM antagonism. Heterologous expression of mutant $AT_{1A}R$ containing individual mutant submembrane domains or a combination thereof results in drastically reduced ERK1/2 phosphorylation induced by AngII. These data strongly indicate that CaM is involved in AngII signaling via direct interactions with multiple domains in $AT_{1A}R$.

8 G

GPER/GPR30 and Components of Store-Operated Ca2+ Entry

Lara Terry, Mark Ver Meer, Sarah Francis, Quang-Kim Tran

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

The circulating concentrations of estrogen are closely associated with cardiovascular health. Following menopause there is a substantial increase in the risk and incidence of cardiovascular diseases. Hormone replacement therapy has yet to bring about the desirable effects, due in part to the lack of a complete understanding of estrogen's mechanisms of action in the cardiovascular system. The novel G protein-coupled estrogen receptor 1 (GPER/GPR30) has been shown to participate in numerous vascular functions. Store-operated Ca^{2+} entry (SOCE) is an essential mechanism required for many cell activities. We found that GPER agonist G-1 inhibits SOCE in endothelial cells. Heterologous expression of GPER causes a 40% decrease in the rate of SOCE.

GPER antagonist G15 acutely increases rates of SOCE by 16% and when treated chronically, increases total Ca^{2+} signals by 50% in vascular smooth muscle. Consistently, GPER gene silencing increases SOCE by approximately 50%. In endothelial and ventricular tissues, GPER coimmunoprecipitates with the stromal interaction molecule 1 (Stim1) and the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), two essential molecular switchers of SOCE. Stim1 colocalizes with GPER when heterologously expressed in HEK 293 cells. In addition, GPER/GPR30 agonist G-1 significantly reduces thapsigargin-induced release of the ER Ca^{2+} stores in endothelial cells. These data suggest that GPER may be an important regulatory input of store-operated Ca^{2+} entry via its interactions with key components of store-operated Ca^{2+} entry.

9 G

Calmodulin Regulates GPER/GPR30-Mediated Signaling

Vahe Matnishian, Jake Jasurda, Mark VerMeer, Quang-Kim Tran

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

The G protein-coupled estrogen receptor 1 (GPER/GPR30) was recently identified as a novel receptor for estrogen, and has attracted much attention for its potential role in tailoring hormone replacement therapy. However, identification of its regulatory inputs is only beginning. Calmodulin (CaM) is the ubiquitous transducer of Ca^{2+} signals and is required for the functions of numerous proteins. We recently developed a novel approach that utilizes fluorescence resonance energy transfer (FRET) biosensor technology to identify and characterize four distinct CaM-binding domains in GPER/GPR30. These domains are located separately in GPER/GPR30's submembrane domains (SMDs) 1-3 and the juxtamembranous (JM) segment of SMD4 ($SMD4_{JM}$). To investigate the impact of CaM binding at these domains on GPER/GPR30-mediated signaling, we generated a series of mutations in SMD2, SMD3 and $SMD4_{JM}$ to alter hydrophobicity and charges of the original domains. Resultant biosensors developed on the mutant domains, $BSGPER_{150\text{-}175mut,}$ $BSGPER_{242\text{-}259mut,}$ and $BSGPER_{330\text{-}351mut}$ still display classic conformational changes upon CaM binding, yet with substantially reduced affinities. The Ca^{2+} sensitivities of the interactions between CaM and these domains also are decreased. Heterologous expression of wild-type GPER/GPR30 in HEK 293 cells increases phosphorylation of the extracellular related kinase (ERK1/2). GPER/GPR30-mediated ERK1/2 phosphorylation is reduced drastically by CaM-binding reducing mutations in SMD2, SMD3, or SMD4 individually, and is virtually abolished by combined mutations in these domains. These data demonstrate that CaM binding to GPER/GPR30 plays an important role in GPER/GPR30-mediated signaling.

