10th Annual Meeting
Michigan Physiological Society

2013 **10th** 2023

Anniversary Celebration

June 26-27, 2023
Alma College
Alma, MI

2023 American Physiological Society – Chapter of the Year

MPS Leadership 2022-2023

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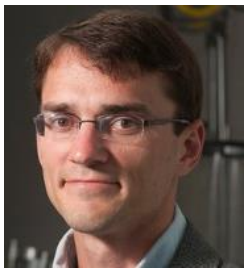

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(Dr. Steven Elmer)

And thank you to the American Physiological Society for ongoing support of MPS!!

Thank you to the following individuals for personal sponsorships toward the MPS annual meeting

Dr. Steven Elmer

Thank you to the following individuals who reviewed abstracts

Dr. Charles Chung
Dr. Robert Larson
Dr. Nkhensani Mogale
Dr. Naveen Sharma
Dr. Erica Wehrwein
Dr. John Zubek
Dr. Subha Bhaskaran

Thank you to the following judges who evaluated oral and poster presentations

Dr. Karen Ball, Professor
Dr. Harold Bell
Dr. Charles Chung
Dr. Jennifer Doherty
Dr. Gregory Fink
Dr. Robert Larson
Dr. Mariela Mendez
Dr. Naveen Sharma
Dr. Christopher Westerkamp
Dr. Beth Zimmer
Dr. John Zubek

2023 MPS Keynote Lecture

Monday, June 26, 2023
2:00 – 3:00 pm

Pablo Ortiz, PhD

Professor of Physiology
Henry Ford Hospital
Wayne State University

It is the Best of Times to be a Physiologist: Harnessing Innovation from Other Fields to Advance Knowledge of Physiology and Human Health

Dr. Pablo A. Ortiz is the Head of the Hypertension and Vascular Research Division and Scientific Director of the Translational and Clinical Research Center at the Henry Ford Hospital. Dr. Ortiz holds the endowed Earl Ward Chair of Hypertension and has received funding from NIH and other agencies (such as the American Heart Association) since 2006. He is a full-time affiliate Professor of Physiology at Wayne State University Department of Physiology. His area of research is broadly defined as the role of the kidneys in hypertension. He is one of the world's leading experts in thick ascending limb and distal tubule salt transport, genetic and molecular mechanisms of salt sensitive hypertension. His latest research includes projects focusing on the renal mechanisms by which obesity, high fructose, high fat, and type 2-diabetes in combination with high salt increases blood pressure, contributing to cardiovascular and kidney diseases. He has authored over 60 publications in the last 22 years, mentored several Ph.D. students, post-doctoral fellows, Instructors and Assistant Professors, many of them from URM backgrounds. He is also one of the founding members of the Translational and Clinical Research Center (TCRC) at the Henry Ford Hospital. For his research, Dr. Ortiz has received numerous National awards, has been invited to National and International meetings and has been a lecturer at several universities. His service includes several positions of leadership at National and International medical research societies including serving as Chairman of the American Heart Association Kidney in Cardiovascular Disease (KCVD) Council, American Physiological Society Annual Conference Program Committee, and member of the American Society of Nephrology YIA committee. He has served in several NIH study sections and is currently a standing member of the NHLBI PPG parent committee. He is a member of the Editorial Board of the American Journal of Physiology-Renal, Hypertension Journal, and Associate Editor of Frontiers in Renal Physiology.

10th Annual Meeting of the Michigan Physiological Society
The Michigan Chapter of the American Physiological Society
Monday, June 26, 2023

12:30 – 1:30 pm **REGISTRATION**
[Alma College, Dow Science Center, Lobby]
Pick up meeting materials
(Those individuals staying in the dorms should check in at Bruske Hall by 12:30pm)
(See map on page 13)

1:30 – 2:00 pm **WELCOME AND MEETING OPENING**
[Dow Science Center, L1]
Steven Elmer, PhD (MPS President, Michigan Tech)
Brianna Harfmann, PhD (MPS President-Elect, Alma College)

2:00 – 3:00 pm **KEYNOTE LECTURE**
[Dow Science Center, L1]
- *Sponsored by Michigan State University, Department of Physiology*

Introduction
Andrew Butcko, MS (Wayne State University)

Pablo Ortiz, PhD
Henry Ford Hospital, Wayne State University
It is the Best of Times to be a Physiologist: Harnessing Innovation from Other Fields to Advance Knowledge of Physiology and Human Health

3:00 – 3:15 pm **BREAK**

3:15 – 4:15 pm **THEMATIC POSTER SESSION #1: Undergraduate Student Research**
[Dow Science Center, Gerstacker Upper Lobby]
***Presenters eligible for awards need to be at or near posters so that judges can score your presentation**
- *Sponsored by Wayne State University, Biological Sciences*

4:15 – 4:45 pm **WALKING BREAK**
[Meet in Dow Science Center, Lobby - Walk to Opera House]
(Transportation also available for anyone who needs it)
- Sponsored by Michigan Technological University, UP and Moving Program

4:45 – 6:00 pm **ORAL SESSION #1: Neuro and Renal Physiology**
[Opera House]
- *Sponsored by Wayne State University, School of Medicine, Office of Research*

Session Co-Chairs
Greg Miodonski, MS (Michigan Technological University)
Isaac Baiden, BS (Wayne State University)

4:45 – 5:00 pm **Anna Murphy** (Undergraduate Student)
Wayne State University
Influence of Ovarian Hormones on proBDNF Levels in the Rostral Ventrolateral Medulla: Influences Related to Neuronal Plasticity and Sympathetic Control of Blood Pressure

5:00 – 5:15 pm **Beatriz Thomasi** (Post-doctoral Fellow)
Michigan State University
S100b Modulates Purinergic Enteric Neuron and Glial Activity Following Inflammation

5:15 – 5:30 pm **Marie Hanscom** (Post-doctoral Fellow)
Michigan State University
Neuromodulation Of Adipocyte Activity in Perivascular Adipose Tissue In Healthy Mice

5:30 – 5:45 pm **Andrew Wu** (Undergraduate Student)
Wayne State University, Henry Ford Hospital
Measuring Urine Concentration Capacity and Luminal Na in Live Mice By Intravital Multi-Photon Microscopy

5:45 – 6:00 pm **Jessica Granados Pineda** (Post-doctoral Fellow)
Henry Ford Hospital
camp Stimulated NKCC2 Phosphorylation At Thr-96,101 Is In Part Independent From SPAK: A Role For TNIK

6:00 – 7:00 pm **DINNER AND CELEBRATING 10 YEARS OF MPS**
[Opera House]
- *Sponsored by Michigan Technological University, Department of Kinesiology and Integrative Physiology*

Host
Steven Elmer, PhD (Michigan Technological University)

MPS Presidents (2014-present)
Gregory Fink, Jason Carter, Erica Wehrwein, Patrick Mueller, Karen Ball, John Durocher, Naveen Sharma, M. Beth Zimmer, Jennifer Vranish, Steven Elmer
Various colleges and universities
10 Years of Physiology in Michigan

7:00 – 8:00 pm **PHYSIOLOGY TRIVIA COMPETITION**
[Opera House]

Co-hosts
Brianna Harfmann, PhD (Alma College)
Jennifer Vranish, PhD (Alma College)

8:30 – 10:00 pm **SOCIAL**
[Downtown]

2023 MPS Distinguished Lecture

Tuesday, June 27, 2023
9:00 – 10:00 am

Paul Fadel, PhD

Professor
Department of Kinesiology
University of Texas at Arlington

Sympathetic Control of the Circulation in Human Health and Disease

Dr. Paul Fadel earned his Bachelor's degree in Physical Education from Brooklyn College in New York, before heading to Northeastern University in Boston to complete his Master's in Clinical Exercise Physiology. He earned a PhD in Biomedical Sciences from the University of North Texas Health Science Center and completed postdoctoral training at the University of Texas Southwestern Medical Center. He then spent 10 years at the University of Missouri's Department of Medical Pharmacology and Physiology, earning tenure and the rank of Associate Professor. In 2015 he transitioned to the University of Texas at Arlington, where is holds the title of Professor in the Department of Kinesiology and serves as the Associate Dean for Research and Director of Clinical Translation Science in the College of Nursing and Health Innovation. He serves on 5 editorial boards of top peer-reviewed journals and has served on study sections for the National Institutes of Health and the American Heart Association. He has received numerous awards highlighting his excellence in teaching, research, and mentoring of the next generation of scientists. Dr. Fadel has established an impressive record of external funding from the NIH, AHA, and DoD and has mentored over 20 PhD students and Postdoctoral fellows to date. Dr. Fadel's research focuses on vascular function and the sympathetic nervous system's regulation of the vasculature in health and disease, such as
Type 2 Diabetes and Chronic Kidney Disease.

2023 MPS Living History Lecture

Tuesday, June 27, 2023
12:30 – 1:30 pm

Susan Barman, PhD

University Distinguished Professor
Department of Pharmacology & Toxicology
Michigan State University

How to Enjoy Life as a Physiologist: Listen to Mentors, See Challenges as Opportunities, and Always be Yourself

Sue Barman has spent her entire professional career at Michigan State University (MSU), arriving in East Lansing on October 31, 1975, after completing her PhD work in Physiology at Loyola University Medical Center, Maywood IL. She is an award-winning biomedical scientist whose research was consistently funded by the National institutes of Health. The focus of her research was on the role of the brainstem in the control of sympathetic nerve activity. Among her awards are a MERIT Award from NIH, Outstanding University Woman Faculty Award from the Faculty Professional Women's Association of MSU, College of Human Medicine Distinguished Faculty Award, Fellow of the American Physiological Society (APS), MSU William S. Beal Outstanding Faculty Award, Bodil M. Schmidt-Nielsen Distinguished Mentor and Scientist Award from the APS, and the MSU Provost Selection as a University Distinguished Professor. She played a major role in bringing the Physiology Quiz to the annual Michigan Physiological Society meeting. In addition to many examples of professional service at a national (e.g., President of the APS) and state (e.g., Chair, Membership and Fundraising Committee of the MPS) level, Sue has been actively engaged in several key committees at MSU, including Steering Committee, Faculty Senate, University Council and Chair of the Institutional Animal Care and Use Committee and University Committee on Faculty Tenure. She is also an author of the popular Ganong's Review of Medical Physiology.

