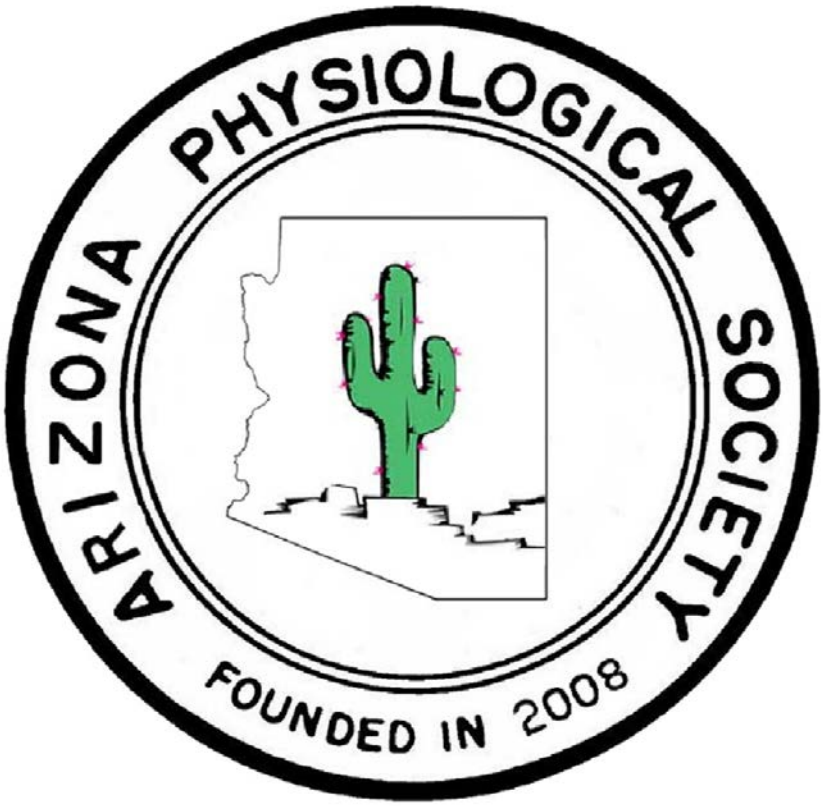
The Arizona Physiological Society



14th Annual Meeting

October 29-30, 2021

Midwestern University

Glendale, Arizona

Institutional Sponsors

We are extremely grateful for the institutional support we have received this year and in the past. Thank you so much for believing in our society's mission and providing the help we need to keep it alive.

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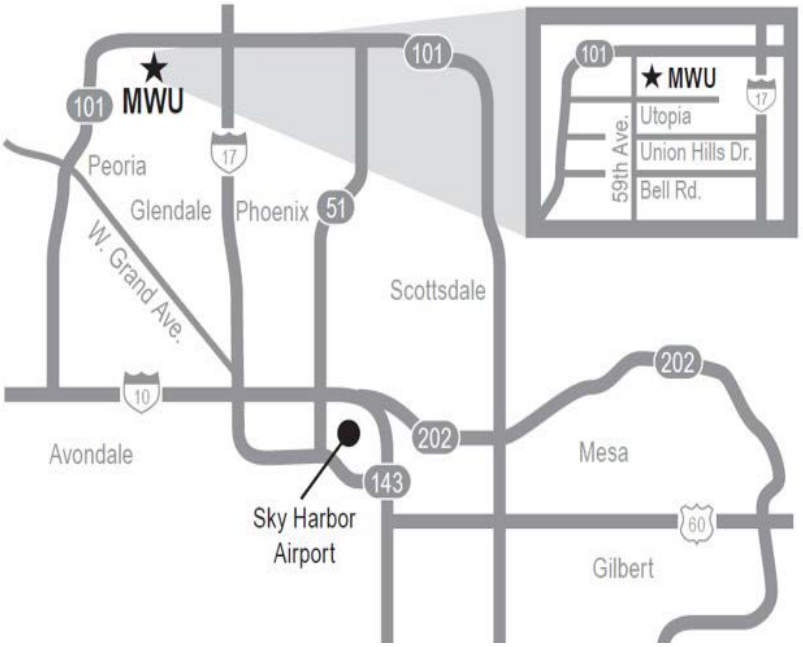

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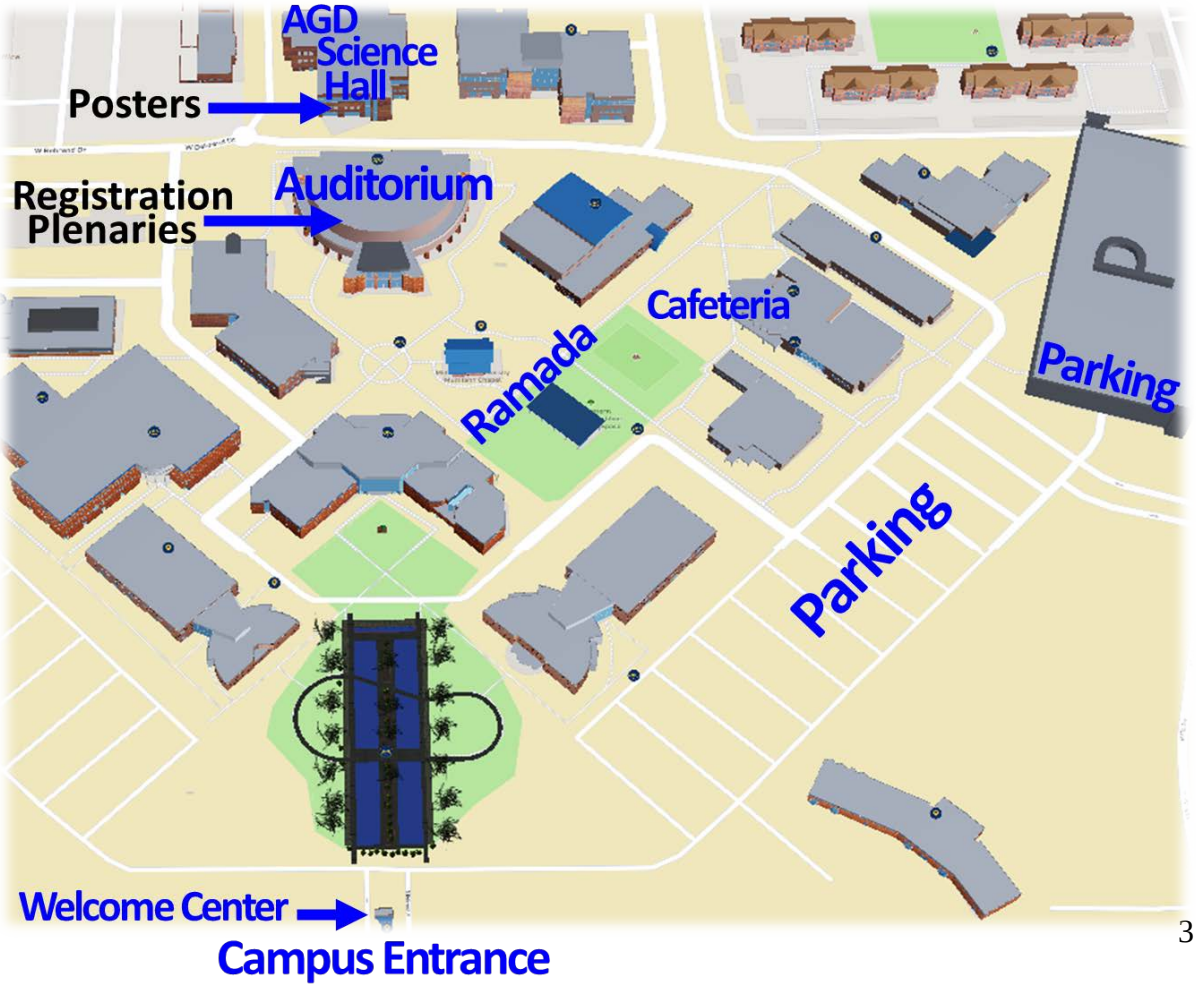
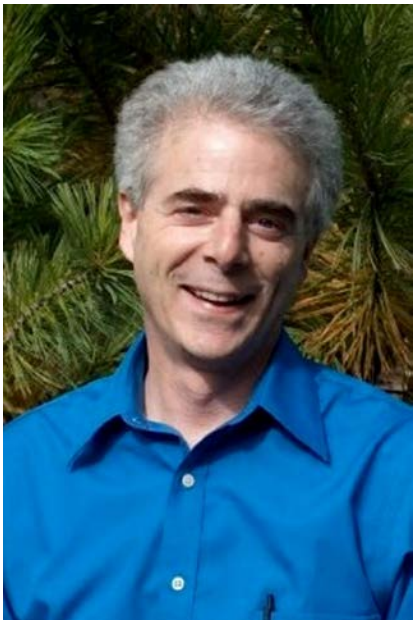
Midwestern University Campus Map