10

Enhanced Linkage in the Vascular Calmodulin Network by Estrogen via a Feedforward at the G Protein-Coupled Estrogen Receptor 1 (GPER/GPR30)

Quang-Kim Tran, Rachel Firkins, Jennifer Giles, Mark VerMeer, Sarah Francis

Department of Physiology and Pharmacology, Des Moines University,Des Moines, IA

Plasma estrogen is strongly linked to cardiovascular health. Calmodulin (CaM) is required for the activities of numerous proteins but is insufficiently expressed for all its targets, resulting in inherent competition for limiting CaM among CaM target proteins. Factors controlling CaM expression and interaction dynamics therefore have substantial physiological and therapeutic impact. It is completely unknown if estrogen modulates cardiovascular functions via the CaM network. We observed in endothelial cells that chronic estrogen treatment (CE_2T) increases total and free CaM. Chronic treatment with G-1, an agonist of the estrogen-sensitive receptor GPER/GPR30 mimics this effect, while agonists of estrogen receptors α (ERα) or β (ERβ) do not. ICI182780, an ERα/ERβ antagonist

and GPER/GPR30 agonist, also increases CaM level. These results suggest that GPER/GPR30 mediates estrogen's effect to upregulate CaM expression in the vascular endothelium. CE_2T increases CaM binding to different categories of CaM target proteins, including the plasma membrane Ca^{2+}-ATPase (PMCA), eNOS, ERα, and GPER/GPR30 itself. For PMCA, CE_2T-induced stimulation of activity through enhanced CaM binding is masked by Src-dependent phosphorylation. These effects sustain cytoplasmic Ca^{2+} for enhanced interactions between CaM and other targets. For eNOS, CE_2T doubles CaM binding. Kinetic modeling using *in-cell* and *in vitro* data allowed comparison of CE_2T's promotion of eNOS point activity and NO accumulation via effects on determinants of eNOS function, including Ca^{2+}, CaM, and phosphorylation. For GPER/GPR30, CaM antagonism or CaM binding-negating mutations in the receptor's multiple CaM-binding domains prevent GPER/GPR30-mediated ERK1/2 phosphorylation. Our data indicate that CE_2T improves endothelial functions via a feed-forward mechanism in which CaM is upregulated through GPER/GPR30 activation, leading to enhanced CaM binding and functional linkage in the network of CaM-binding proteins.

11 G

Inhibition of the G Protein-Coupled Receptor T1R1/T1R3 Induces Autophagy in Cardiomyocytes

Samuel Engman, Matthew Boehme, Jennifer Giles, Eric Wauson

Department of Physiology and Pharmacology, Des Moines University, Des Moines, IA

Although development of novel strategies to decrease cardiomyocyte death during acute myocardial infarction have been actively pursued for several decades, the most effective treatment remains reperfusion therapy via percutaneous coronary intervention (PCI). While PCI limits cardiomyocyte death from ischemia injury by restoring blood flow, its overall effectiveness is limited because reperfusion can further damage cardiomyocytes. Results from recent studies suggest that the induction of autophagy, a highly ordered process in which cytoplasmic contents are degraded and recycled by lysosomes in cardiomyocytes, reduces cell death caused by both ischemia and reperfusion injury. One of the most potent inducers of autophagy is the depletion of amino acids, which promotes autophagy by inhibiting mechanistic target of rapamycin (mTOR). Recent work from our lab demonstrated that a cell surface G protein-coupled receptor (GPCR) T1R1/T1R3 relays extracellular amino acid sufficiency signals to mTOR. We observed that T1R1/T1R3 was highly expressed in cultured cardiomyoblasts and mouse heart. In this study we demonstrate that reduction of T1R1/T1R3 expression increases autophagy in both of these model systems. Thus, we have begun studies to test the hypothesis that T1R1/T1R3 inhibition will protect cardiomyocytes from ischemia/reperfusion injury by elevating autophagy. We demonstrate that autophagy and apoptosis are induced in H9C2 cardiomyoblasts and neonatal mouse cardiomocytes subjected to simulated ischemia (SI). Inhibition of autophagy increased apoptosis, consistent with autophagy as protective in our experimental conditions.