10th Annual Meeting of the Michigan Physiological Society
The Michigan Chapter of the American Physiological Society
Tuesday, June 27, 2023

6:30 – 7:00 am **UP AND MOVING - VIRTUAL PHYSICAL ACTIVITY WORKOUT**
[From dorm/hotel room]
(Get your 30 min of physical activity in, no equipment needed)
(www.upandmoving.org, click on join live workout, click Zoom, passcode up2021)

Co-Hosts
UP and Moving - Exercise is Medicine® on Campus Team
Isaac Lennox, BS (Michigan Tech)
Abby Brooks, BS (Michigan Tech)
Kyle Wehmanen, MS (Michigan Tech)

7:30 – 8:00 am **CONTINENTAL BREAKFAST**
[Dow Science Center, Lobby]

8:00 – 9:00 am **THEMATIC POSTER SESSION B**
[Dow Science Center, L1, L2, and L4]
- *Sponsored by Michigan State University, Department of Physiology*

9:00 – 10:00 am **DISTINGUISHED LECTURE**
[Dow Science Center, L1]
- *Sponsored by Henry Ford Health Division, Hypertension and Vascular Research Division*

Introduction
Jennifer Vranish, PhD (Alma College)

Paul Fadel, PhD
University of Texas at Arlington
Sympathetic Control of the Circulation in Human Health and Disease

10:00 – 10:30 am **BREAK** (Coffee and Snacks)
[Dow Science Center, Lobby]
(Those individuals staying in the dorms need to checkout by 10:30am)

10:30 – 12:00 pm **PROFESSIONAL DEVELOPMENT BREAKOUT SESSIONS**
- *Sponsored by Michigan State University, Graduate School*

CMU Health Sciences Tour
[Central Michigan University]
John Zubek, MS, DPT (Michigan State University)
(Students should sign up by Tuesday morning)

OR

ALMA Breakout Sessions
[Dow Science Center]

Each session will last 30 min and be repeated. See description on page 14 for summaries of each session.

Breakout Session 1: Shifting Trajectories: Transitioning from Graduate School to Industry
[Dow Science Center, L1]
Hayden Stoub, MS (Xilis Inc)
Brandon Coughlin, PhD (Alimera Sciences)

Breakout Session 2: Teaching Pedagogies: Promoting Classroom Engagement with AI
[Dow Science Center, L2]
Subha Bhaskaran, PhD (Oakland University)
Christopher Shaltry, PhD (Michigan State University)

Breakout Session 3: Science Policy: Current Topics and Integration with Your Career
[Dow Science Center, L3]
Laura McCabe, PhD (Michigan State University)

12:30 – 1:30 pm **LUNCH AND LIVING HISTORY LECTURE**
[Dow Science Center, L1]
(Pick up box lunch in Dow Science Center Lobby)
- *Sponsored by Michigan Technological University, Department of Kinesiology and Integrative Physiology*

Introduction
Naveen Sharma, PhD (Central Michigan University)

Susan Barman, PhD
Michigan State University
How to Enjoy Life as a Physiologist: Listen to Mentors, See Challenges as Opportunities, and Always be Yourself

1:30 – 2:30 pm **POSTER SESSION**
[Dow Science Center, Gerstacker Upper Lobby]
***Presenters eligible for awards need to be at or near posters so that judges can score your presentation**
- *Sponsored by Michigan Technological University, Department of Biological Sciences*

2:30 – 3:30 pm **ORAL SESSION #2: Cardiovascular Physiology**
[Dow Science Center, L1]
- *Sponsored Wayne State University, Detroit Cardiovascular Training Program*

Session Chair
Jessica Granados Pineda, PhD (Henry Ford Hospital)

2:30 – 2:45pm **Haley Marchese** (Undergraduate Student)
Michigan Technological University

Sympathetic Activity to The Heart is Increased in a Mouse Model of Hypertrophic Cardiomyopathy

2:45 – 3:00pm **Erin McLean** (Undergraduate Student)
Grand Valley State University
Determining the role of ERK1/2 in the development of diabetic cardiomyopathy

3:00 – 3:15pm **Andrew Butcko** (Graduate Student)
Wayne State University
Does the I148M Mutation in PNPLA3 Alter the Association Between Fatty Liver and Cardiovascular Disease Risk

3:15 – 3:30pm **Ruijie Liu** (Faculty)
Grand Valley State University
Mutation of PKA and GRK Phosphorylation Sites on Beta 2 Adrenergic Receptor Impair its Stability

3:30 – 3:45 pm **BREAK**
Judges Convene for Final Award Selections
[Dow Science Center, Lobby]

3:45 – 4:00 pm **PHOTO SESSION**
[Meet in Dow Science Center Lobby]
[Photo in McIntyre Mall]

4:00 – 4:30 pm **MPS BUSINESS MEETING AND LEADERSHIP TRANSITION**
[Dow Science Center, L1]
Led by MPS Executive Committee

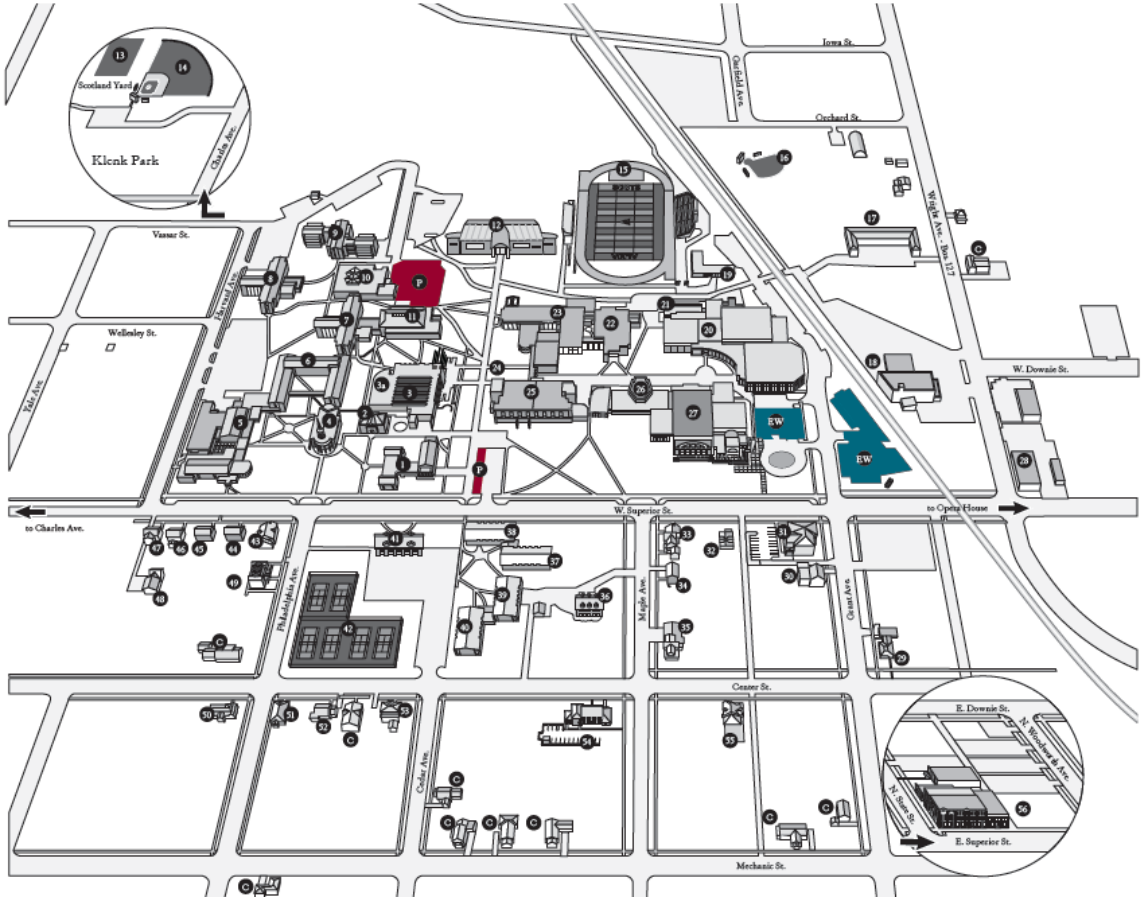
4:30 – 4:45 pm **AWARDS AND CLOSING REMARKS**
[Dow Science Center, L1]
Subha Bhaskaran, PhD (MPS Awards Chair, Oakland University)
Steven Elmer, PhD (MPS President, Michigan Tech)
Brianna Harfmann, PhD (MPS President-Elect)

Please mark your calendars for future MPS events!