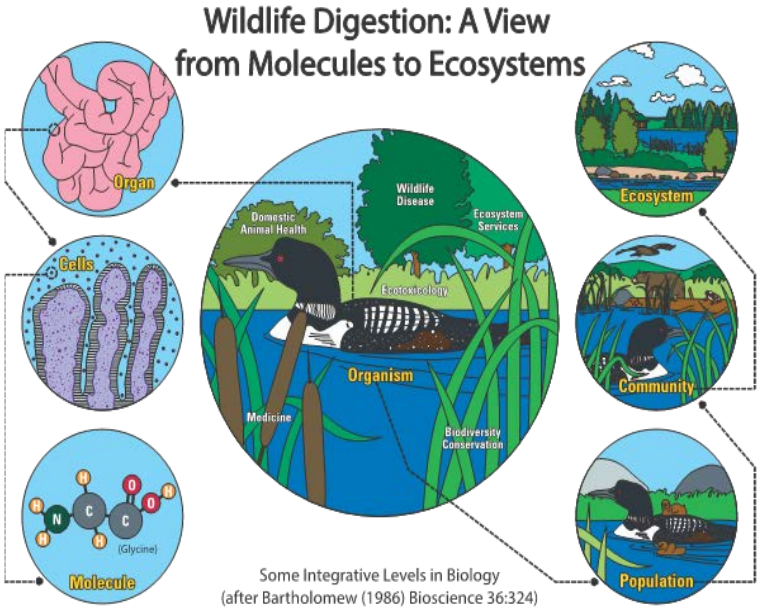
2021 Arizona Physiological Society Keynote Speaker

William H. Karasov, Ph. D.
University of Wisconsin, Dept. of Forest and Wildlife Ecology



Wildlife Digestion: A View from Molecules to Ecosystems

Digestive physiology links physiology to applications valued by society, such as understanding ecology and ecological toxicology and managing and conserving species. I illustrate this applied and integrative perspective with several case studies. The match between digestive features and diet provides evidence of tradeoffs that preclude doing well on all possible substrates with a single digestive design, and this influences ecological niche partitioning. But some birds, such as wild house sparrow (Passer domesticus) nestlings, are digestively very flexible. Their intestinal maltase activity and mRNA for intestinal maltase glucoamylase specifically and reversibly change when they switch among foods with different starch content. House sparrows, many other birds and bats absorb water-soluble monomers such as glucose mainly passively via tight junctions between enterocytes (i.e., paracellular absorption). Such species might be good models for studying this process, which is important biomedically for absorption of drugs or low molecular weight natural water-soluble toxins. Determining absorption of environmental contaminants is another important ecological application. Common loon (Gavia immer) chicks absorbed 83% of methyl mercury in fish meals, eliminate the mercury slowly, and consequently are predicted in the wild to bioaccumulate mercury to higher concentrations than in their foods. The quantitative details can be used to set regulatory levels for mercury that will protect wildlife.



2021 Arizona Distinguished Lecture

Dr. Steve Wright
University of Arizona, Department of Physiology

Maintaining a Positive Outlook: Mechanisms of Organic Cation Transport

The broad selectivity of the renal transport proteins, OCT2 and MATE1, allows them to work in concert to actively secrete many organic cations, including about 40% of prescribed drugs. However, that broad selectivity also makes these processes targets for unwanted drug-drug interactions, some of which result in marked changes in the pharmacokinetics of clearance of co-administered compounds. I will discuss current understanding of mechanisms of interaction of substrates and inhibitors with these transporters.

Dr. Wright received Bachelor's and Master's degrees at the University of California, Davis and a PhD in Marine Biology at the University of California, Irvine. After pursuing a postdoctoral fellowship with Dr. Ernest Wright in the Department of Physiology at the UCLA School of Medicine, he joined the faculty of the Department of Physiology in the College of Medicine at the University of Arizona in 1982 and has been Professor of Physiology since 1992 (and of Biochemistry and Molecular Biophysics since 2004). The focus of his research has been on mechanisms of organic electrolyte transport, primarily in the mammalian kidney. The emphasis in recent years has been on the kinetics, energetics and selectivity of organic cation transporters, particularly OCT2 and MATE1.

2021 AZPS ANNUAL MEETING – PROGRAM SCHEDULE

Note: All plenary sessions will take place in the Auditorium (#4). The poster session will take place in Dr. Arthur G. Dobbelaere Science Hall, Lab 150. Breakfast, lunch, and refreshments will be served in the Auditorium Lobby. Please refrain from bringing food into the Auditorium.

Friday, October 29th, 2021

1:00 PM **Registration (Auditorium #4)**
Poster Setup (AGD Science Hall, Lab 150)

1:45 – 2:00 PM **Welcome to the Meeting**

2:00 – 3:00 PM **Session 1: Tales of Neurophysiology – Part 1**

Chairs: Darien Hall, Ph.D., Grand Canyon University
Ricardo Gomez, Grand Canyon University

2:00 PM – **Tala Curry, College of Medicine-Phoenix, University of Arizona**

S1.1 Fibrillin-1 Mutation Accelerates Blood Brain Barrier Dysfunction and Cerebrovascular Aging, Leaving the Brain More Vulnerable to Traumatic Brain Injury

2:15 PM – **Sophia Koziol, AZCOM, Midwestern University**

S1.2 Effects of postnatal maturation on muscarinic acetylcholine receptor distribution in hypoglossal neurons

2:30 PM – **Jesse Jauhal, Biomedical Sciences Program, Midwestern University**

S1.3 Maternal dietary deficiencies in one-carbon metabolism during early neurodevelopment results in sex differences in stroke outcome in middle-aged male and female mice offspring

2:45 PM – **Luke Endicott, AZCOM, Midwestern University**

S1.4 Age-related changes in the retinoic acid synthesis enzyme, ALDH1A2, in the zebra finch vocal circuit

3:00 – 3:45 PM **One Minute Poster Presentations**
Chairs: Rayna Gonzalez, Ph.D., College of Medicine-Phoenix, U of Arizona
Bobby Garvin, Ph.D., College of Medicine-Phoenix, U of Arizona

3:45 – 4:45 PM **Session 2: One-Health Physiology**
Chairs: Layla Al-Nakkash, Ph.D., Midwestern University
McCoy Clementson, AZCOM, Midwestern University

3:45 PM – **Charles Schaefer, College of Graduate Studies, Midwestern University**

S2.1 Predicting and Preventing Outbreaks of Rocky Mountain Spotted Fever, the deadliest Tick-borne Disease in the United States

4:00 PM – **Stephany Gonzalez, College of Health Solutions, Arizona State University**

S2.2 Myosin heavy chain mRNA isoform expression is not affected by exercise or "western-type" diet in mice models

4:15 PM – **Robert Folk, College of Graduate Studies, Midwestern University**

S2.3 Decreased aortic smooth muscle contraction in the mouse model of Marfan syndrome: Role of nitric oxide

4:30 PM – **Paniz Jasbi, College of Health Solutions, Arizona State University**

S2.4 Microbiome and Metabolome Profiles of High Screen Time in a Cohort of College Students

4:45 – 5:00 PM **Break**

5:00 – 6:00 PM **Arizona Physiological Society Keynote Speaker**
William H. Karasov, Ph. D.
University of Wisconsin Department of Forest and Wildlife Ecology
Wildlife Digestion: A View from Molecules to Ecosystems
Introduction by: Christopher Olson, CGS, Midwestern University