12 UG

Contributory Role of ATP as a Sympathetic Cotransmitter During Whole-Body Cooling in Human Skin

Neha Patel[1], Kevin Smaller[1], James A. Lang[2]

[1]*College of Pharmacy and Health Sciences, Drake University, Des Moines, IA*
[2]*Department of Physical Therapy, Des Moines University, Des Moines, IA*

Norepinephrine contributes to ~60% of the reflex cutaneous VC response whereas the remainder comes from coreleased sympathetic adrenergic neurotransmitter(s) that have yet to be identified. Despite conflicting evidence for neuropeptide Y in this role, we hypothesize that ATP functions as a cotransmitter by contributing to reflex VC during whole-body cooling (T_{sk} = 30.5 ^{o}C). Nine individuals (25 ± 1 years; 4 males, 5 females) participated in 2 visits where 3 microdialysis (MD) fibers were placed in the forearm skin for infusion of drugs (visit 1: lactated Ringer's (control), 10 mM L-NAME, L-NAME + 1 mM suramin (purinergic receptor antagonist); visit 2: Ringer's, L-NAME + suramin, L-NAME + suramin + 5 mM yohimbine + 1 mM propranolol). Laser Doppler flux (LDF) was measured over each MD site and cutaneous vascular conductance (CVC) was calculated as CVC = LDF / MAP and expressed as percent change from baseline (%ΔCVC). L-NAME blocked the vasodilatory influence of ATP and unmasked P_2X-mediated VC to exogenous ATP (-18 ± 2 %ΔCVC). This response was blocked at the suramin pretreated site (-2 ± 1 %ΔCVC). During whole body cooling (T_{sk} = 30.5 ^{o}C), the VC response at the suramin site was attenuated (-23 ± 3 %ΔCVC; $p < 0.05$) compared to control (-32 ± 3 %ΔCVC). Combined purinergic and adrenergic receptor blockade (yohimbine + propranolol) further attenuated the reflex VC response (-13 ± 3 %ΔCVC). These data indicate that ATP contributes to reflex VC in young human skin and provides functional evidence supporting ATP as sympathetic cotransmitter.

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13 UG

The Effect of Celiac and Renal Denervation in Angiotensin-Induced Hypertension

Anne Turco, Gage State, Clare Slagel, Shannon Wilson, Scott H. Carlson

Department of Biology, Luther College, Decorah, IA

The sympathetic nervous system contributes to hypertension in several experimental models, although the mechanisms by which elevated sympathetic activity chronically elevate arterial pressure are unclear. Much of the focus is sympathetic control of renal function, which is supported by observations that renal denervation ameliorates uncontrolled hypertension in many individuals. However, in angiotensin II-high NaCl hypertensive rats renal denervation fails to lower blood pressure, suggesting that in some forms of hypertension the sympathetic nervous system may target other vasculatures. In support of this are studies demonstrating that denervation of the splanchnic vasculature via celiac ganglionectomy reduces blood pressure in both angiotensin II-NaCl and Dahl-S rats. The present study investigated the contribution of renal denervation or celiac ganglionectomy in angiotensin II-induced hypertension. Male Sprague Dawley rats (7-10 weeks old) underwent either celiac ganglionectomy (n=3), renal denervation (n=5) or sham surgery (n=5) and were implanted with telemetry probes for continuous monitoring of mean arterial pressure and heart rate. Following a three-day recovery period osmotic minipumps were implanted for delivery of angiotensin (4.2 ug/hour) for 10 days. In sham-treated rats angiotensin raised mean arterial pressure, while both RDx and CGx significantly decreased the hypertensive response to angiotensin (152.0 +/- 15.1 vs. 117.2 +/- 8.2 and 99.6 +/- 8.3 mmHg, respectively). Heart rate was not significantly different between groups. These results indicate that elevated angiotensin levels increase sympathetic nervous system activity in rats, and raise arterial pressure through targeting both the splanchnic and renal vasculatures.