Michigan Indiana Physiology Understanding Week ("MI-PhUn" Week)
November 2023
(exact dates TBA)

Michigan Physiological Society Mid-Year Virtual Symposium
February 2024
(exact dates TBA)

Alma College Campus Map



1 Reid-Knox Administration Building
2 Hood Building
3 Greg Hatcher Learning Commons
3a Colina Library Wing
4 Dunning Memorial Chapel
5 Tyler-Van Dusen Campus Center
6 Gelston Hall
7 Newberry Hall
8 Mitchell Hall
9 Bruske Hall
10 Hamilton Commons
11 Clack Art Center
Flora Kirsch Beck Gallery
12 Alan J. Stone Center for Recreation
13 Scotland Yard Soccer Field
14 Klenk Park Baseball Field
15 Bahlke Stadium
16 Scots Park Softball Field
17 Wright Avenue Apartments
18 Facilities and Service Management
19 Wilcox Health Center
20 Hogan Center
21 McIntyre Center for Health Science
22 Ronald O. Kapp
Science Laboratory Center
23 Dow Science Center
24 McIntyre Mall
25 Swanson Academic Center
26 Eddy Music Center
27 Oscar E. Remick Heritage Center
for the Performing Arts
28 Alma College Bookstore/Starbucks
Mail and Copy Center
29 Appelt House
30 Communication and Marketing
Office
31 Zeta Sigma Fraternity House
32 Environmental Studies House
33 Model U.N. House
34 Centennial House
35 Sigma Chi Fraternity House
36 Tracy House
President's Home
37 Brazell Hall
38 Brazell-West Hall
39 Carey Hall
40 Bonbright Hall
41 Wright Hall
42 Tennis Courts
43 Smith Alumni House
44 Gamma Phi Beta Sorority House
45 Alpha Xi Delta Sorority House
46 Kappa Iota Sorority House
47 Alpha Gamma Delta Sorority House
48 Phi Sigma Sigma Sorority House
49 Tau Kappa Epsilon Fraternity House
50 Class of 1980/Altman House
51 Meyer House
52 Chapel House
53 MacCurdy House
54 Delta Gamma Tau Fraternity House
55 Phi Mu Alpha Fraternity House
56 Wright Leppien Opera House

C College-Owned Housing
EW Visitor parking evenings and weekends
P Visitor parking

Professional Development Breakout Session Descriptions

Breakout Session 1: Shifting Trajectories: Transitioning from Graduate School to Industry
[Dow Science Center, L1]
Hayden Stoub, MS (Xilis Inc)
Brandon Coughlin, PhD (Alimera Sciences)

This breakout session, led by former physiology graduate students now working in industry, explores their transitional journey and the opportunities they discovered. Providing practical advice and an open forum for questions, the session offers firsthand knowledge on a successful post-graduation pivot to the industrial sector.

Breakout Session 2: Teaching Pedagogies: Promoting Classroom Engagement with AI
[Dow Science Center, L2]
Subha Bhaskaran, PhD (Oakland University)
Christopher Shaltry, PhD (Michigan State University)

AI-powered tools such as ChatGPT and Google Bard can offer personalized one-on-one tutoring assistance to students. By affording all students access to personalized, anytime, any-place assistance, these tools have the potential to enhance classroom engagement and inclusiveness in ways not previously possible. This session will consider these strategies (along with potential issues) to understand the benefits of this groundbreaking technology and its utilization.

Breakout Session 3: Science Policy: Current Topics and Integration with Your Career
[Dow Science Center, L3]
Laura McCabe, PhD (Michigan State University)

Join Dr. Laura McCabe, who has served on national science policy committees with the Federal Demonstration Project, Federation of American Societies for Experimental Biology (FASEB), and the American Physiological Society (APS) to learn about the importance of advocating for science to help advance the interests of physiological science and the broader scientific community.

Poster Board Layout

Poster Board #1 *The Protective Role of Hepatic ChREBPα Against the Activation of Hepatic Stellate Cells During NASH/Liver Fibrosis*
Rawdat Hussain
University of Michigan

Poster Board #2 *Hepatocyte Tgf-B (Transforming Growth Factor Beta) Signaling Promotes Activation of Hepatic Stellate Cells and Liver Fibrosis Via Induction Of Orp3 (Oxysterol-Binding-Protein-Like 3)*
Gary Zhang
University of Michigan

Poster Board #3 *Establishing In Vitro Evidence that ChREBPα Promotes Fatty Acid Oxidation*
Rafee Mirza
University of Michigan

Poster Board #4 *Inhibiting Local Brain Metabolism of Ethanol in the Central Nucleus of the Amygdala Blunts Sympathoexcitatory Responses Induced by Ethanol in Sprague Dawley Rats*
Derrick Simet
Michigan Technological University

Poster Board #5 *Effects of Inspiratory Muscle Strength Training on Metabolic and Cardiovascular Responses to a Glucose Challenge*
Audrey Plouffe
Alma College

Poster Board #6 *Comparison of Vascular Anatomy, Strain Patterns, and Ultimate Tensile Strength Across Cadaveric Achilles Tendons*
Abigail Wohlfert
Alma College

Poster Board #7 *Enhancing Learning Opportunities in Laboratory Science Using Virtual Reality Lessons: A Use Case*
Sarah Shine
Michigan State University

Poster Board #8 *Promoting Physical Activity in the Rural and Medically Underserved Upper Peninsula of Michigan*
Abigail Brooks
Michigan Technological University

Poster Board #9 *Teaching K-12 Students Using Jenga! The Impact of Health Behaviors on Community Wellbeing and Resilience*
Kyle Wehmanen
Michigan Technological University

Poster Board #10 *Exercise Is Medicine® On Campus: A National Analysis and Assessment of Community Impact*
Isaac Lennox
Michigan Technological University

Poster Board #11 *Oaks to Arteries: The Physiology Core Concept of Flow Down Gradients Supports Transfer of Student Reasoning*
Jennifer Doherty
Michigan State University

Poster Board #12 *Metabolic Stress Induces Rnf8-Mediated Ubiquitination and Degradation of Chrebpa During Diet-Induced Nash*
Yuee Zhao
University of Michigan

Poster Board #13 *Activation of Hepatocyte E4BP4-OPN Axis Induces Liver Fibrosis in Non-alcoholic Steatohepatitis*
Sujuan Wang and Jiashi Gao
University of Michigan

Poster Board #14 *Sex Differences in Calcium Tolerance of Isolated Cardiac Mitochondria*
Alyssa Vadovsky
Michigan State University

Poster Board #15 *Endothelial Cell Specific Adam10 Activation Regulates Pathological Retinal Neovascularization*
Purnima Gogoi and Anamika Sharma
Wayne State University

Poster Board #16 *Il-33 Cleaved by Neutrophil Proteases are More Potent Regulators of Human Retinal Microvascular Endothelial Cells Activation and Angiogenesis*
Shivantika Bisen
Wayne State University

Poster Board #17 *Transcriptional Control of Mammary Gland Development by E2f5*
John Vusich
Michigan State University

Poster Board #18 *Hepatic Chrebpα Protects Against Both Diet and Chemical-Induced Liver Fibrosis by Blocking the Activation of Hepatic Stellate Cells*
Jian Zhang
University of Michigan

Poster Board #19 *Exercise Augments Small Conductance Ca2+ -Activated Potassium Channel (Sk) Function in the Paraventricular Nucleus (PVN) of Sprague Dawley Rats to Reduce Sympathetic Outflow*
Gregory Miodonski
Michigan Technological University

Poster Board #20 *PVN Sk Channel Blockade Alters Sympathetic Nerve Bursting Pattern in Angiotensin II-Infused Rats*

Robert Larson
Michigan Technological University

Thematic Poster Session #1: Undergraduate Student Research

The Protective Role of Hepatic ChREBPα Against the Activation of Hepatic Stellate Cells During NASH/Liver Fibrosis

Rawdat Hussain(1), Gauthami Pulivendala(2), Deqiang Zhang(1), Sujuan Wang(1), Sarah Cooke(1), Xin Tong(1), Lei Yin(1)

(1) Department of Molecular & Integrative Physiology, University of Michigan Medical School, (2) University of Miami Miller School of Medicine

Liver diseases have been reported to be responsible for 2 million deaths per year globally. Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease, afflicting 20-25% of the adult population worldwide. A quarter of NAFLD patients develop non-alcoholic steatohepatitis (NASH), increasing the risk for cirrhosis, liver failure, and hepatocellular carcinoma. Liver fibrosis is the primary determinant of mortality among patients with NASH. The transition from a normal liver to a fibrotic one involves intricate mechanisms that facilitate the crosstalk between hepatocytes and hepatic stellate cells (HSCs), which play a key role in the initiation and progression of a fibrotic liver. In this study, we aimed to investigate the role of the metabolic regulator ChREBPα in HSC activation during NASH/liver fibrosis. Our RNA-seq results showed that following NASH diet feeding, Chrebpα liver-specific-KO (Chrebpα-LKO) mice display higher expression levels of various multiple pro-fibrotic markers such as Thbs1 and Ctgf compared to wild-type (WT) mice. Upon treatment with TGF-β1, one of major factors that drives fibrosis, primary mouse hepatocytes (PMH) and Hepa1c1c7 mouse hepatoma cells showed downregulation of mRNA and protein levels of ChREBPα. We demonstrated the repression of ChREBPα by TGF-β1 treatment is independent of the canonical SMAD signaling pathway. Furthermore, we identified a ChREBPα downregulation-mediated potential crosstalk between hepatocytes and HSCs that triggers HSC activation and potentially fibrosis. In summary, our study revealed a novel protection function of ChREBPα against the release of pro-fibrotic mediators required for hepatic stellate cell activation during NASH development.

Hepatocyte Tgf-B (Transforming Growth Factor Beta) Signaling Promotes Activation of Hepatic Stellate Cells and Liver Fibrosis Via Induction of Orp3 (Oxysterol-Binding-Protein-Like 3)

Gary Zhang, Deqiang Zhang, Sujuan Wang, Gauthami Pulivendala, Sarah Cooke, Xin Tong, Lei Yin

University of Michigan Department of Molecular and Integrative Physiology

Targeted inhibition of hepatocyte TGF-β signaling has been shown to protect mice against diet induced liver steatosis, injury, and fibrosis. However, the exact mechanisms by which activation of hepatocyte TGF-β signaling promotes liver fibrosis remain poorly understood. Here we report that ORP3 (oxysterol-binding-protein-like 3) is a novel downstream target of TGF-β in hepatocytes. Elevated ORP3 mRNA levels were observed in the livers of ob/ob mice, mice with NASH, and humans with hepatocellular carcinoma. Interestingly, we found that TGF-β induces ORP3 and regulates its expression through a non-canonical signaling pathway. Furthermore, ORP3 is both sufficient and required for induction of several profibrogenic targets of TGF-β which include Ctgf, Thbs1, and PdgfB. Mechanistically, ORP3 enhances protein stability of YAP, a transcriptional coactivator involved in promoting liver fibrosis, and enhances hepatic stellate cell (HSC) activation via cell-to-cell communication which is largely abrogated by YAP-knockout in primary mouse hepatocytes (PMH). In summary, we uncovered the role of ORP3 in a novel pathway underlying hepatocyte TGF-β signaling, HSC activation, and liver fibrosis.