6:00 – 7:30 PM **Dinner (Cafeteria)**

7:30 – 9:30 PM **Poster Session – Beer and Wine Reception**

Saturday, October 30th, 2021

8:00 – 8:30 AM **Continental Breakfast**

8:30 – 10:15 AM **Session 3: Metabolism, Exercise and Cardiovascular Physiology**
Chairs: Jose Ek Vitorin, Ph.D., Physiology, University of Arizona
Sara Djurich, Physiology, University of Arizona

8:30 AM – **Kailin Johnsson, School of Life Sciences, Arizona State University**

S3.1 Reproducibility of a High Fat Diet Induced Weight Gain Over Independent Years

8:45 AM – **Linda Wu, Physiological Sciences, University of Arizona**

S3.2 Impact of an Exercise Training Intervention on DNA Methylation in Skeletal Muscle

9:00 AM – **Dallin Tavoian, Department of Physiology, University of Arizona**

S3.3 High-Resistance Breathing Training Enhances Respiratory Strength and Endurance and Blunts Cardiac Response to Exercise

9:15 AM – **Christian Priday, Biomedical Sciences Program, Midwestern University**

S3.4 Marfan syndrome-associated aortic aneurysm: the role of nitric oxide

9:30 AM – **Matthew Klass, College of Medicine-Tucson, University of Arizona**

S3.5 Calcium Exchange with Troponin C in Hypertrophic Cardiomyopathy

9:45 AM – **Alexandra Garvin, College of Medicine-Phoenix, University of Arizona**

S3.6 Is Prohibitin a Mediator of Cardiac Fibroblast Activation?

10:00 AM – **Dana Floyd, Basic Medical Sciences, University of Arizona**

S3.7 Transient ACE Inhibition Sex-Selectively Impacts Angiotensin II-Induced Fibrogenic Responses

10:15 – 10:30 AM **Break**

10:30 – 12:00 PM **Session 4: Charles Tipton Undergraduate Session**
Chairs: Mitra Esfandiarei, Ph.D., CGS, Midwestern University
Tala Curry, College of Medicine-Phoenix, University of Arizona

10:30 AM – **Remembrance to Dr. Charles "Tip" Tipton, Ph.D., University of Arizona**

By: Dawn Coletta, Ph.D., University of Arizona

10:45 AM – **Chaitanya Sanghadia, College of Medicine-Phoenix, University of Arizona**

S4.1 TBI-Induced and Age-Related Neuroinflammation Intersect at 6-Months Post-Injury

11:00 AM – **Kristiann Ferreira, Basic Medical Sciences, University of Arizona**

S4.2 Impact of Doxorubicin and Metformin on Cardiac Mitochondrial Electron Transport Chain Proteins

11:15 AM – **Ellaine Villano and Yasmin Leon, Biology, Northern Arizona University**

S4.3 Can Astaxanthin Improve Redox Signaling in Older Adults?

11:30 AM – **Megan Anderson, Anatomy and Physiology, Grand Canyon University**

S4.4 Neuroprotective Effects of An Over-The-Counter Curcumin Supplement Against Rotenone Induced Toxicity

11:45 AM – **Nafis Eghrari, College of Medicine-Phoenix, University of Arizona**

S4.5 Differential expression profiles of S1PR types 1-5 following hypoxia plus glucose deprivation in human cerebrovascular cells

12:00 – 1:00 PM **Box Lunch**

1:00 – 2:15 PM **Session 5: Tales of Neurophysiology – Part 2**

Chairs: Paulo Pires, Ph.D. University of Arizona
Madeline Gauthier, Physiological Sciences, U of Arizona

1:00 PM – **Trevor Wendt, Biology, University of Arizona**

S5.1 Unveiling a detrimental role for oxLDL/LOX-1 during occlusive stroke: targetingendothelial health and function

1:15 PM – **Sabeeha Reshi, School of Life Sciences, Arizona State University**

S5.2 Therapeutic Potential Of Novel Rexinoids In Prevention And Treatment Of Alzheimer'sDisease

1:30 PM – **Jade Blackwell, Department of Physiology, University of Arizona**

S5.3 Post-menopausal impairment in brain arteriolar endothelial K+ channel function in amouse model of Alzheimer's disease

1:45 PM – **Kellie Jeong and Asha Kurup, AZCOM, Midwestern University**

S5.4 Investigating muscarinic receptor subtype roles on inspiratory bursting at hypoglossalmotoneurons of neonatal mice

2:00 PM – **Abdul Algamdy, College of Pharmacy, Midwestern University**

S5.5 Alcohol effects on Dopamine Signaling in the Zebra Finch vocal circuit

2:15 – 2:30 PM **Break**

2:30 – 3:30 PM **Arizona Distinguished Physiologist Lecture**
Stephen H. Wright, Ph. D.
University of Arizona, Department of Physiology
Maintaining a Positive Outlook: Mechanisms of Organic CationTransport
Introduction by: Lucy J. Martinez Guerrero, Ph.D., University of Arizona

3:30 – 3:45 PM **Break**

3:45 – 4:30 PM **Business Meeting and Awards**

Poster Session

In addition to presenting their poster during the Poster Session, each poster presenter gets one minute (without slides) to present the primary question and/or results of their poster during the One Minute Poster Session on Friday October 29th from 3:00-3:45 PM.

No.	Lead Author (s)	Institution	Poster Title
P1	Johana Vallejo-Elias	MWU-College of Graduate Studies	Brenner Tumor in a 36-year-old Premenopausal Female with Fertility Issues
P2	Seungyong Lee	MWU-College of Graduate Studies	Augmented Skeletal Nerves Are Associated with High-Intensity Aerobic Exercise-Induced Bone Gain in Middle-Aged Mice
P3	Zhiyu Dai	UofA-College of Medicine PHX	Fatty Acid-binding Proteins Control Endothelial Cells Glycolysis in Pulmonary Hypertension
P4	Juliana Lessa Sacoman	UofA-College of Medicine Tucson	Introducing Physiology to Freshmen Students – The PSIO101 Course Experience at the University of Arizona
P5	José F. Ek-Vitorín	UofA-College of Medicine Tucson	A Piece of (the) Cake: Combining Two Patch-clamp Configurations in a Single Cell
P6	Jeffrey Patterson	ASU-College of Health Solutions	Targeted Metabolomics Reveals Plasma Biomarkers and Metabolic Alterations of the Aging Process in Healthy Young and Older Adults
P7	Anaissa Ruiz Tejada	ASU-School of Life Sciences	Effects of Transcranial Direct Current Stimulation on Physical Activity and Intrinsic Motivation towards Exercise
P8	Anthony Basile	ASU-School of Life Sciences	The Majority of Avian Metabolites are Not Altered in Urban Birds: Results form a Systematic Review
P9	Eunice Barrameda	MWU-College of Graduate Studies	Evaluation of cerebral vascular function in a mouse model of Marfan Syndrome
P10	Breanna Aikens	MWU-College of Graduate Studies	Combining confocal imaging and SDS-page to measure variation in mitochondrial volume density and fiber type in primate skeletal muscle
P11	Morgan Hirsh and Melissa Kasai	MWU-College of Veterinary Medicine	The Pathology and Incidence of Building-Caused Bird Mortality
P12	Shelby Marsh	MWU-College of Veterinary Medicine	Functional Anatomy of the Snow Leopard (*Panthera uncia*) Tail
P13	McCoy Clementson	MWU-Arizona College of Osteopathic Medicine	Maternal Dietary Deficiencies in Folic Acid or Choline Impact Stroke Outcome in 3-Month-Old Male and Female Mouse Offspring