14 UG

Autophagy in Skeletal Muscle Regrowth After Ischemia

Jay Blomme[1], Jarrod A. Call[2], Ana K. Lira[1], Ayotunde O. Dokun[3], Vitor A. Lira[1]

[1]Department of Health and Human Physiology, Obesity Research and Education Initiative (OREI), Fraternal Order of Eagles Diabetes Research Center (FOEDRC), University of Iowa, Iowa City, IA
[2]Department of Kinesiology and Regenerative Bioscience Center, University of Georgia, Athens, GA
[3]Department of Endocrinology and Metabolism, University of Virginia School of Medicine, Charlottesville, VA

Peripheral Artery Disease (PAD) affects around 8 million people in the U.S., but treatment is lacking. Autophagy, a catabolic process required for cell efficiency and energy homeostasis, may hold therapeutic potential. In this experiment, we used a mouse model of PAD where the left femoral artery was ligated, causing profound ischemia and muscle atrophy, while keeping the right artery open to serve as a control. We have observed that reduced expression of Beclin1, a critical protein for autophagy activation, compromises muscle mass recovery in this mouse model. Here, the goal was to define the flux and overall activation of autophagy shortly after the ischemia onset and during the 1st and 2nd week of recovery as blood flow was slowly re-established. Analysis of samples from the plantaris muscle revealed that signaling for autophagy stimulation (i.e., increased phosphorylation of AMPK (Thr172) and of ULK1 (Ser555)) occurred at both 1h and 3h post-surgery; however this was not immediately translated into higher autophagy flux (assessed via LC3-II/LC3-I and p62 protein levels). Interestingly, high autophagy flux was observed at 1 week post-surgery based on a ~60% increase in LC3 II/I and a ~90% decrease in p62. At this point blood flow had recovered to about 60% of the contralateral leg. These preliminary findings suggest that autophagy may play an important role in muscle recovery and re-growth after ischemia, and it may represent an alternative therapeutic target for PAD.

15 UG

Spermidine-Induced Autophagy as a Potential Way to Protect Cardiomyocytes Against Apoptosis Associated with Obesity and Diabetes

Sara Strandlund, Ana K. Lira, Vitor A. Lira

Department of Health and Human Physiology, Obesity Research and Education Initiative (OREI), Fraternal Order of Eagles Diabetes Research Center (FOEDRC), University of Iowa, Iowa City, IA

Diabetes and obesity have been increasing significantly in the United States, with heart failure being much more common among these patients. In this context, there are multiple metabolic unbalances contributing to cardiac dysfunction, and the development of new treatments is becoming more important. Of note, the quality control process of autophagy, which is required for turnover of proteins and organelles, can be insufficient in the diabetic heart. This experiment was designed to test if upregulation of autophagy using the naturally occurring molecule spermidine would protect H9C2 cardiac fibroblast cells from apoptosis induced by a high glucose and high fatty acid environment. Cells were incubated in high glucose (4.5g/mL) and palmitate (250 μM) conditions with or without spermidine (8 μM) for 24 hours. Western Blot analysis revealed an increase in autophagy (reduction of p62 and increase of LC3-II/LC3-I) in all spermidine treated groups. Flow Cytometry experiments revealed a protective effect of spermidine against apoptosis in cells cultured in low glucose medium. However, spermidine failed to provide protection against apoptosis in high glucose and high palmitate media. The precise mechanisms responsible for the inconsistent results are currently not known. Future studies will re-examine the protective potential of autophagy activation by spermidine and other natural compounds against glucose and fatty acid toxicity in primary cardiac myocytes.

16

TLR3 Activation Preferentially Enhances IL-17F Expression in SHR Immune Cells

Madhu V. Singh, Michael Z. Cicha, Mark W. Chapleau, François M. Abboud

Abboud Cardiovascular Research Center, Carver College of Medicine, University of Iowa, Iowa City, IA

We have shown abnormally large age-related increase in CD161+ immune cell populations in splenocytes from spontaneously hypertensive rats (SHR). A subpopulation of CD161+ cells (Th17, CD4+CD161+) expresses IL-17A and IL-17F. IL-17A plays a key role in hypertension and related vascular injury. However, the structurally and functionally similar IL-17F has not been studied in hypertension. Using flow cytometry, we found a greater abundance of CD4+CD161+ cells in prehypertensive SHR splenocytes than in normotensive Wistar-Kyoto rats (WKY). These cells increased with age reaching levels of 14.7 ± 0.1% in spleens from 38 week old SHR compared to 8.5 ± 0.6% in age matched WKY. While PMA-ionomycin caused equivalent induction of TNF-a (WKY 6.7 fold, SHR 6.7 fold) and IL-17A RNA (WKY 14.4 fold, SHR 12.8 fold), the induction of IL-17F RNA was significantly greater in SHR splenocytes (WKY 45.8 fold, SHR 65.2 fold). When challenged with poly-IC, a TLR3 agonist, TNF-a and IL-17A expressions were modestly increased in SHR, however, expression of IL-17F was enormously and specifically increased in SHR compared to WKY (27 fold vs. 3 fold in WKY). We conclude that (1) SHR splenocytes have significantly greater potential for IL-17F induction under inflammatory conditions, and (2) increased expression of IL-17F more pronounced than that of IL-17A in response to TLR3 activation in SHR making IL-17F a preferred therapeutic target in hypertension. Funded by NIH PPG HL14388.