Establishing In Vitro Evidence that ChREBPα Promotes Fatty Acid Oxidation

Rafee Mirza, Deqiang Zhang, Xin Tong, Lei Yin

University of Michigan Medical School, Department of Molecular and Integrative Physiology

Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common chronic liver condition in the Western Hemisphere, affecting approximately 24% of the general U.S. adult population. NAFLD is initiated when lipid accumulation exceeds lipid output, particularly when an imbalance between de novo lipogenesis (DNL) and fatty acid oxidation (FAO) occurs. Carbohydrate response element binding protein (ChREBPα) is a classical lipogenic transcription factor involved in maintaining hepatic lipid homeostasis in response to carbohydrate intake. The role of ChREBPα in lipogenesis regulation is currently well understood, however whether it controls FAO remains unclear. The aim of this study was to investigate the role of ChREBPα in fatty acid oxidation in an in vitro context through cultured hepatocytes. Our results showed that FAO gene expression and FAO rate were both downregulated in primary mouse hepatocytes isolated from ChREBPα-liver-specific-KO (ChREBPα-LKO) mice in comparison to a wild-type control, whereas they were both upregulated in primary hepatocytes with adenovirus-mediated ChREBPα overexpression (Ad-ChREBPα). Furthermore, we showed that in the presence of etomoxir, an irreversible chemical inhibitor for the rate-limiting step of mitochondrial β-oxidation, lipid droplet size and fluorescence intensity increased in ChREBPα-LKO cultured Huh7 human hepatoma cells but decreased with Ad-ChREBPα overexpression. This demonstrated that ChREBPα deficiency reduced the activity of PPARα, an agonist-dependent nuclear receptor that activates hepatic FAO genes. In summary, our study revealed that ChREBPα is both necessary and sufficient for promoting PPARα-mediated FAO in hepatocytes. Thus, targeting ChREBPα may serve as a novel avenue to prevent NAFLD.

Inhibiting Local Brain Metabolism of Ethanol in the Central Nucleus of The Amygdala Blunts Sympathoexcitatory Responses Induced by Ethanol in Sprague Dawley Rats

D. Simet, G. Miodonski, A.D. Chapp, Q.H. Chen.

Department of Kinesiology and Integrative Physiology, Michigan Technological University

Binge alcohol consumption elicits robust sympathoexcitation and excitatory neuronal output. However, the central mechanism that mediates these effects remains elusive. We hypothesized that local brain metabolism of ethanol to acetic acid/acetate in the central nucleus of the amygdala (CeA) would drive in vivo sympathetic nerve activity (SNA) through activation of N-methyl-D-aspartate receptors (NMDAR). Furthermore, inhibiting local CeA ethanol metabolizing enzymes or NMDAR antagonists would blunt the sympathoexcitatory responses elicited by either ethanol or acetate. We demonstrate that in Sprague Dawley rats, local brain metabolism of ethanol in the CeA to acetic acid/acetate elicits sympathoexcitatory responses in vivo through activation of NMDAR. Alcohol dehydrogenase or aldehyde dehydrogenase inhibition using fomepizole or cyanamide and NMDAR antagonism using AP5 or memantine blunted the effects of ethanol and acetate, respectively. CeA microinjected fomepizole or cyanamide had no effect on altering baseline SNA, and cyanamide did not impact the sympathoexcitatory effect of acetate. These findings suggest that within the CeA, ethanol induced sympathoexcitatory response through local brain metabolism, which generates acetic acid/acetate leading to activation of local NMDAR. Understanding potential active metabolites of ethanol and their mechanism of action may be beneficial for reducing alcohol use disorder and its cardiovascular sequelae.

Effects Of Inspiratory Muscle Strength Training on Metabolic and Cardiovascular Responses to a Glucose Challenge

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Purpose: Inspiratory muscle strength training (IMST) has been shown to improve respiratory and cardiovascular health after chronic training. However, less is known about the acute effects of IMST, particularly with metabolic and cardiovascular responses to an oral glucose tolerance test (OGTT). Methods: Participants (n=12, 67% female) aged 20-35 years completed three randomized laboratory visits during which they completed either no training (control), or a single bout of IMST with resistance at either 15% or 75% of their maximal inspiratory pressure, before an OGTT. First, participants' baseline blood glucose, blood pressure, heart rate, and brachial artery blood flow were measured with subjects fasted and following a minimum of 5 minutes of supine rest. Next, 30 breaths of IMST were performed prior to glucose ingestion. Measurements were repeated at 15, 30, 45, 60, and 90 minutes post-glucose consumption.

Results: Heart rate, mean arterial pressure, and brachial artery blood flow were not different between visits ($P > 0.05$). Baseline blood glucose was not different for 15% and 75% IMST visits relative to control ($P=0.13$ and $P=0.37$, respectively). Similarly, peak blood glucose ($P=0.42$ and $P=0.75$, respectively) and glucose area under the curve during the OGTT ($P=0.87$ and $P=0.54$, respectively) were not significantly different from control, yet the glucose peak tended to occur approximately 15 minutes later during the 75% visit. The overall change from baseline blood glucose to the 90-minute timepoint was significantly increased from control to 75% training ($P=0.049$); e.g., blood glucose took longer to return to baseline when the glucose challenge was preceded with high intensity IMST.

Conclusion: At the 75% IMST visit, blood glucose increased more gradually and returned to baseline more slowly relative to control. These findings suggest that preceding a glucose challenge with a bout of high intensity IMST may facilitate a greater degree of glycemic control. From a clinical standpoint, a better understanding of the acute metabolic effects of IMST is important to determine the feasibility of implementation in patient populations. Further investigation is also warranted to better understand the chronic metabolic effects of this training.

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Comparison of Vascular Anatomy, Strain Patterns, and Ultimate Tensile Strength Across Cadaveric Achilles Tendons

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PURPOSE: The Achilles tendon (AT) is one of the largest and strongest tendons within the human body, yet it is one of the most common tendons to rupture. The purpose of this study is to determine the limiting factor of ultimate tensile strength (UTS) in the AT using cadaveric tissue. Previous research suggests that tendon failure may be related to hypovascularity and arterial anatomy within the midsection. This area is perfused by the smaller fibular artery, whereas the proximal and distal sections are fed by the larger posterior tibial artery. The present study aims to relate vascular anatomy and AT dimensions to UTS and strain patterns across the tendon.

METHODS: Ten preserved cadaveric (age 51–104y.o.) ATs were harvested, and posterior tibial and fibular arterial diameters were measured. To investigate the strain pattern, tendons were dyed in methylene blue and speckled in a random pattern using white paint. Once clamped into a load frame, tendons were pulled at a rate of 5 mm/min and a digital image correlation (DIC) camera and software were used to track each painted point on the tendon. The tendons were then pulled until rupture to determine UTS and assess strain patterns across different regions of the tendon.

RESULTS: Qualitatively, strain patterns differed across the various regions of the tendon, particularly for the sections served by different blood vessels. Greater UTS tended to correlate with a larger fibular artery diameter ($R = 0.87$). Similarly, a larger posterior tibial artery was associated with a greater UTS ($R = 0.82$).

CONCLUSIONS: The findings of our study suggest heterogeneity in strain patterns in distinct vascular regions of the human AT. In addition, diameter of the fibular and posterior tibial arteries was related to the overall strength of the AT. This may be due to a greater supply of oxygen and nutrients to living tissue, and future studies might investigate strain patterns of living human subjects in relation to blood flow. In the clinical context, a better understanding of the biomechanical properties of this tendon, in addition to any potential predictors of rupture, may better inform diagnostic or rehabilitation practices.

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Influence of Ovarian Hormones on proBDNF Levels in the Rostral Ventrolateral Medulla: Influences Related to Neuronal Plasticity and Sympathetic Control of Blood Pressure

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Rates of cardiovascular disease (CVD) are lower in females of reproductive age compared to age-matched males. However, the onset of menopause marks a dramatic rise in the incidence of CVD in females. Therefore, the presence of ovarian hormones may be cardioprotective, possibly due to actions at ovarian hormone receptors in the brain. In the brainstem, the rostral ventrolateral medulla (RVLM) influences the cardiovascular system via its direct impact on blood pressure. In addition to receptors for ovarian hormones, the RVLM also contains receptors for brain-derived neurotrophic factor (BDNF), a key neurotrophin. BDNF in its pro form (proBDNF) can decrease neuronal excitability via structural changes and could be responsible for the "cardioprotective" effects observed in females of reproductive age. We hypothesized that the presence of ovarian hormones maintains proBDNF levels in the RVLM, minimizing activation of the RVLM, thereby conferring cardioprotection.

Four-week-old female Sprague-Dawley rats received ovariectomy (OVX) or sham surgery (n=5 and n=4, respectively). Rats were sacrificed at 16 weeks of age and the hindbrain was cut into 80µm sections from which the RVLM was isolated by tissue punches. Punches were pooled into 4 discrete rostrocaudal subregions and western blotting was performed to determine proBDNF levels in the RVLM relative to the loading control GAPDH.

Preliminary results suggest that the average proBDNF/GAPDH ratio is higher in the RVLM of sham versus OVX females at all rostrocaudal levels; however, this difference did not reach significance ($p=0.169$, main effect). There is no significant rostrocaudal variation in proBDNF/GAPDH ratios ($p=0.598$, main effect), and there is no significant interaction between main effects ($p=0.687$). These results suggest that the presence of ovarian hormones may maintain proBDNF expression in the RVLM; however, increasing the low sample sizes will provide more definitive conclusions. Future studies examining the influence of ovarian hormones on expression of (mature) mBDNF levels could also address potential differences in the cleavage of proBDNF to mBDNF. Our studies will illuminate the relationship between ovarian hormones and cardioprotection via the RVLM, thus providing insight into sex differences in CVD. (R01-HL161233)

S100b Modulates Purinergic Enteric Neuron and Glial Activity Following Inflammation

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Aims: S100B is a quintessential enteric glial protein; however, its relevance to ENS function in health and disease remains poorly understood. We tested the hypothesis that glial S100B is altered by inflammation and that impairing S100B synthesis disrupts ENS activity.