No.	Lead Author (s)	Institution	Poster Title
P14	Trevor Wendt	UofA-College of Medicine PHX	Insight into LOX-1 Splice Variant Expression in Brain VSM Following oxLDL Exposure and Ischemia-like Injury
P15	Lakshmi Madhavpeddi	UofA-College of Medicine PHX	Impact of Gonadectomy on Sex-Selective Dysregulation of Cardiovascular Function Resulting from *In Utero* Exposure to Dexamethasone
P16	Michelle Conway	UofA-College of Medicine Tucson	Presence of Asthma May Decrease Susceptibility to SARS-CoV-2
P17	Carrie Standage-Beier	UofA-College of Medicine Tucson	Fruit, Vegetable and Physical Activity Guideline Adherence and Metabolic Syndrome El Banco por Salud
P18	Yassin Hamzaoui	UofA-College of Medicine Tucson	Unraveling the Role of Mitochondrial DNA Methylation in Insulin Resistant Skeletal Muscle
P19	Angel Morales	ASU-School of Life Sciences	Ultra-processed Foods Have a Lower Glycemic Index and Load Compared to Minimally Processed Foods
P20	Kavita Singh	ASU-School of Life Sciences	Effect of Macronutrient and Micronutrient Manipulation on Avian Blood Glucose Concentration: A Systematic Review
P21	Linnu Shaji and Jordyn Oliver	GCU-College of Science, Engineering & Technology	Effects of Cyanidin Chloride on the human mouth and skin microbiome
P22	Daniela Millan	NAU-Department of Biological Sciences	An Assessment of Recruitment of Minority Populations into Clinical Research Studies
P23	Zackary Sabetta	ASU-College of Health Solutions	Sex, Age, and Region-Specific Changes in Astrocytes Following TBI in a Behaviourally Relevant Circuit

Faculty

P1 Brenner Tumor in a 36-year-old Premenopausal Female with Fertility Issues

[1]Kothati, N, MD, ***[2]Johana Vallejo-Elias, PhD**, [2]Talley, NA, [2]Santiago, M, [2]Lang, Z,

1. Steward Medical Group, Mesa, Arizona

2. Arizona College of Osteopathic Medicine, Midwestern University, Glendale Arizona

The Brenner tumor of the ovary is a rare neoplasm with few cases reported in medical literature. Nearly all Brenner tumors are considered to be benign tumors and most commonly are seen unilaterally, with bilateral Brenner tumors arising in approximately 5-15% of the cases. The aim of this study is to describe a Brenner tumor that was initially seen as a mass on imaging studies in a premenopausal woman while investigating causes of two spontaneous abortions. The patient is a 36-year-old. During robotic assisted right oophorectomy procedure, the mass was identified and inspection revealed the entire ovary was covered. Histopathologic findings were consistent with a benign Brenner tumor which are considered rare neoplasms making up less than 5% of all ovarian tumors. The average age of presentation is 50, with 71% of patients being older than 40 years. The identification of this Brenner tumor was incidental as the instigating symptoms for the laparoscopic procedure were fertility issues. Most that are discovered are unilateral and are candidates for surgical removal. As the molecular basis for the benign tumor growth is not agreed upon, there is not definitive way to prevent recurrence. However, surgical resection is typically curative. The presentation of a 36-year-old female with this tumor is irregular. Not only does it not fall in the most common age range, it is also a rare neoplasm. Surgical resection of the tumor is curative due to the lack of metastases, leading to a positive prognosis. The histopathology of the resected tumor illustrating transitional cells without stromal invasion indicated the benign Brenner tumor as the diagnosis. The overall prognosis of patients with Brenner tumors are positive with continued screening.

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Faculty

P2 Augmented Skeletal Nerves Are Associated with High-Intensity Aerobic Exercise-Induced Bone Gain in Middle-Aged Mice

***[1]Seungyong Lee**, [2]Shin YA, [3]Cho J, [4]Park DH, Lang, Z, [5]Kim C,]

1. Midwestern University, College of Graduate Studies, Glendale, AZ

2. Dankook University, Cheonan, South Korea

3. Korea Institute of Sport Science, Seoul, South Korea

4. Inha University, Incheon, South Korea

5. Dongduk Women's University, Seoul, South Korea

Advancing age leads to significant bone loss and elevated osteoporosis risk. Furthermore, the spatial distribution, innervation, and functional role of skeletal nerves have been previously described in detail. Since exercise training improves bone metabolism, age-associated bone loss, and peripheral nerve regeneration, we sought to determine the effects of aerobic exercise training on bone parameters, skeletal nerve fiber density of femora, and tibiae in middle-aged mice. 14-months-old male C57BL/6 mice were randomly assigned to 8-weeks of either (a) high-intensity exercise (EX_HI), (b) higher volume, moderated-intensity exercise (EX_MHV), (c) lower volume, moderate-intensity exercise (EX_MLV), or (d) non-exercising control (CON) (n=6-7). Hindlimb BMD and BMC were evaluated by dual-energy X-ray absorptiometry, and trabecular and cortical bones were measured by micro-computed tomography among four groups following the exercise training. Since a clear difference in bone radiographical outcomes only existed between CON and EX_HI, immunohistochemistry staining and confocal microscopy were used to determine skeletal nerve fiber density and alkaline phosphatase (ALP) reactivity between CON and EX_HI only. Femoral and tibial BMD and BMC were significantly higher ($p<0.05$) in EX_HI compared to CON. Although distal femoral trabecular bone and femoral and tibial mid-diaphyseal cortical bone did not differ among groups, proximal tibial trabecular number (Tb.N, /mm2) was higher ($p<0.05$), and bone volume (BV, mm3), fractional bone volume (BV/TV, %), and trabecular thickness (Tb.Th, mm) tended to be higher ($p<0.10$) in EX_HI than in CON. There were no meaningful changes in bone parameters following moderate-intensity exercise. Significantly increased skeletal nerve fiber density was observed in the distal femoral ($p<0.05$) and proximal tibial ($p<0.01$) periosteum. Although not significant, ALP reaction was higher in EX_HI compared to CON. Thus, BMD, BMC, and bone volume, especially tibial trabecular bone, were enhanced by EX-HI, and this effect paralleled the significant increase of skeletal nerve fibers. Taken together, high-intensity aerobic exercise may be an effective and applicable exercise regimen to enhance bone metabolism by increasing skeletal nerve stimulation. The extent to which aerobic exercise-induced increases in bone innervation contribute to improvements in skeletal cell metabolism remains an intriguing unanswered question.

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Faculty

P3 Fatty Acid-Binding Proteins Control Endothelial Cells Glycolysis in Pulmonary Hypertension

[1]Liu, B, [1]Yi, D, [2]Singh, I [2]Frye, R, ***[1]Zhiyu Dai**

1. University of Arizona, Phoenix, AZ

2. Phoenix Children Hospital, Phoenix, AZ

Introduction: Pulmonary arterial hypertension (PAH) is a disaster disease characterized by obliterative vascular remodeling and persistent increase of vascular resistance, leading to right heart failure and premature death. Understanding the cellular and molecular mechanisms will help develop novel therapeutic approaches for PAH patients.

Hypothesis: We hypothesis that endothelial fatty acid metabolism is critical for obstructive vascular remodeling in the pathogenesis of PAH.

Methods: Here we applied single-cell RNA sequencing (scRNA-seq) to profile the pulmonary cells in a severe mouse model (Egln1Tie2Cre mice) of PH. Human hPAEC from idiopathic PAH patients and healthy donors were used to measure fatty acid-binding protein 4 and 5 (FABP4 and FABP5) expression. siRNA mediated knockdown of FABP4 and FABP5 was performed to study cell proliferation and apoptosis. Glycolysis assay was performed to evaluate the role of FABP4-5 on ECs. Egln1Tie2Cre mice were bred with Fabp45-/- mice to generate Egln1Tie2Cre/Fabp45-/- mice.

Results: scRNA-seq analysis demonstrated that both FABP4 and 5 were highly induced in the ECs of Egln1Tie2Cre mice. PAECs from IPAH patients also showed higher expression of FABP4 and 5. Knockdown of FABP4-5 reduced EC proliferation and starvation-induced Caspase 3/7 activity. Overexpression of FABP4-5 promoted EC glycolysis and proliferation. Genetic deletion of Fabp4 and 5 in Egln1Tie2Cre mice exhibited a reduction of RVSP, RV hypertrophy, and reduction of EC glycolysis gene programming compared to Egln1Tie2Cre mice.

Conclusions: FABP4 and 5 control EC glycolysis and contribute to the development of PAH.

Funding: NIH grants R00HL13827, AHA Career Development Award 20CDA35310084, ATS Foundation and PHA Research Fellowship and UA Departmental Startup fund to Z.D.