17

Central Sympathoinhibition by Rilmenidine Abrogates AngII-Induced Autonomic Dysfunction and Hypertension in Mice

Rasna Sabharwal, Francois M Abboud, Mark W Chapleau

University of Iowa and Veterans Affairs Medical Center, Iowa City, IA

We recently reported that mice deficient in methionine sulfoxide reductase-A (MsrA), a unique antioxidant, exhibit sympathovagal imbalance and exacerbation of angiotensin II (Ang II)-induced hypertension. In this study, we tested the hypothesis that central administration of the sympathoinhibitory drug rilmenidine (RIL) will improve autonomic regulation and abrogate the enhanced Ang II-induced hypertension in MsrA-/- mice. Blood pressure (BP) and heart rate (HR) were measured in control C57BL/6 (n=7) and MsrA-/- (n=8) mice by telemetry, before and during four weeks of Ang II infusion (1000ng/kg/min). Subgroups of mice were infused ICV with RIL (42 ng/g/hr, n=4) over the last 2 weeks of Ang II infusion. As expected, RIL profoundly inhibited sympathetic tone (HR response to propranolol) in Ang II-infused C57BL/6 and MsrA-/- mice (Table). RIL reversed hypertension (Table) and increased vagal tone and baroreflex sensitivity (sequence technique) in both groups of mice. Moreover, enhanced Ang II-induced increases in BP and BP variability (BPV, SD of systolic BP) in MsrA-/- mice were abolished by RIL (Table). We conclude that targeting excessive sympathetic activity with sustained infusion of RIL abrogates Ang II-induced autonomic dysregulation, hypertension, and BPV. (HL14388, VA)

*P<0.05 *vs.* Baseline †P<0.05 *vs.* C57BL/6		Baseline	Ang II	
			4wk	4wk+RIL
Symp-Tone (Δbpm)	C57BL/6	-72±8	-216±30*	-61±3
	MsrA-/-	-148±9†	-255±16†*	-77±9*
24hr-BP (mmHg)	C57BL/6	108±2	170±6*	115±3
	MsrA-/-	117±3†	192±7†*	122±4
BPV (mmHg)	C57BL/6	4±1	39±13*	15±2*
	MsrA-/-	22±2†	78±7†*	7±2†*

18 Post-Doc

TMEM16B is a Dominant Component of the Cholecystokinin–Activated Cl- Conductance in Vagal Afferents that is Down-Regulated in Mice on High Fat Diet

Runping Wang, Yongjun Lu, Michael Z. Cicha, Mark W. Chapleau, Christopher J. Benson, Francois M. Abboud

University of Iowa Abboud Cardiovascular Research Center and Veterans Affairs Medical Center, Iowa City, IA

We have reported cholecystokinin (CCK) sensitive Ca^{2+}-activated chloride (Cl^-) currents (CaCCs) in DiI labeled intestinal nodose ganglia neurons from C57BL/6 mice. These CaCCs were significantly reduced from 24.8±4.9 (n=7) to 6.1±2.9 pA/pF, (n=7, p<0.01) with mice fed a 60% high fat diet (HFD) for 10 weeks. Here we characterize the effect of CCK on the anoctamins (Ano1 and 2/TMEM16A and B) that function as Ca^{2+}-activated Cl^- conductance. They are expressed in nodose ganglia, downregulated by HFD, and hence may regulate satiety signaling. We found that the CCK-induced Cl^- current was only inhibited by a high dose of niflumic acid (NFA) (300 uM) which inhibits both TMEM 16A and 16B currents (26.9±4.7 pA/pF before vs. 10.3±2.1 pA/pF after NFA, n=10, p<0.01).