Methods: Inflammation was studied using the 2,4-dinitrobenzene sulfonic acid (DNBS) colitis model in male and female mice. S100B content was measured by ELISA in Longitudinal Muscle-Myenteric Plexus (LMMP) tissue and supernatants during peak colitis and following resolution (7 days). Ca2+ imaging in Wnt1CreGCaMP5g-tdTom mice was used to study enteric neuron and glial evoked by the purine. S100B production was modulated in vitro with the S100B mRNA inhibitor arundic acid (AA).

Results: Tissue levels of S100B levels increased in LMMP at 7 days post-DNBS while the amount of S100B in supernatants decreased by 83% at 72h and 87% at 7 days. Inflammation did not change the number of myenteric glia responsive to ADP, but the magnitude of glial responses decreased by 60% following DNBS. Blocking glial S100B synthesis with AA did not affect myenteric glial activity in preparations from healthy animals, but treatment with AA reduced Ca2+ responses in male neurons. In contrast, AA had a major suppressive effect on glial and neuron activity following DMNS in males with a reduced percentage of responsive glial cells and neurons as compared to DNBS alone or controls. In females, impairing glial S100B production restored the number of responsive myenteric glia and neurons following DNBS to control levels.

Conclusions: Myenteric glial S100B is increased in LMMP post-inflammation. Blocking glial S100B production decrease glial and neuronal responsiveness in males while seems to restore female ENS activity DNBS-induced. Given the differential effects of AA on ENS excitability, S100B may play an important role in regulating ENS excitability in health and contribute to sex-related neuroplasticity following inflammation.

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Neuromodulation Of Adipocyte Activity in Perivascular Adipose Tissue in Healthy Mice

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While a positive relationship between blood pressure and cardiovascular disease risk is well established, the factors contributing to dysregulated blood pressure (BP) are not fully understood. Perivascular adipose tissue (PVAT) has emerged as a potential regulator of BP by releasing anticontractile factors. The production of these factors from adipocytes is driven by norepinephrine (NE), a sympathetic neurotransmitter. However, the source of this NE has yet to be determined and may derive from neural innervation, among others. This study examined neuromodulation of adipocyte activity in mesenteric (mPVAT), aortic (aPVAT), and subcutaneous fat (sc) in healthy male and female mice aged 8-12 weeks. Immunostaining with neuronal and vasculature markers in adipose tissue from wild-type mice was performed to establish physical interaction between nerves and adipocytes (n=3 region/sex). Neural regulation of adipocyte activity was assessed by measuring live-cell calcium responses in adipose tissue from transgenic mice expressing a genetically encoded calcium indicator in adipocytes (125-350 cells/group) to stimulation with a parasympathomimetic (10uM, bath application), as well as direct activation of nerve fibers by electrical field stimulation (EFS; +100V, 0.1ms, 10 Hz). We found that innervation in adipose tissue ran primarily adjacent to the larger blood vessels within the tissue, rather than radiating throughout. Both the parasympathomimetic and EFS induced minimal adipocyte responses (parasympathetic - female: 0.36±0.34, 0.16±0.15, 0.14±0.06 dF/F0, male: 0.18±0.09, 0.15±0.17, 0.11±0.07 dF/F0 in aPVAT, mPVAT, sc, respectively; EFS - female: 0.29±0.18, 0.14±0.03, 0.14±0.06 dF/F0, male: 0.21±0.19, 0.14±0.07, 0.10±0.02 dF/F0 in aPVAT, mPVAT, sc, respectively). Stimulation with NE induced large responses (female: 0.91±0.73, 1.15±0.73, 1.45±0.9 dF/F0; male: 0.75±0.57, 1.01±0.78, 0.73±0.53 dF/F0 in aPVAT, mPVAT, sc, respectively). These findings together suggest that, while PVAT is innervated, this innervation does not functionally regulate adipocyte activity, lending further support to the idea that autocrine signaling, mediated by adipocyte uptake and release of NE, is a primary regulator of adipocyte activity within PVAT.

Measuring Urine Concentration Capacity and Luminal Na in live Mice By Intravital Multi-Photon Microscopy

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Multiphoton (MP) microscopy of live animals is a useful tool for visualizing the structure and function of the kidney cortex with intact regulatory systems. However, measuring and quantifying dynamic changes in urine concentration capacity and luminal Na in distal tubules have not been done by intravital MP microscopy. We hypothesize that intravital MP microscopy can be used to perform dynamic measurements of sodium and urine concentrating capacity in the nephron in vivo. Male C57BL/6 mice were anesthetized with isoflurane and canulated through the left carotid artery. Tetramethylrhodamine-Dextran (TMR-Dextran 10,000 M.W., which filters freely and is not reabsorbed) and CoroNa Green, a Na ion indicator, were injected as a bolus. We exposed the left kidney and imaged distal tubules using MP microscopy at 850 nm excitation while acquiring emission at >580 nm (TMR-Dextran) and 525/25 nm (CoroNa Green). After obtaining baseline measurements, we injected a timed bolus of furosemide (0.5 mg/kg) to inhibit the Na-K-2Cl cotransporter (NKCC2) and rapidly decrease urine concentration. Given that NKCC2-mediated salt reabsorption is necessary to establish the interstitial concentration gradient, we predicted that furosemide would cause a rapid dilution of dextran and increase sodium concentration in distal tubules. 5 minutes after furosemide treatment, we observed a 33±7% ($p<0.05$) decrease in TMR-Dextran fluorescence intensity (FI) in distal tubules, which further decreased by 55±19% and plateaued after 20 min (n=10 mice). Changes in flow rate and concentrating capacity affect the CoroNa Green FI in distal tubules, independently of Na concentration. Therefore, we ratioed changes in CoroNa Green FI over those of TMR-Dextran. We found that furosemide increased the CoroNa Green/dextran ratio FI in the distal tubules by 42±18% at 5 minutes, which further increased to 131±25% after 20 minutes ($p<0.05$). Time controls after saline injection showed no effect on TMR-dextran nor CoroNa Green/dextran FI (n=5). These results indicate that we were able to effectively measure the changes in sodium and urine concentration capacity after furosemide treatment in vivo using intravital MP. Future experiments will focus on the effect of other diuretics, salt diets, and hydration status on renal tubular dynamics.

cAMP Stimulated NKCC2 Phosphorylation at Thr-96,101 Is In Part Independent From SPAK: A Role For TNIK

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Abnormally enhanced NaCl reabsorption by the thick ascending limb of the loop of Henle (TAL) contributes to the development of salt-sensitivity. NaCl reabsorption by the TAL is mediated by the apical Na/K/2Cl cotransporter NKCC2. NKCC2 activity can be stimulated by phosphorylation at Thr-96,101 by upstream kinases SPAK or OSR1. We found that Thr-96,101 phosphorylation is enhanced in TALs of Dahl Salt Sensitive rats (Dahl SS) on normal or high salt diet. Genetic deletion of SPAK in Dahl SS lowers NKCC2 phosphorylation by 40% and blunts salt-sensitive hypertension but does not completely restore these to baseline. Other kinases may be involved in NKCC2 phosphorylation. We identified TNIK (Traf2 and NCK interacting kinase) as a kinase that binds and phosphorylates Thr-96,101 in NKCC2 in rats and mice. In addition, we and others have reported that cAMP is a potent stimulus for NKCC2 Thr-96,101 phosphorylation. We hypothesize that TNIK is in part responsible for cAMP-stimulated NKCC2 phosphorylation at Thr-96,101. First, we tested the TNIK inhibitor NCB-0846 to decrease baseline NKCC2 phosphorylation in Dahl SS rats. Treating TALs from Dahl SS with NCB-0846 (0.1 μM) for 25 min decreased NKCC2 Thr-96,101 phosphorylation by 21 ± 2% compared to the vehicle group ($p<0.0001$, n=3). Next, we measured NKCC2 phosphorylation in rats with genetic deletion of SPAK in a Dahl SS background. In SPAK KO rats, the cAMP analogue db-cAMP (500 μM) increased NKCC2 phosphorylation at Thr-96,101 by 626 ± 46% ($p<0.0001$, n=3) and the TNIK inhibitor NCB-0846, blunted cAMP-stimulated NKCC2 phosphorylation by 56 ± 4.3% ($p=0.0013$, n=3). These data indicate that in the absence of SPAK, TNIK mediates cAMP-stimulated NKCC2 phosphorylation at Thr-96,101. To further support this, we studied TALs from whole animal TNIK knock-out mice (TNIK KO). db-cAMP (500 μM) increased NKCC2 phosphorylation by 1330 ± 268% in wild-type mice ($p<0.01$) whereas cAMP-stimulated NKCC2 phosphorylation was blunted by 49 ± 15% in TNIK KO TALs ($p<0.05$, n=3). We conclude that enhanced NKCC2 phosphorylation at baseline in Dahl SS TALs is in part caused by TNIK and that cAMP-stimulated NKCC2 Thr-96,101 phosphorylation in TALs is in part independent from SPAK and involves TNIK.

Enhancing Learning Opportunities in Laboratory Science Using Virtual Reality Lessons: A Use Case

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Animal dissections are a common approach to teaching anatomy and physiology, but they are costly, pose safety risks, and raise ethical concerns. Alternatives like computer simulations and synthetic specimens have been explored, but they lack the realism of actual dissections. Virtual reality (VR) technology provides a promising solution by immersing learners in a virtual environment that closely mimics real-life dissections and allows for skill development and feedback. VR also removes ethical and emotional concerns associated with dissections and enhances learning opportunities. To explore the effectiveness of VR in anatomy and physiology education, we surveyed students (n=21) taking PSL 311L who performed both a VR frog dissection and an in-person dissection, and provided feedback through a post-survey. While all participants thought VR was not a perfect replacement for in-person dissections, 80% of participants were of the opinion that animal dissections were still a necessary part of a science laboratory course. While student comments were mostly positive, 43% of participants were even more "pro" live dissections as it was more exciting and felt more informative. By contrast 25% of participants felt live dissections were unnecessary if there were good alternative choices as it made them more comfortable and less squeamish. A common theme by participants was their perception that VR was a comfortable alternative for those who may be reluctant to live dissections or as a way to prepare for future dissections. Overall, our study highlights the potential of VR to address the limitations of traditional dissection methods and the need for further research to explore the effectiveness of VR technology in achieving anatomy and physiology education learning outcomes. In this study we are hoping to encourage discussion around the utility of alternate technologies to enhance learning opportunities for students in laboratory or clinical sciences.