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Faculty

P4 Introducing Physiology to Freshmen Students – The PSIO101 Course Experience at the University of Arizona

[1]Ngo A, [1]Rankin L, ***[1]Juliana Lessa Sacoman**

1. University of Arizona, Tucson, AZ

Physiology undergraduate majors usually have an interest in careers that require post graduate education, such as medical and dental schools. Obtaining a degree in physiology can be intensive and, at times, overwhelming when considering all the extracurriculars that students have to partake in order to reach their career objectives. We propose that introducing students to physiological concepts, as well as professional skills, while freshman can positively impact their performance during college. With that in mind, we launched a freshman course called PSIO101- "Tackling Physiological Topics in Today's Society" on Fall 2019. Our objective was to analyze if students taking this course have a better overall performance in college by analyzing parameters such as GPA, grades in intensive required courses (PSIO201 and PSIO202 (two-semester sequence of Human Anatomy and Physiology) and whether good performance in this course correlates with higher performance overall on the parameters above. In this study, we collected data from a total of 582 students in our major which were divided into two categories: students that have completed PSIO101 and non-PSIO101 students. Our results showed that students that have completed PSIO101 have a significantly higher cumulative GPA (Mean = 3.512±0.4585, n=87) than non-PSIO101 students (Mean = 3.272 ± 0.6477, n=495) (p=0.0016, Mann Whitney), as well as higher final grades in PSIO201 (Mean = 3.329 ±0.875, n=85) than non-PSIO101 students (Mean = 2.986 ± 1.095, n=494) (p =0.0121, Mann-Whitney test). No statistical difference was found in the PSIO202 grade between PSIO101 (Mean = 3.274 ± 0.8331, n=62) and non-PSIO101 students (Mean = 3.071 ± 0.9975, n=295) (p=0.1349, Student's t-test); however, the cumulative frequency distribution of grades in PSIO202 showed that PSIO101 students have a higher prevalence of better letter grades ("A" and "B") than non-PSIO101 students. We also found a positive correlation between PSIO101 grade and students' PSIO201 and 202 grades (PSIO101/PSIO201: r=0.3393, R^2=0.1151, n= 85, p=0.0015; PSIO101/PSIO202: r=0.4314, R^2= 0.1861, n=62, p=0.0005) as well as cumulative GPA (r=0.3715, R^2= 0.1380, n =87, p = 0.0004). In conclusion, positive results in overall performance were observed for students who took PSIO101, leading to the idea that early introduction to physiology, professional skills and college resources can potentially direct students to a more successful college path. Future studies include continuing this analysis for upcoming PSIO101 cohorts as well as tracking their graduation rate and time.

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Faculty

P5 A Piece of (the) Cake: Combining Two Patch-clamp Configurations in a Single Cell

*[1]José F. Ek-Vitorín, Delamere N

1. Department of Physiology, University of Arizona, Tucson, AZ, USA

There are four well known patch-clamp configurations to record cell membrane current (Im). In whole cell voltage clamp (WCVC), Im from all channels that open at any given condition, is recorded, but the channel components of this Im are not readily evident. Cell-attached (CAVC), inside-out (IOVC) and outside-out voltage clamp (OOVC) configurations are used to detect single channels. However, in CAVC the resting potential (Vm) of the cell is generally unknown, and thus the real voltage gradient across channels is inaccurate; in IOVC and OOVC, the cytoplasm of the cell is missing, and so is an important regulatory environment. Here, by combining WCVC and CAVC, we show that total Im and its channel components can be simultaneously recorded, with and intact cytoplasm and full Vm control. In addition, agents/drugs can be applied by three different routes (two extracellular and one intracellular), allowing for a fine gradation of treatment. This technical variation of patch-clamp can be useful in cells with large Im values and strong response to experimental treatments.

Funding: R01 EY029171-01A1 to ND

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Graduate/Professional Student

P6. Targeted Metabolomics Reveals Plasma Biomarkers and Metabolic Alterations of the Aging Process in Healthy Young and Older Adults

***[1]Jeffrey Patterson**, [1]Jasbi, P, [2]Twigg, H, [1]Gu, H,

1. Arizona State University, College of Health Solutions, Phoenix, AZ

2. Indiana University School of Medicine, Indianapolis, IN

With the exponential rise in the older population for the coming years, many studies have aimed to further investigate potential solutions to the aging process. It has been well understood that age is the largest risk factor for chronic disease due to younger individuals possessing more prevalent and adaptive metabolic networks that result in overall health and homeostasis. During the lifecycle, several physiological alterations ensue throughout the metabolic system that attribute to functional decline. In this cross-sectional analysis, a targeted metabolomic approach was applied to investigate the plasma metabolome of 151 young (n = 75) and older adults (n = 76). A corrected MANOVA model was generated, with such covariates as gender, BMI, and chronic condition score (CCS), to analyze the aging process of the two populations. Metabolites associated with impaired fatty acid metabolism were found to be most significant: palmitic acid ($p < 0.001$), 3-hexenedioic acid ($p < 0.001$), stearic acid ($p = 0.005$), and decanoylcarnitine ($p = 0.036$). Derivatives of amino acid metabolism, 1-methlyhistidine ($p = 0.035$) and methylhistamine ($p = 0.027$), were found to be increased in the younger population and several novel metabolites were identified, such as cadaverine ($p = 0.034$), 4-ethylbenzoic acid ($p = 0.029$), and 3-hexenedioic acid ($p < 0.001$). Principal component analysis was conducted and highlighted a shift in the metabolome for both groups. Pathway and enrichment analyses uncovered several impacted pathways that elucidate the metabolic alterations in the older population and aid in further explanation of the aging process. As a result, we offer a better understanding of the aging metabolome and potentially reveal new biomarkers for future study.

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P7 Effects of Transcranial Direct Current Stimulation on Physical Activity and Intrinsic Motivation towards Exercise

***[1]Anaissa Ruiz-Tejada**, [1]Foelber Holmes C, [1]Neisewander J, [1]Sadleir R, [1]Buman M, [1]Katsanos CS

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The negative effects of insufficient levels of physical activity (PA) on health are widely recognized (Lavie *et al.*, 2019). Regular PA is often resisted due to a lack of motivation. According to the Self Determination Theory, motivation is categorized as either external (EM) or intrinsic (IM)(Ryan and Deci, 2000). Increasing IM could increase sustained regular PA and in turn, improve overall health (Fishman *et al.*, 2016). Motivation is linked to activation of dopamine (DA) pathways in the brain (Salamone and Correa, 2012). In this regard, transcranial direct current stimulation (tDCS) increases DA availability in the striatum (Fonteneau *et al.*, 2018; Fukai 2019), which is a part of the brain involved in motivated behavior. What is yet to be shown is whether tDCS can enhance IM and, hence, PA.

In a single-blinded parallel design, study participants were assigned to two groups undergoing either active (n=8) or sham (ie. no active/control) (n=4) tDCS. Participants underwent 20 minutes of tDCS (ie. active or sham), followed by fast-paced walking for 30 mins. We hypothesized that 3 weeks of intervention including active tDCS coupled with exercise will increase IM towards exercise as well as PA. IM was determined using the BREQ-3 questionnaire (Cid et al., 2018; Duncan et al., 2010) before (PRE) and after (POST) the intervention. PA was monitored for 2 weeks before (PRE), 3 weeks during (DUR), and 2 weeks after (POST) the tDCS intervention.

PA was assessed using total daily steps (TDS), as well as activity score (AS) expressed as METs/hr with the thigh-worn activPAL micro accelerometer. Means PRE vs DUR and PRE vs POST were compared using a paired t-test. TDS and AS were significantly higher DUR when compared to PRE (TDS/PRE= 5173±2148 steps, TDS/DUR= 7070±2303 steps; $P<0.001$; AS/PRE= 32.43±0.86 METs/hr, AS/DUR= 33.04±0.92 METs/hr; $P= 0.0013$). TDS scores in the sham/control group were also higher DUR compared to PRE (TDS/PRE= 4640±1080 steps, TDS/DUR= 6738±1829 steps; $P= 0.04$). Neither group showed significant differences in either AS or TDS in the PRE vs POST comparisons ($P> 0.05$). Only the active group showed increase in IM as a result of the tDCS intervention (PRE= 1.77±0.97, POST= 2.64±0.96; $P= 0.003$), but not sham/control (PRE= 1.66±0.72, POST= 1.76±1.03; $P= 0.14$).