However, the specific TMEM16A inhibitor T16Ainh-A01 (30 uM) did not reduce the current (30.4±6.1 pA/pF before vs. 26.9±5.2 pA/pF after, n=8, p>0.1). The excised inside-out patch recording showed that a very high $[Ca^{2+}]_i$ (>1 uM) was required to activate the Cl^- current, which is more consistent with the response of the TMEM16B subunit rather than TMEM16A which is much more sensitive to $[Ca^{2+}]_i$. Transfection of lentivirus carrying shRNA targeting TMEM16B reduced the CCK-current to 22.03±3.7 (n=8) from the value of 35.1±3.4 pA/pF (n=6, p<0.05) obtained with scrambled shRNA. Co-transfection of shRNA targeting both TMEM16A and 16B did not result in further reduction of the CCK-induced current (20.0±4.2 pA/pF, n=6). We conclude that TMEM16B is a dominant component of the CCK-induced Ca^{2+}-activated Cl^- conductance. A dysfunctional TMEM16B may impair satiety in HFD obesity.

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Anoctamins are Determinants of Reduced Cholecystokinin Sensitivity of Vagal Afferents and Impaired Satiety in Obese Mice on High Fat Diet

Yongjun Lu[1], Runping Wang[1], Michael Z. Cicha[1], Mark W. Chapleau[1,2], Francois M. Abboud[1]

[1]*University of Iowa, Iowa City, IA*
[2]*Veterans Affairs Medical Center, Iowa City, IA*

Anoctamin proteins (Ano1 & Ano2) are novel transmembrane proteins (TMEM16A & 16B) that function as calcium-activated chloride channels (CaCCs). Using patch-clamping technique, we previously showed that the response of CaCCs to cholecystokinin (CCK) is significantly decreased in vagal sensory nodose neurons (VSNN) from mice on high fat diet (HFD). Here we define the molecular determinants of this impaired CCK response. Six weeks old C57BL/6 male mice were fed either HFD (60% fat) or a regular diet (control, 6.2% fat). At 4-5 months the HFD mice were significantly heavier (41.4±4.7g, n=24) than control (28.4±3.6g, n=24, p<0.01). Nodose ganglia were removed under anesthesia. Expression of mRNA (qPCR) of CCKR (receptors) was slightly increased in ganglia from HFD (n=3) vs. control mice (n=3) (147±29% for CCKRA, p<0.05 and 117±22% for CCKRB, p>0.05). The CCKRA mRNA in individual intestinal nodose neurons labeled with DiO injected into the wall of the small intestine confirmed that the expression of CCK receptors was not reduced by HFD. On the other hand the mRNA expression of Ano1 and Ano2 in ganglia from HFD mice was reduced to 59±9% and 29±7% (n=4, p<0.01) of the corresponding values in ganglia from control mice; and the corresponding proteins (immunofluorescence) were also reduced to 64±13%

and 61±11% (n=3, p<0.05) of control values, respectively. We conclude that impaired CCK mediated satiety signaling in HFD-induced obesity is caused by downregulation of the CCK- sensitive anoctamins and not by reduced CCK receptor expression in intestinal VSNN (HL14388).

20

Differential Involvement of POMC and AgRP Neurons in the Regional Sympathetic Responses to Leptin