Promoting Physical Activity in the Rural and Medically Underserved Upper Peninsula of Michigan

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Physical inactivity poses a major public health problem as 80% of U.S. adults do not meet the current physical activity guidelines. Further, physical activity levels are lower in rural areas such as the Upper Peninsula of Michigan, which are often also medically underserved. The beneficial effects of physical activity remain underestimated and underutilized by the medical community, policy makers, and public at large. The purpose of this community outreach project was to implement an Exercise is Medicine® on Campus (EIM-OC) program at Michigan Technological University to provide physical activity resources to the campus and broader community. A team of students, faculty, and fitness professionals: 1) promoted physical activity through a widespread media campaign (i.e., website, social media, radio, newspaper, TV, public town hall) and 2) delivered over 300 virtual home-based workouts to community members using several platforms (i.e., Zoom, Facebook Live, YouTube, TV). Together, these efforts highlight the extent to which EIM-OC bolstered physical activity infrastructure for our rural and medically underserved region. Current efforts of the program include establishing physical activity as a vital sign for health during patient exams in the student health clinic on campus and distributing an exercise DVD to members of the community. Physical activity is a robust form of medicine to help prevent and treat both chronic and infectious disease. For substantial health benefits adults of all ages should engage in at least 150 min of moderate-to-vigorous intensity physical activity each week (~20 min/day) and limit time spent sitting. Importantly, any amount of activity, even below the ideal range, provides health benefits. As future leaders in health science and healthcare, we urge MPS students and trainees to help promote and facilitate physical activity in their communities.

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Teaching K-12 Students Using Jenga! The Impact of Health Behaviors on Community Wellbeing and Resilience

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As society continues to move forward from the COVID-19 pandemic, outreach with K-12 schools is: 1) critical for reestablishing connections with students and teachers and 2) generating interest in health-focused science, technology, engineering, and math (H-STEM) careers. The Department of Kinesiology and Integrative Physiology at Michigan Technological University leveraged the Michigan-Indiana Physiology Understanding Week (MI-PhUn) and National Rural Health Day events to organize a health science-based outreach visit with local schools. Graduate students met with middle and high school students and presented a hands-on activity using the game Jenga to demonstrate the links between health behaviors, diseases, and community health. For the activity, students worked together in small teams (e.g., 4-8 students) and were given two Jenga towers (Tower A and Tower B), each representing a community of individuals. The goal of the activity was to keep both towers standing as strong as possible. Teams were presented with 12 strips of paper labeled with either a 'health behavior' (e.g., physical activity, diet, body weight, smoking) or a 'disease' (e.g., heart disease, diabetes, influenza, COVID-19) and accompanying instructions on whether to add or remove blocks from each tower. When presented with a health behavior, students added blocks to Tower A representing positive health behaviors (e.g., not smoking) and removed blocks from Tower B representing negative health behaviors (e.g., smoking). When a disease was presented, students removed blocks from both towers, but fewer blocks were removed from Tower A compared to Tower B, demonstrating relatively lower diseases rates in this community. As the activity progressed, Tower A retained more blocks than Tower B. For the grand finale, students observed that with the greater strength and stability of Tower A it was better equipped to withstand a natural disaster such an earthquake that was simulated by students shaking the table that held both towers. At the end of the activity students were able to describe the connections between positive health behaviors and lower rates of disease, and how taken together, these impact overall community health and resilience. This activity was delivered to 15 different science classes and 247 students ranging from 6-12th grade. The activity was well received by students and teachers and aligned with educational standards that focus on three-dimensional learning. The inclusion of graduate students as guest instructors improved their understanding of public health promotion and provided them with practice communicating science to a lay audience. Importantly, connecting with K-12 schools to increase interest in H-STEM is a critical step for helping to address the current healthcare workforce shortage.

Exercise Is Medicine® On Campus: A National Analysis and Assessment of Community Impact

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Exercise is Medicine® on Campus (EIM-OC) calls upon colleges and universities to promote and increase physical activity. The distribution of EIM-OC programs across the U.S. and community impact have yet to be described in detail.

Purpose: To perform a national analysis of the recognized EIM-OC programs in the U.S. and their community impact.

Methods: Recognized EIM-OC programs were analyzed with respect to recognition level (gold, silver, bronze), school population, presence of a medical school on campus, ACSM region, and state. County level population density (i.e., metro or non-metro county), physical inactivity prevalence, and presence of EIM-OC program were recorded. Data were obtained from the EIM-OC, U.S. Department of Agriculture, and Robert Wood Johnson Foundation websites. The number of EIM-OC programs in each ACSM region was normalized to number of states in that region.

Results: Of the 131 recognized programs, there were 59 gold, 53 silver, and 19 bronze. School populations for gold (23,338), silver (15,688), and bronze (10,779) programs differed ($P<0.01$). The frequency of medical schools present at gold (40%), silver (20%), and bronze (17%) level programs differed ($p<0.05$). The Midwest and Southeast chapters had the highest frequency of total and gold EIM-OC programs. Thirty-five states had at least one EIM-OC program, with 26 states having at least one gold program. Ninety-two percent of EIM-OC programs and 90% of gold programs were in metro counties (i.e., ≥50,000 people). Compared to those counties with an EIM-OC program, physical inactivity prevalence was higher in counties without an EIM-OC program (26±4 vs 30±6 %, $P<0.01$).

Conclusions: Universities earning EIM-OC gold level status were mostly large flagship and/or research focused institutions with 40% also having a medical school. Midwest and Southeast ACSM regions ranked at the top for total and gold level EIM-OC programs. Two-thirds of states had an EIM-OC program with most gold programs in the eastern half of the country. Promotion of physical activity at smaller universities in non-metro counties is needed because physical activity levels are lower among rural residents and counties lacking an EIM-OC program. These findings may direct future implementation of EIM-OC programs at the campus, county, state, regional and/or national level.

Oaks to Arteries: The Physiology Core Concept of Flow Down Gradients Supports Transfer of Student Reasoning

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The Physiology Core Concept of flow down gradients is a major concept in physiology as pressure gradients are the key driving force for the bulk flow of fluids in biology. However, students struggle to understand this principle is foundational to the mechanism governing bulk flow across diverse physiological systems (e.g., blood flow, phloem sap flow). In this study, we explore if bulk flow items that differ in context (i.e., taxa, amount of scientific terminology, living or non-living system) or which aspect of the pressure gradient is kept constant (i.e., starting pressure or pressure gradient) influences undergraduate students' reasoning. We found item context did not impact the type of reasoning students used. However, students were more likely to use the Physiology Core Concept of "flow down [pressure] gradients" when the pressure gradient was kept constant and less likely to use this concept when the starting pressure was kept constant. We also investigated if item context or which aspect of the pressure gradient is kept constant impacted how consistent students were in the type of reasoning they used across two bulk flow items on the same homework. We found most students were consistent across item contexts (76%) and aspects of the pressure gradient kept constant (70%). Students who reasoned using "flow down gradients" on the first item were the most consistent (86, 89%) while students using "pressures indicate (but don't cause) flow" were the least consistent (43, 34%). Students who are less consistent know pressure is somehow involved or indicative of fluid flow but do not have a firm grasp of the concept of a pressure gradient as the driving force for fluid flow. These findings are the first empirical evidence to support the claim that using Physiology Core Concept reasoning supports transfer of knowledge across different physiological systems.

Metabolic Stress Induces Rnf8-Mediated Ubiquitination and Degradation of Chrebpa During Diet-Induced Nash

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Nonalcoholic steatohepatitis (NASH), the progressive form of nonalcoholic fatty liver disease (NAFLD), is characterized by liver steatosis, inflammation and fibrosis. Carbohydrate response element binding protein (ChREBP) is a transcription factor regulating genes for glycolysis and lipogenesis in liver. Our unpublished data demonstrate that liver ChREBPalpha (ChREBPα) protein was markedly downregulated in mouse models of diet-induced NASH. However, the molecular pathways triggering the suppression of hepatic ChREBPα protein remains unclear. Here we investigated potential post-translational modifications that regulated the hepatic ChREBP protein turnover in the context of NASH. We discovered that combination of nutritional (saturated fatty acid palmitate) and inflammatory (TNFα) stresses induced the ChREBPαα degradation in cultured hepatocytes. Next, we identified the E3 ligase Ring-finger 8 (RNF8) as an E3 ligase is required for ChREBPα degradation induced by metabolic stress. Furthermore, a ChREBPα phosphorylation mutant (T311A, a putative phosphorylation site for JNK/p38) was resistant to the RNF8-mediated degradation. In summary, our study revealed a novel RNF8-dependent ubiquitination pathway for degrading hepatocyte ChREBPα in response to metabolic stresses during diet-induced NASH.

Activation of Hepatocyte E4BP4-OPN Axis Induces Liver Fibrosis in Non-alcoholic Steatohepatitis

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As the most common chronic liver disease, non-alcoholic fatty liver disease (NAFLD) may progress from simple steatosis to non-alcoholic steatohepatitis (NASH) with liver injury, inflammation, and fibrosis. Persistent activation of hepatic stellate cells (HSCs) is the key driver of liver fibrosis during this disease progression towards liver fibrosis. Understanding of molecular mechanisms of HSCs activation is critical for identifying novel avenues for the prevention and treatment of NAFLD-related liver fibrosis.

We previously reported that E4 promoter-binding protein 4 (E4bp4) is induced in the liver of diet-induced NASH mice. However, the role of E4BP4 in the pathogenesis of NASH-diet-induced liver fibrosis remains unknown.