In conclusion, we found increased physical activity levels during the course of the intervention, an effect that may be explained by increased intrinsic motivation towards exercise. A greater sample size is needed to confirm the relationships between tDCS, motivation, and physical activity, and the potential for neurostimulation to prevent sedentary behavior in individuals who have lower levels of IM.

Funding: Arizona State University (ASU) Graduate College and ASU Graduate and Professional Student Association (GPSA)

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Graduate/Professional Student

P8 The Majority of Avian Metabolites are Not Altered in Urban Birds: Results form a Systematic Review

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It is estimated that the North American bird population has decreased by 2.9 billion since 1970 and the urban environment may be partly responsible. Therefore, the aim of this project was to conduct a systematic review to identify whether birds residing in an urban environment have altered blood metabolites compared to non-urban birds. Three scientific databases were searched (PubMed, Web of Science, and SCOPUS) using the search terms ("Avian" OR "Bird" OR "Aves") AND ("Urban" OR "Non Rural") AND ("Rural" OR "Non Urban") AND ("Plasma" OR "Blood" OR "Serum") to identify articles that met inclusion criteria: examined at least one blood metabolite concentration in at least one avian species in an urban and rural environment or along an urban-to-rural gradient. The literature search yielded 151 unique articles and 50 articles met inclusion criteria which produced 283 datasets (one species and one metabolite). Ninety-two unique metabolites were identified and were grouped into 13 categories: immunology, glucose, reproductive hormones, vitamins, cortisone, carotenoids, oxidation and antioxidant, thyroid hormones, triglyceride, melatonin, hemoglobin, fatty acids, and others. Most datasets included male and female (81%) adult (53%) birds and included 29 unique species. Studies were predominately conducted in Sweden (59%) and included 27 unique first authors with a mean publication year of 2013 ± 8.19. Across all datasets, 54% showed no differences in blood metabolite concentrations between urban and rural, with 24% and 22% having higher and lower concentrations in the urban group compared to rural, respectively. For most metabolite groups (n=11/13), either the majority or the largest effect was no difference between urban and rural groups. Glucose (n=5 datasets) and cholesterol (n=3 datasets) were two categories wherein the majority of datasets (60% and 67%, respective) showed a higher concentration in the urban group compared to rural. Corticosterone was most often studied (n=25 datasets), where 64% showed no difference between urban and rural groups. Overall, with the exception of glucose and cholesterol, an urban environment does not appear to be associated with major changes in avian blood metabolites. This systematic review serves to better summarize the effects of an urban environment on avian species and to identify possible trends and gaps in the literature.

Funding: AJB was awarded the 2021-2022 Arizona State University School of Life Sciences Completion Fellowship.

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Graduate/Professional Student

P9 Evaluation of Cerebral Vascular Function in a Mouse Model of Marfan Syndrome

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Marfan Syndrome (MFS) is an autosomal- dominant connective tissue disorder resulting from defects in the gene that encodes for fibrillin-1 (Fbn1). The Fbn1 protein activates signaling pathways that regulate growth factors, specifically the transforming growth factor beta (TGF-β), in the extracellular matrix (ECM). Fbn1 also forms a scaffold of microfibrils, which supports elastic fibers that structurally stabilize elastic and non- elastic connective tissues throughout the body. In MFS, mutations in the Fbn1 gene are associated with increased stiffness and weakening of the vessel wall and aortic root enlargement. Cerebrovascular effects of MFS are not well understood, but cerebrovascular function (permeability, blood flow) may be impaired due to the damaging effects of Fbn1 dysfunction on three layers of the blood vessel. Given individuals with MFS experience early- age dysfunction in the vasculature that are usually associated with normal aging in healthy old- age individuals, MFS may serve as an appropriate and novel model for accelerated aging. Thus, we analyzed aortic root diameter, aortic pulse wave velocity (PWV), and posterior cerebral artery (PCA) peak blood flow in male and female 6- month- old MFS and 6 and 12- month- old C57BL/6 wildtype (WT) control to further evaluate outcomes of age-associated vascular dysfunction in the MFS transgenic mouse model.

In vivo imaging of aortic root diameter, aortic PWV, and PCA peak blood flow were performed on 6 and 12- month- old WT and 6- month- old MFS mice using the high- resolution Vevo2100 ultrasound system. Increased aortic root diameter was found in 6- month- old MFS and 12- month- old control, which is indicative of vessel wall weakening. Aortic PWV was increased in 6- month- old MFS and 12- month- old control mice as well. This indicates increased vessel wall stiffness, compared to 6- month- old control. Decreased PCA peak blood flow was observed in 6- month- old MFS and 12- month- old control mice, suggesting altered function in the cerebral vasculature during the normal aging in control mice as well as in MFS mice. PCA peak blood flow measures the average blood volume movement through time, and its decrease may be consistent with compromised wall strength in the cerebrovasculature, as observed in the vessel wall in the peripheral vasculature.

Our data supports that MFS mice have impairments in the peripheral and cerebral vasculature similar to those observed in aged control mice, indicating that the MFS mouse model may be used as an appropriate and novel experimental animal model for accelerated aging of cerebral vasculature.

Funding: Midwestern University Graduate Fund, Valley Research Partnership-2232011, NIH-R15HL145646, NIH-R01NS100793

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P10 Combining Confocal Imaging and SDS-Page to Measure Variation in Mitochondrial Volume Density and Fiber Type in Primate Skeletal Muscle

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The evolution of primate musculoskeletal physiology requires a tradeoff between power generation and endurance capability. Previously, myosin heavy chain content (MHC) has been used as a proxy for estimating muscle performance. A predominance of MHC I isoforms should reduce dynamic force and power output and is hypothesized to facilitate repetitive, low cost contractile behavior associated with increased mitochondrial volume density, while a predominance of MHC II should increase dynamic force and power output with comparatively less mitochondrial volume density. However, while the ratio of MHC slow twitch type I isoforms to MHC fast twitch type II isoforms varies across primate and terrestrial mammals, fiber type analysis alone has been unable to fully predict aerobic differences and muscle performance in primates. Additionally, mitochondrial measurements using TEM have not matched the whole muscle fiber type analyses and has shown to be inadequate in estimating muscle energetics due to a small area being extrapolated to the whole fiber calculation. Here, we demonstrate a new technique combining confocal microscopy and SDS-page which allowed us to determine the fiber type and mitochondrial volume density of the entire fiber length in the same muscle fiber to attempt to resolve this apparent conundrum. This technique was applied to the gastrocnemius and vastus lateralis muscles in three macaque individuals allowing us to analyze mitochondrial volume relative to total fiber volume giving us mitochondrial volume density and fiber type of individual fibers within 1) the same muscle, 2) different muscles, and 3) between individuals. Images were analyzed for mitochondrial volume density using Amira 3D. Our results demonstrate that a combination of fiber type analysis and mitochondrial measurement can be used to predict muscle performance providing important new insight into the musculoskeletal evolution in primates.

Funding: Midwestern University College of Graduate Studies

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P11 The Pathology and Incidence of Building-Caused Bird Mortality

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Anthropogenic hazards are largely responsible for the net loss of nearly 3 billion birds from North American skies between 1970 and 2018. The incidence of bird-window collisions is a major driver of these losses and is estimated to indiscriminately kill 0.5 to 1 billion birds annually. Clearly, windows are a ubiquitous threat to sustainable continental, and likely global, bird populations. To understand window-caused mortality and increase successful treatment outcomes, this research opportunistically investigated the incidence of building-caused bird mortality on Midwestern University's Glendale campus. During twice daily walks on campus over the past two summers, over 200 window-killed birds were found from 29 species, yielding 178 reliable postmortem examinations. We found that window-killed birds have characteristic gross pathology, most of which resulted in death, but it was not the pathology we initially expected to see. Rather than injury to the head, birds died from blunt force trauma sustained by and/or translated through their pectoral girdle/muscle area. Specifically, 84% had lower respiratory tract injury, 77% had hepatic/splenic injury of which 72% resulted in hemocoelom, and 48% had cardiovascular pathology. Skeletal fractures were also common, including pectoral fractures (56%), and rib fractures/luxations (48%). In contrast, only 17% of birds had cranial injuries, and only 1% had vertebral column fracture, suggesting that cranial and spinal injury are far less common. 143 (80%) of the examined birds had fatal pathologies from multiple categories and, in 36 cases (20%), it was primary skeletal pathology that caused the fatal visceral injuries. Interestingly, many birds had previous injuries that were healed, suggesting that not all collisions are fatal, and survival is not uncommon. Indeed, many birds end up in wildlife rehabilitation centers, and our work describing the cause of death of these birds will improve the treatment outcomes of those injured birds that survive.