Balyssa B. Bell, Shannon M. Harlan, Donald A. Morgan, Kamal Rahmouni

Department of Pharmacology, University of Iowa, Iowa City, IA

Leptin action in the brain mediates metabolic homeostasis and promotes energy expenditure by increasing sympathetic nerve activity (SNA) to thermogenic brown adipose tissue (BAT). Leptin also increases SNA to other tissues such as the blood vessels and liver. We previously demonstrated the importance of the hypothalamic arcuate nucleus (Arc) in mediating leptin-induced increases in regional SNA, but the specific neuronal populations within the Arc that mediate these responses is unknown. We hypothesized that proopiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons of the Arc differentially mediate regional SNA responses to leptin. To test this, we generated mice lacking leptin receptors in POMC ($POMC^{Cre}/LepR^{fl/fl}$) or AgRP neurons ($AgRP^{Cre}/LepR^{fl/fl}$). We used multifiber sympathetic nerve recording to assess the effects of intracerebroventricular (ICV) leptin (2 μg) on regional SNA. ICV leptin increased BAT SNA in control mice (326±61%). Interestingly, this response was blunted in both $POMC^{Cre}/LepR^{fl/fl}$ (148±29%, p<0.05) and $AgRP^{Cre}/LepR^{fl/fl}$ mice (172±62%, p<0.05). In contrast, ICV leptin led to a similar increase in splanchnic SNA in control (266±40%) and $AgRP^{Cre}/LepR^{fl/fl}$ mice (214±50%), but the response was reduced in $POMC^{Cre}/LepR^{fl/fl}$ mice (56±38%, p<0.05). Similarly, the renal and lumbar SNA responses to leptin were blunted in $POMC^{Cre}/LepR^{fl/fl}$, but not in $AgRP^{Cre}/LepR^{fl/fl}$ mice. Conversely, the hepatic SNA response to leptin was reduced in $AgRP^{Cre}/LepR^{fl/fl}$ mice (76±21%, p<0.05), but not in $POMC^{Cre}/LepR^{fl/fl}$ mice (120±49%) relative to controls (196±36%). We concluded that POMC and AgRP neurons are differentially involved in mediating the regional SNA effects of leptin.

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Dissociating the Metabolic and Cardiovascular Effects of Leptin Through mTORC1 Signaling

Mohamed Rouabhi, **Balyssa B. Bell,** Donald A. Morgan, Kamal Rahmouni

Department of Pharmacology, University of Iowa, Iowa City, IA

Leptin is an adipocyte-derived hormone which acts in the brain to regulate energy homeostasis by suppressing appetite and increasing energy expenditure. Leptin also promotes arterial pressure elevation by increasing the sympathetic nerve activity (SNA). Recent evidences indicate that the mechanistic target of rapamycin complex 1 (mTORC1) plays a key role in mediating the metabolic and sympathetic effects of leptin. To test the consequence of disrupting mTORC1 on leptin actions, we conditionally deleted Raptor, a critical subunit of mTORC1, in leptin receptor (LRb) expressing cells using genetically modified mice in which the Raptor gene is flanked by Lox-P sites ($Raptor^{fl/fl}$) and Cre recombinase driven by the LRb promoter (LRb^{Cre}). We measured body weight weekly from 4 weeks of age and observed no differences between $LRb^{Cre}/Raptor^{fl/fl}$ and control littermates (29.6±0.8g vs 31.0±0.8g at 14 weeks). Additionally, food intake and body weight were recorded daily at baseline and after treatment with vehicle or leptin (1μg/g bw, intraperitoneally, twice daily) for 4 days. We found no significant difference in the cumulative decrease in food intake (-1.6±0.8g vs -1.1±1.7g) or body weight (-5.9±0.8% vs -5.7±0.7%) caused by leptin between $LRb^{Cre}/Raptor^{fl/fl}$ mice

and WT littermates. Finally, we performed multifiber nerve recordings of renal SNA to determine the contribution of mTORC1 to the cardiovascular sympathetic action of leptin. Interestingly, intracerebroventricular injection of leptin (2 μg) increased renal SNA in control mice (106±20%), but not in $LRb^{Cre}xRaptor^{fl/fl}$ mice (-28±11%, P<0.05 vs controls). We concluded that mTORC1 is necessary for the renal SNA effect of leptin, but not critical for the metabolic actions of leptin.

22 G

Mechanisms of Vagal Nerve Stimulation-Induced Effects on Blood Glucose Concentration in Anesthetized Rats

Erin E. Meyers, Michelle S. Asare, Nicholas B. Cavanaugh, Shaohan Deng, Taylor J. Glab, Shawn M. Sexton, Harald M. Stauss

Department of Health and Human Physiology, University of Iowa, Iowa City, IA

Vagal nerve stimulation (VNS) causes weight loss in obese patients and parasympathetic activation of the liver reduces hepatic glucose release. Thus, VNS may be highly effective in treating obese type II diabetic patients. We hypothesized VNS reduces blood glucose concentration [Glu] in anesthetized rats and studied potential underlying mechanisms.