In this study, we detected a significant increase of hepatic E4bp4 in both CCI4 and NASH diet-induced fibrosis models. Meanwhile, liver-specific E4bp4 knockout (E4bp4-LKO) protected the mice from NASH diet-induced liver injury and fibrosis. E4bp4 deficiency in hepatocytes attenuated activation of HSCs. Conversely, E4bp4 overexpression in hepatocytes promoted HSCs activation. Furthermore, RNA-seq analysis revealed decreased expression of the secreted profibrogenic gene, Osteopontin (Opn), in the liver of NASH diet-fed E4bp4-LKO mice. Hepatic overexpression of E4bp4 increased both the expression and secretion of Opn in hepatocytes, indicative of a positive correlation between hepatic E4bp4 expression and stellate cells activation. Mechanistically, our data support that hepatic E4bp4 promotes Opn expression and secretion by enhancing the stability of the Opn transcriptional activator YAP via protein-protein interaction.

In summary, we identified a protective role of hepatic E4bp4 deficiency against NASH diet-induced liver fibrosis and uncovered Opn as a potential profibrotic factor in promoting E4bp4-dependent HSCs activation through a YAP-dependent way.

Sex Differences in Calcium Tolerance of Isolated Cardiac Mitochondria

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Calcium overload constitutes a significant factor in the development of numerous pathological or disease states. Since the 1950's, heart failure has been the leading cause of death amongst Americans. However, women are at a lower risk of heart disease until the onset of menopause as estrogen and progesterone exhibit cardioprotective effects. These sex hormones have no known direct association with mitochondrial calcium handling proteins such as the Na+/Ca2+/Li+ exchanger (NCLX) and the mitochondrial calcium uniporter (MCU); therefore, there exists a large gap in knowledge regarding the mechanisms behind this protection. To address this gap, we conducted a sex as a biological variable (SABV) study to define differences in calcium sensitivity between female and male 10–12-week-old Sprague Dawley rats. Calcium tolerance ranges in both sexes were tested from concentrations of 5-20 μM CaCl2 in the presence of respiration buffer supplemented with 20 mM final NaCl. Cardiac mitochondria isolated from female rat hearts have higher state 2 and 3 respiration rates across all substrate and calcium conditions when compared to male mitochondria. Transiently elevated oxygen consumption rates induced by the CaCl2 bolus challenges were similar between males and females. In addition, calcium stimulated leak state respiration was higher in females relative to males, suggesting that females can cycle calcium at quicker rates. These data strongly point to the notion that females have higher calcium handling and tolerance due to the differing expression of NCLX and MCU.

Endothelial Cell Specific Adam10 Activation Regulates Pathological Retinal Neovascularization

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Background: Retinal neovascularization leads to various pathological conditions related to vision diminution, such as retinopathy of prematurity (ROP), diabetic retinopathy (DR), and age-related macular degeneration (AMD). Although anti-VEGF therapy for retinal neovascularization treatment is successful, but it also co-exists with various side effects. Various studies have shown that deletion of A Disintegrin and metalloproteinase domain-containing protein (ADAM10) is embryonically lethal and results in organ-specific vascular defects, but little is known regarding its role in proliferative retinopathies.

Methods: We have used human retinal microvascular endothelial cells (HRMVECs) and Oxygen induced retinopathy (OIR) as models to understand the role of ADAM10 in proliferative/ischemic retinopathies. To comprehend the role of ADAM10 in retinal neovascularization, endothelial cell-specific ADAM10 conditional knock-out mice were generated (ADAM10iΔEC). At P11 & P12, tamoxifen injections (i/p) were given to induce Cre recombinase for endothelial-specific deletion of ADAM10 in these mice. At P13, P15, and P17, eyes were enucleated, and retinas were isolated and evaluated for retinal neovascularization, avascular area, tip cell formation, and proliferation. In addition, we used 3' mRNA sequencing human phosphor-RTKs and human Angiogenesis Proteome Profiler assays to assess ADAM10 mediated angiogenic signaling involved in HRMVECs angiogenic events.

Results: We observed a significant reduction in retinal neovascularization in endothelial-specific ADAM10 knock-out mice (ADAM10iΔEC) compared to the C57BL/6 (WT) mice. We also observed that hypoxia-induced vascular leakage and edema were significantly reduced in ADAM10iΔEC mice compared to WT mice. Endothelial cell sprouting was also significantly decreased in ADAM10iΔEC mice. Our findings also emphasize that ADAM10-mediated retinal neovascularization is independent of notch signaling. Our sequencing data revealed that the depletion of ADAM10 results in the downregulation of various angiogenic genes, including EFNB2/ EphB2. Studies have shown that EFNB2/ EphB2 regulates developmental angiogenesis, but its role in pathological retinal neovascularization is not well reported. We observed downregulation of EphB2/EFNB2 in ADAM10iΔEC mice, which might suggest its probable regulation by ADAM10 in retinal neovascularization.

Conclusion: Our findings provide evidence that ADAM10 might be used as a therapeutic agent for retinal neovascularization.

Il-33 Cleaved by Neutrophil Proteases are More Potent Regulators of Human Retinal Microvascular Endothelial Cells Activation and Angiogenesis

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Background: Human interleukin-33 (IL-33) is a 270 amino acid protein belonging to IL-1 family cytokine with important roles in inflammatory diseases. Inflammatory proteases from neutrophils (Cathepsin G and Elastase), and mast cells (tryptase and chymase) regulate the activity of IL-33 by processing full-length IL-33 into mature forms. Despite recent advances on the role of IL-33 in allergic diseases, arthritis, cancer, and cardiovascular diseases, nothing is known regarding the role of these IL-33 mature forms in retinal endothelial cell signaling and angiogenesis.

Methods: Here, we first cloned the various mature forms of human IL-33, such as IL-3395-270, IL-3399-270, IL-33109-270, and IL-33112-270 into pET30a vector and expressed these mature IL-33 constructs in E.coli strain BL21(DE-3) and purified by immobilized metal affinity chromatography (IMAC). We next evaluated the role of these recombinant mature IL-33 proteins on human retinal microvascular endothelial cells (HRMVECs) proliferation, migration, tube formation and sprouting angiogenesis. We also investigated the role of these recombinant mature IL-33 proteins on various cellular signaling involved in retinal endothelial cell angiogenic events by 3'-mRNA sequencing and western blotting.

Results: We observed that these mature forms of IL-33 produced by inflammatory proteases are potent in inducing HRMVEC proliferation, migration, tube formation and sprouting angiogenesis. We also observed that these mature forms of IL-33 are more potent in inducing angiogenic signaling and endothelial cell activation. More specifically, IL-3399-270 produced by Cathepsin G (neutrophil protease) cleavage is more potent in inducing endothelial cell activation and angiogenesis.

Conclusion: Our study suggests that blockage or inhibition of IL-33 cleavage by neutrophil proteases could be useful to limit IL-33-regulated proliferative retinopathies.

Transcriptional Control of Mammary Gland Development by E2f5

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Characterization of transcriptional control is paramount to understanding the mechanisms that drive development. Using transcriptomics and genetically engineered mouse models, we previously identified E2F transcription factors as crucial regulators of mammary gland development. The E2F family of eight transcription factors includes canonical transcriptional activators E2F1-3a and repressors E2F3b-8. However, many E2Fs, including E2F5, exhibit mixed activator and repressor activity. Our prior data showed that E2F1 and 3 are key regulators of mammary outgrowth and involution. However, E2F5 has been understudied due to hydrocephaly and early lethality in the knockouts. Recently, our lab has found that conditional knockout of E2F5 in the mammary epithelium leads to defects in mammary gland outgrowth. Given that characterization of transcriptional control during mammary development is of critical importance, this necessitates follow-up studies defining the mechanistic role of E2F5. The current objective of this project is to identify genes directly regulated by E2F5 using CUT&RUN to further characterize the mechanism by which E2F5 regulates mammary gland development.

Hepatic Chrebpα Protects Against Both Diet and Chemical-Induced Liver Fibrosis by Blocking the Activation of Hepatic Stellate Cells

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As the most common chronic liver disease (25% in U.S. adults), non-alcoholic fatty liver disease (NAFLD) poses a serious health risk since approximately 20% of NAFLD patients may progress from simple steatosis to non-alcoholic steatohepatitis (NASH)/liver fibrosis, cirrhosis, and eventually liver failure/liver cancer. and other relatively rare conditions. So far, there are no FDA-approved drugs to slow or block NAFLD progression given the fact that the underlying mechanisms are still poorly understood. Our previously reported studies demonstrate that hepatic ChREBPα protects against the early stage of NAFLD: simple steatosis. However, its function in diet-induced NASH/liver fibrosis remains unclear. In this study, we showed that loss of hepatic Chrebpα promotes liver injury and fibrosis both in NASH diet and CCl4-injected mice. Adenoviral overexpression of ChREBPα in cultured hepatocytes inhibits the activation of hepatic stellate cells (HSCs) and dampens the response of primary mouse hepatocytes to the profibrogenic TGF-β treatment. Lastly, we detected elevated expression of the transcription factor E2F1 in the liver of CCl4-injected liver-specific Chrebpα knockout mice, suggesting that ChREBPα might reverse liver fibrosis via its inhibition of E2F1. In summary, hepatocyte ChREBPα protects against both diet and chemical induced-liver fibrosis through its inhibition of HSCs activation.