Funding: Midwestern University Student One Health Grant

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Graduate/Professional Student

P12 Functional Anatomy of the Snow Leopard (*Panthera uncia*) Tail

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The snow leopard (*Panthera uncia*) inhabits cold, mountainous environments, with sheer cliff faces often steeped in snow. As part of a larger project, we dissected the tail of the snow leopard in order to describe its anatomy and detail adaptations to climate, locomotion, and posture. Particularly, we sought to understand how P. uncia utilizes its tail for balance and warmth. Fat thickness was greatest in the proximal third of the tail, which may aid to keep P. uncia warm in their frigid environment. On the dorsal surface, the superficial tendons of mm. sacrocaudalis dorsalis lateralis (SDL) and sacrocaudalis medialis (SDM) were covered by a thin fascial retinaculum oriented perpendicular to the long axis of the tendons. A superficial retinaculum held the main tendons together, and deeper formed an aponeurosis. This created a layered effect within the grouping, with superficial, intermediate, and deep tendons coursing over the tail. SDL tendons coursed together within their respective layered grouping of the deep caudal fascia to eventually join the aponeuroses, then separately dove deep to attach to bone. SDM does not have its own set of robust tendons; tendons of SDL integrated themselves into SDM. This same pattern repeated ventrally within the ventral lateral muscles. The tendons spanned eight caudal vertebrae from the formation point of the tendon to the insertion site onto bone, crossing medially and laterally to imbed into adjacent muscles. This extensive tendinous arrangement permits more fluid motor control of the tail that P. uncia needs to stabilize itself. Taken together, the muscular adaptations of the tail reveal a complex mechanism of balance and leverage for navigating the diverse alpine environment.

Funding: Boehringer Ingelheim Veterinary Scholars Program to S.M.

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P13 Maternal Dietary Deficiencies in Folic Acid or Choline Impact Stroke Outcome in 3-Month-Old Male and Female Mouse Offspring

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Maternal one-carbon metabolism, including dietary levels of folic acid and choline, play an important role in early life programming. There is a well-established connection between the fetal environment and the health status of the offspring. However, there is a gap in knowledge on how maternal nutrition will affect the health status of the offspring after a cardiovascular event like ischemic stroke. The aim of our study was to investigate the role of maternal dietary deficiencies in folic acid or choline on stroke outcome in 3-month-old male and female offspring. We hypothesize that maternal dietary deficiencies of folic acid or choline will impact early life programming of the fetus, and therefore lead to worse health outcomes after ischemic stroke in early adulthood. Adult female mice were fed a folic acid deficient diet (FD), a choline deficient diet (ChDD), or a control diet (CD) 4 weeks prior to pregnancy to deplete stores, they were continued on diets during pregnancy and lactation. Male and female offspring were weaned onto a control diet and at 2 months of age were subject to ischemic stroke within the sensorimotor cortex via the photothrombosis ischemic damage model. At 3 months of age, motor function was measured in offspring and tissue was collected for analysis. Mothers maintained on either a folic acid or choline deficient diet had reduced levels of S-adenosylmethionine in liver tissue. In offspring, there was no sex difference between male and female mice, so all the data has been grouped together. After ischemic stroke, motor function was impaired in 3-month-old offspring from deficient mothers compared to control diet offspring. There was no difference in ischemic brain tissue damage volume between offspring dietary groups. Betaine levels in ischemic tissue were reduced in offspring from choline deficient mothers compared to controls. Maternal dietary deficiencies in folic acid and choline result in worse outcome after ischemic stroke in 3-month-old male and female offspring.

Funding: American Heart Association 20AIREA35050015

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Graduate/Professional Student

P14 Insight into LOX-1 Splice Variant Expression in Brain VSM Following Oxldl Exposure and Ischemia-Like Injury

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One of the critical factors mediating vascular injury and found to be clinically correlated with acute ischemic stroke (AIS) is elevated oxidized low-density lipoprotein (oxLDL) levels. OxLDL, via the lectin-like oxLDL receptor 1 (LOX-1), has been shown to disrupt VSM function and involve MMP-9 activation, thus contributing to the pathogenesis of occlusive stroke. LOX-1 is characterized by three alternative splice variants that confer differential protein outcomes. The characterization of LOX-1 variants the cerebrovasculature has yet to be addressed following physiological conditions, oxLDL exposure, or in the context of ischemic injury. Therefore, this study investigated the splice variant expression profile of LOX-1 and MMP-9 mRNA levels in brain vascular smooth muscle cells (VSMCs) following an in vitro acute ischemic injury (HGD; hypoxia plus glucose depravation) ± oxLDL. Male human brain VSMCs were conditioned with human oxLDL (high dose-50µg/dL; low dose-25µg/dL) for 12h, and then exposed to normoxia (NX; 21% O2) or HGD (1% O2) and treated with BI-0115 (10µM; selective LOX-1 inhibitor) for 6h in the continued presence of ± oxLDL. In the dish, LOX-1 variants were visualized using semi-quantitative analysis. MMP-9 mRNA (LOX-1 downstream inflammatory mediator) was assessed using quantitative real time-PCR (qRT-PCR). VSMCs exhibited a differential expression profile of the three splice variants (V) under NX: 1 (V1) > 3 (V3) > 2 (V2). During NX, oxLDL (high & low dose) increased V1 expression, had no effect on V2 levels, and increased V3 expression in a dose dependent manner. Following HGD, we observed a decrease in V1 expression with no change in V2 or V3 in comparison to NX. During HGD, oxLDL (high & low dose) increased expression of V1 and V2; however, V2 expression was dose dependent. V3 expression was increased only by high oxLDL+HGD in comparison to HGD alone. Under NX we observed an increase in MMP-9 gene expression only following high oxLDL. During HGD there was no change in MMP-9 expression relative to NX; however, we observed a dose dependent increase with HGD + high and low oxLDL in comparison to HGD alone. Finally, LOX-1 inhibition attenuated the oxLDL-mediated increase in MMP-9 expression following HGD. In conclusion, the beneficial downregulation of LOX-1 V1 by HGD was attenuated by the presence of oxLDL, suggesting that the combinatory effect predisposes the cerebrovasculature to an exacerbated response during AIS. Moreover, LOX-1 inhibition and the resulting attenuation of oxLDL-mediated increases in VSMC MMP-9 transcription suggests that LOX-1 may be a viable therapeutic target for AIS.

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Graduate/Professional Student

P15 Impact of Gonadectomy on Sex-Selective Dysregulation of Cardiovascular Function Resulting from *In Utero* Exposure to Dexamethasone

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It is well established that even transient prenatal insults can impact cardiovascular function in adulthood, and that men and women demonstrate a different risk for and progression of cardiovascular disease. We have hypothesized that adult cardiovascular disease may have its origins in utero as a result of exposure to elevated levels of glucocorticoids. In support of this, we have shown that when pregnant rat dams are treated with the glucocorticoid, dexamethasone (DEX), for the last 4 days of gestation, female-specific changes resulting in enhanced pressor and tachycardic responses to stress occur in adult offspring. We hypothesize that the sex-specific impact of prenatal stress on cardiovascular stress responses is due to the activational effect of gonadal steroid hormones. Pregnant dams were administered DEX (0.4mg/kg per day, s.c.) or vehicle on gestation days 18-21. This resulted in a significant reduction in birthweight in DEX-exposed males and females. At 8 weeks, rats underwent a gonadectomy (GDX) or sham surgery, or remained intact, and at 10 weeks rats were instrumented with radiotelemetric transmitters for direct recording of arterial pressure in conscious, freely moving male and female rats. At 11-12 weeks rats were placed in a restraint tube for 20 minutes, followed by a 3-hour recovery period, to assess whether GDX alters the sex-specific stress responses in DEX-exposed offspring. Restraint-stress testing was performed on diestrus in intact and sham females, and absence of cycling in GDX females was confirmed via cytological analysis. We demonstrate that intact females, but not males, that were exposed to DEX in utero exhibit an exaggerated pressor response to restraint, as compared to vehicle exposed females. We found that GDX did not alter stress-responsive MAP in males regardless of prenatal treatment, suggesting testosterone does not play a role in acute cardiovascular stress responses adult rats. In vehicle exposed females, when compared to intact, both sham and GDX surgery resulted in an exaggerated pressor response to restraint. However, in females that were prenatally exposed to DEX, there was no difference in the pressor response to restraint between intact, sham, and GDX rats. This suggests that the exaggerated pressor response observed in DEX females compared to males is not due to activational effects of estradiol. It is possible that gonadal steroids act at an organizational level to mediate the sexual dimorphism observed in rats exposed to DEX in utero. Future studies to identify the mechanisms by which prenatal dexamethasone produce long-term changes in cardiovascular function will be important for better understanding the sex-specific consequences of prenatal programming over the lifespan.