Blood pressure (BP), heart rate (HR), and [Glu] (HD-XG, DSI) were continuously monitored in anesthetized rats (1.5% isoflurane in O_2). Stimulation electrodes were placed around the right cervical vagus nerve. After establishing constant baseline conditions, continuous VNS (5 Hz, 3 V, 1 ms) was initiated and maintained for two hours. Then the stimulator was turned off, the vagus nerve severed either proximal (for efferent VNS) or distal (for afferent VNS) to the electrodes, and new baseline conditions were reestablished. Then efferent or afferent VNS was initiated for another two hours.

Combined afferent and efferent VNS (intact nerve) did not significantly affect mean BP or HR but significantly increased [Glu] presumably via an increase in plasma glucagon levels. Afferent VNS also tended to increase [Glu], which may be the result of mild increases in glucagon and reductions in insulin plasma levels. Efferent VNS tended to reduce [Glu] probably via an increase in plasma insulin levels.

Table 1: Results

	Δ mean BP (mmHg)	Δ HR (bpm)	Δ [Glu] (mg/dL)	Δ Glucagon (pg/dL)	Δ Insulin (pg/dL)
Intact nerve	+6.4±4.0 (n=9)	-12.5±16.4 (n=9)	**+149±37 (n=9) P<0.05**	**+57.6±27.2 (n=6) P=0.09**	+137±141 (n=6)
Afferent VNS	-0.5±8.2 (n=4)	+14.5±22.0 (n=4)	**+110±58 (n=4) P=0.15**	+19.4±33.6 (n=2)	-238±474 (n=2)
Efferent VNS	-5.7±4.0 (n=6)	+22.1±19.2 (n=6)	**-19±12 (n=6) P=0.16**	-5.0±7.6 (n=3)	**+782±529 (n=3) P=0.28**

In conclusion, VNS increases [Glu] presumably by afferent pathways activating central nervous system-mediated glucagon release. VNS using parameters selectively recruiting efferent nerve fibers may potentially lower [Glu] in type II diabetic patients by increasing insulin and inhibiting glucagon secretion from the islets of Langerhans.

Low Force Muscle Activity Regulates Energy Expenditure After Spinal Cord Injury

Jessica R. Woelfel[1], Amy L. Kimball[2], Richard K. Shields[2,3]

[1]*Carver College of Medicine, University of Iowa, Iowa City, IA*
[2]*Department of Physical Therapy and Rehabilitation Science, Carver College of Medicine, University of Iowa, Iowa City, IA*
[3]*Department of Veterans Affairs, VA Medical Center, Iowa City, IA*

People with spinal cord injury (SCI) have reduced activity for a lifetime, which increases morbidity and mortality. Osteoporosis occurs soon after SCI and precludes high muscle force generation due to risk of fracture. We examined the effects of low frequency and low force electrical stimulation on energy expenditure in humans with SCI. We also studied the influence of stimulation intensity, body mass index (BMI), and visceral adipose tissue (VAT) on energy expenditure during low frequency stimulation. Oxygen consumption, carbon dioxide exhalation, and heart rate were measured during varying frequencies (1 Hz, 3 Hz, and 5 Hz) and intensities (50 and 100 mA) of bilateral stimulation applied to the quadriceps and hamstring muscles. Ten humans with complete paralysis (1 female, 4 paraplegics, and 6 quadriplegics) participated on multiple days to receive the stimulation protocols. Gas exchange measurements were made using a metabolic cart, expenditure was calculated using the Weir equation: (kcal/day= [3.9 (VO2) + 1.1 (VCO2)] 1.44), and VAT was measured using ultrasound imaging. We found that energy expenditure increased with stimulation frequency and intensity ($p<0.05$). 1 Hz stimulation induced over 80% of the increase in energy expenditure achieved at 3 Hz and 5 Hz stimulation ($p<0.05$). Heart rate increased only during the 5 Hz condition ($p<0.05$). BMI and VAT were strong inverse predictors of energy expenditure ($r = -0.86$ and -0.82, respectively). We conclude that patients with chronic paralysis may benefit from regular long duration and low force muscle stimulation to safely increase daily activity and improve health.

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