Exercise Augments Small Conductance Ca2+ -Activated Potassium Channel (Sk) Function in the Paraventricular Nucleus (PVN) Of Sprague Dawley Rats to Reduce Sympathetic Outflow

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Elevated sympathetic outflow is a key feature of cardiovascular disease (CVD) that worsens disease progression. Our lab has shown that SK channels expressed in the PVN play a crucial role in regulating neuronal activity and sympathetic outflow, and that SK channels become dysfunctional in rats fed a high salt diet. Exercise has been shown to be an effective treatment for reducing sympathoexcitation in CVD including hypertension and heart failure, but the underlying mechanisms are not fully understood. We hypothesized that aerobic exercise would upregulate SK channel function in the PVN to reduce sympathetic nerve activity (SNA). To test this, 5–6 week old Sprague Dawley rats were randomly divided into sedentary (SED) and exercise (EXT) two groups and fed a 0.4% NaCl normal salt diet. Following acclimation, EXT groups ran on a motorized treadmill 5 days/week for 8-10 weeks. Conscious blood pressure was measured weekly via tail plethysmography. After 8-10 weeks, animals were anesthetized and underwent in vivo surgery to record the renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) following PVN microinjection of the SK channel blocker, apamin (0.25mM, 100nL/unilateral). The data showed that the RSNA response to PVN apamin was significantly enhanced in EXT rats compared with SED rats (320.8 ± 174.6 % baseline, n=9 vs 184.8 ± 143.1 % baseline, n=9; p = 0.02). The corresponding ABP response to apamin was not significantly different in EXT rats compared with SED rats (20.40 ± 9.98 mmHg, n=9 vs 25.27 ± 9.97 mmHg, n=8; p = 0.1658). Our data indicates exercise enhances PVN SK channel function to reduce sympathetic outflow. This improvement of SK channel function may be one mechanism by which exercise reduces SNA in CVD including hypertension and heart failure.

PVN Sk Channel Blockade Alters Sympathetic Nerve Bursting Pattern in Angiotensin II-Infused Rats

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Sympathetic nerve activity (SNA) demonstrates rhythmic activity that arises from integration of signals from lung inflation afferents, baroreceptor afferents, and respiratory neurons in the brainstem that influence presympathetic neurons in the rostral ventrolateral medulla (RVLM). The paraventricular nucleus (PVN) is a prominent regulatory center for SNA and PVN neurons have axon projections to the RVLM. Blockade of small conductance calcium-activated potassium (SK) channels in the PVN significantly increases splanchnic and renal SNA. The aim of this study was to determine the influence of chronic AngII infusion on SNA firing patterns at rest and following PVN SK channel blockade with apamin. Experiments were performed in ventilated, male Sprague-Dawley control (Ctrl; n=5) rats, or rats infused with AngII (150 ng·kg−1·min−1) for 2 weeks (n=4). Power spectral density was calculated on 5-minute segments of SNA during baseline, and during the maximum response to apamin. Splanchnic and renal SNA spectral power in the 0-2Hz (low) frequency band was similar between Ctrl and AngII rats at baseline. PVN microinjection of apamin significantly ($p<0.05$) increased spectral power in the 0-2Hz band similarly in both groups. In contrast, baseline spectral power in the 5-7Hz (cardiac) frequency band was significantly higher in AngII rats compared to control for both splanchnic (Ctrl 10.4±2.3 vs. AngII 26.8±2.8%; $p<0.05$) and renal (Ctrl 19.9±3.8 vs. AngII 35.3±1.5%; $p<0.05$) SNA. Interestingly, PVN microinjection of apamin significantly ($p<0.05$) attenuated spectral power in the 5-7Hz band in the AngII group alone for splanchnic (Ctrl 9.3±2.8 vs. AngII 7.7±0.8%) and renal (Ctrl 12.3±4.7 vs. AngII 11.1±1.9%) SNA. In conclusion, baseline cardiac-related spectral power was greater in AngII rats compared to Ctrl likely reflecting increased input from baroreceptor afferents. PVN SK channel blockade shifts the SNA burst pattern in both Ctrl and AngII rats towards lower frequencies bursts known to have a greater influence on vascular tone.

Sympathetic Activity to the Heart is Increased in a Mouse Model of Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disorder. HCM is characterized by abnormally thick cardiac muscle and an increased risk of other potentially fatal conditions including arrhythmias and sudden cardiac death. Previous studies in humans demonstrate increased cardiac norepinephrine spillover. Similarly, myocardial beta-1 receptor (B1R) expression is decreased in the left ventricles (LV) in HCM, consistent with increased local norepinephrine levels. We have previously demonstrated that cardiac sympathetic tone is elevated in an alpha-tropomyosin mutant mouse model of HCM. The aim of this study is to further characterize cardiac and autonomic function in HCM mice. First, we recorded left ventricular pressure in male HCM and littermate wild-type (WT) control mice (n=5 mice each group) anesthetized with isoflurane (2% in O2). Heart rate (HR) was significantly ($p<0.05$) lower in HCM (438±22 beat/min) compared to WT (525±6 beat/min) mice. Similarly, dP/dt max was also significantly ($p<0.05$) reduced in HCM (5857±452 mmHg/s) compared to WT (7684±258 mmHg/s) mice. In contrast, end diastolic pressure was similar between HCM (5.8±0.7 mmHg) and WT (6.1±0.8 mmHg) mice. Next, we utilized western blot to measure protein expression in LV tissue from HCM and littermate WT mice. Results are expressed relative to WT mice (n=4 male mice in each group). B1R expression was significantly reduced in the left ventricle (LV) of HCM mice compared to WT littermate controls (HCM 60±1 vs. WT 100±4; $p<0.05$). Tyrosine hydroxylase (TH) is the rate limiting enzyme in the production of norepinephrine. TH protein expression (standardized to cardiac neuronal content with PGP9.5) was significantly higher in the LV of HCM mice compared to WT mice (HCM 135±15 vs. WT 100±1; $p<0.05$). In summary, anesthetized HCM mice demonstrate reduced cardiac contractility and heart rate. Furthermore, LV B1R expression is decreased, and LV TH expression is increased. In conclusion, our findings suggest that cardiac and autonomic abnormalities are consistent between HCM mice and humans allowing us to utilize mouse models to explore new treatment targets for HCM.

Determining the role of ERK1/2 in the development of diabetic cardiomyopathy

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Diabetes mellitus is a chronic metabolic disease with a hyperglycemic state. Without proper treatment, diabetic patients suffer damage to many organs, with cardiovascular complications being the main cause of death. Indeed, about 19~26% of diabetic patients develop cardiac dysfunction characterized by ventricular remodeling, myocardial stiffness, and eventual heart failure. Mitogen-activated protein kinases ERK1/2 have been shown to be involved in glucose and lipid metabolism, however, their role in the development of diabetic cardiomyopathy is not clear. In this study, we used U0126 to pharmacologically inhibit ERK1/2 activity in streptozocin (STZ)-induced diabetic mice for 6 weeks to determine the effects on cardiac function. We found out that consecutive injections of U0126 at a dose of 15 mg/kg/day for 7 days significantly reduced the phosphorylation of ERK1/2 in mice. Mice demonstrated hyperglycemia 14 days post STZ injection and continued maintaining a high glucose level during the 6 weeks period. Compared to the control mice, diabetic mice had significant reduction of body and heart weights, although the cross-sectional areas were increased. In summary, we established a diabetic model by STZ injection to induce hyperglycemia in mice. We will compare the effects of U0126 on cardiac remodeling and expression of disease markers at the end of this study.

Does the I148M Mutation in PNPLA3 Alter the Association Between Fatty Liver and Cardiovascular Disease Risk

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Increased sedentary lifestyle and greater access to high caloric foods has led to the obesity pandemic and its associated complications of non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD). A hallmark of these disorders is the accumulation of triacylglycerol (TAG) in non-adipocyte cells. While environmental factors, such as diet and exercise, are critical in determining risk of developing cardiometabolic disorders such as NAFLD and CVD, genetic factors are also known to play an important role. PNPLA3-I148M is the greatest genetic risk factor for NAFLD susceptibility. Paradoxically, patients that express PNPLA3-I148M display modest protection against coronary artery disease (CAD), even though NAFLD typically increases risk of CAD. In order to investigate how PNPLA3-I148M increases NAFLD susceptibility while mitigating risk of CAD we took whole body PNPLA3 knockout mice and over-expressed either human wild-type PNPLA3 (WT), human PNPLA3-I148M or a GFP control, using a liver specific adeno-associated virus. In agreement with others, our results demonstrate that under chow fed conditions mice expressing PNPLA3-I148M develop greater hepatosteatosis when compared to WT expressing mice. After 16-weeks on a fatty liver promoting diet (GAN-diet), high in fructose, cholesterol, and saturated fat, we discovered a trend for greater liver to bodyweight ratios and hepatic TAGs in mice expressing PNPLA3-I148M when compared to WT and GFP expressing mice. We detected no differences in insulin sensitivity, daily food consumption, energy expenditure, oxygen consumption, or respiratory exchange ratios suggesting that the changes in hepatic lipid accumulation were independent of differences in these metabolic parameters, between genotypes on matched diets. In-vivo imaging of hearts using 2D echocardiography showed no changes to cardiac function after 16-weeks of chow diet; however, the fatty liver diet led to changes in cardiac morphology of WT and I148M expressing mice. Our current results suggest that PNPLA3-I148M does not protect against the negative effects of a fatty liver promoting diet on cardiac health. Future work will investigate the metabolic pathways by which PNPLA3-I148M promotes non-alcoholic fatty liver disease as well as measures of atherosclerotic plaque formation to determine if it is a potential mechanism for how PNPLA3-I148M mediates protection against CAD.

Mutation of PKA and GRK Phosphorylation Sites on Beta 2 Adrenergic Receptor Impair its Stability

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Summary: Phosphorylation of β2 adrenergic receptor (β2AR) by PKA and GRK is critical for β2AR functionally coupling to downstream signaling proteins. In this study, we generated two β2AR mutant DNA constructs containing alanine substitution of either putative PKA phosphorylation sites (serines 261, 262, 345 and 346) or GRK phosphorylation sites (serines 355, 356 and 358), and compared receptor stability in a HEK293 cell culture model. We demonstrated that these serine to alanine substitutions led to significant loss of β2AR level at the plasma membrane under both resting and chronic isoproterenol stimulation conditions. Immunofluorescence staining showed that β2AR phosphorylation mutants had normal internalization but impaired ability of recycling to cell surface. Instead, they were targeted to lysosomes for degradation, which could be reversed by lysosome inhibitor chloroquine. Mechanistically, we showed that both of β2AR mutants had enhanced ubiquitination compared to wild type of β2AR, suggesting a functional interaction between receptor phosphorylation and ubiquitination. Together, our data suggest a novel role of PKA and GRK phosphorylation of β2AR in maintenance of β2AR stability.

Congratulations to all the participants who participated in the Physiology Trivia!

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