Funding: NIH U54 MH118919

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Graduate/Professional Student

P16 Presence of Asthma May Decrease Susceptibility to SARS-CoV-2

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The purpose of this study is to determine the effects of allergic asthma and the type 2 cytokine, IL-13, on ACE2 expression and potential SARS-CoV-2 susceptibility. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the novel coronavirus that has negatively impacted our world, communities, and families. To infect cells, SARS-CoV-2 uses a spike glycoprotein present on its surface to bind to its receptor angiotensin converting enzyme 2 (ACE2), which is expressed in bronchial and nasal epitheliums. Increased severity and mortality of SARS-CoV-2 infection has been associated with several lung comorbidities, notably, with the exception of asthma. Our group investigated the possible influence Interleukin 13 (IL-13), a type 2 cytokine upregulated in asthma, may have on ACE2 expression. Primary bronchial and nasal epithelial cells were collected from non-atopic normal, atopic normal, non-severe asthma, and severe asthma participants who underwent nasal swabbing as well as bronchoscopies with brushing. Epithelial cells were cultured and differentiated for two weeks at air-liquid interface, then stimulated with IL-13 (10 ng/ml) for 48 and 72 hours. ACE2 gene expression and protein levels were assessed using qRT-PCR and ELISA, respectively. Vero E6 cells, an ACE2-expressing epithelial cell line, were incubated with a recombinant his-tagged S1 spike protein and treated with IL-13 (10 ng/ml) for 72 hours. Binding analysis was performed using flow cytometry. Additionally, two microarray datasets from a public data repository were analyzed for associations between ACE2 and the signatures of type 2 inflammation. ACE2 gene expression and protein levels were reduced in both primary bronchial and nasal epithelial cells after IL-13 stimulation. Flow cytometry showed cells treated with IL-13 exhibited reduced S1 spike protein binding. Analysis of datasets from public database showed a significant negative correlation between ACE2 expression and the presence of asthma and atopy. Also, participants with asthma and/or allergic rhinitis had lower ACE2 expression compared to healthy participants in both bronchial and nasal epithelial cells. A type 2 cytokine, IL-13, modulates ACE2 gene expression, protein levels, and function in epithelial cells. Allergic asthma inflammation may reduce the susceptibility to SARS-CoV-2 infection by inhibiting ACE2 expression and function.

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P17 Fruit, Vegetable and Physical Activity Guideline Adherence and Metabolic Syndrome El Banco por Salud

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This study's purpose was to evaluate adherence to fruit, vegetable and physical activity guidelines and association with Metabolic Syndrome (MetS) in El Banco por Salud. Baseline questionnaire and physiological data from 972 participants enrolled in the University of Arizona's Center for Disparities and Diabetes, Obesity and Metabolism El Banco por Salud (wellness bank) were assessed. Eligible patients were prescreened by clinic staff through their electronic health record. Eligibility criteria include self-reported Latino ethnicity, age 18–75 years, and a HbA1c of 5.7 or greater. Recruited patients then served as probands in the study design. Family (including significantly close friends considered kin/family) were also recruited. Self-reported data included weekly fruit and vegetable consumption and average weekly estimates of physical activity time and intensity. Fruit and vegetable intake and physical activity were coded into meeting, partially meeting, and not meeting guidelines. Cardiometabolic factors for MetS were defined by the Adult Treatment Panel III. MetS traits were defined as; dyslipidemia was when triglycerides values were 150 mg/dL, elevated fasting blood glucose was when values were 5.6 mmol/L, high density lipoproteins- (HDL) cholesterol was when values were <40 mg/dL for men and <50 mg/dL for women, hypertension was when systolic blood pressure was >130 mmHg and >85 mmHg for diastolic, large waist circumference was when men had 40 inch waists and women had 35 inch waits. MetS was defined as having ≥3 traits. Wellness bank participants (n=972) were self-reported Hispanic/Latino with an average age of 51.3, 67% female, mostly married or in a domestic partnership 53.1%, and prefer only Spanish spoken at home (33.3%). Three or more MetS traits were experienced by 64.8% of participants. Overall, those fully meeting guidelines for fruit, vegetable, and physical activity were 14.6%, 24.5%, and 23.5%, respectively. Large waist circumference was found to be the most prevalent MetS trait present in this sample at 77.9%. Fully adjusted logistic regression models demonstrated that those with full adherence to physical activity guidelines had a reduction in odds of MetS (OR 0.67, 95%CI 0.47, 0.96). There was no significant association with adherence to fruit or vegetable guidelines and MetS in the mutually adjusted model. Overall adherence to guidelines was low in this sample. Participants following physical activity guidelines had a reduced odd of MetS. Thus, increased adherence to guidelines may improve cardiometabolic factors in El Banco por Salud.

Funding: The University of Arizona's Center for Disparities and Diabetes, Obesity and Metabolism

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Graduate/Professional Student

P18 Unraveling the Role of Mitochondrial DNA Methylation in Insulin Resistant Skeletal Muscle

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The methylation of mitochondrial DNA (mtDNA) has been widely overlooked. It is unknown whether mitochondrial DNA methylation occurs in skeletal muscle. Moreover, whether mtDNA methylation is altered in insulin-resistant states, therefore, this study aimed to determine whether mitochondrial DNA methylation in skeletal muscle differs between obese insulin-resistant versus lean insulin-sensitive participants. We studied 32 participants, 22 females and 10 males, 37.7 ± 2.1 years. There were 12 lean (22.7 ± 0.4 kg/m2) and 20 obese (36.2 ± 1.1 kg/m2) participants. Each participant underwent euglycemic hyperinsulinemic clamps in combination with vastus lateralis muscle biopsies. Genomic DNA was extracted from the skeletal muscle using the QIAamp DNA Tissue Kit. Methylation analysis was performed on select mitochondrial encoded genes (ND6, LSP, HSP, and D Loop) using the Qiagen Q48 Pyrosequencer. Our findings showed that LSP sequence 1 was not significantly different between groups: Lean 3.3 ± 0.2 versus Obese 3.1 ± 0.1%, P = NS. In addition, LSP sequence 3 was not changing (Lean 5.8 ± 0.4 versus Obese 5.4 ± 0.3%, P = NS). Likewise, ND6 was not significantly altered (Lean 4.1 ± 0.3 versus Obese 4.1 ± 0.2%, P = NS). Our results for D Loop, LSP sequence 2, and HSP data are pending and currently being analyzed. From the data collected thus far, specifically for ND6 and LSP sequence 1 and 3, mitochondrial methylation is not changing between the insulin-sensitive lean versus the insulin-resistant obese participants. Future experiments will be performed on additional mitochondrial encoded genes to determine the exact role of mtDNA methylation in skeletal muscle insulin resistance.

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P19 Ultra-processed Foods Have a Lower Glycemic Index and Load Compared to Minimally Processed Foods

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Consumption of ultra-processed foods (UPF) is associated with numerous chronic diseases (e.g., obesity, diabetes, and cardiovascular disease) and has been shown to make up the majority of calories in the US diet. Glycemic index (GI) and load (GL) are measures of the quality and quantity of carbohydrates in food incorporating their effect on blood glucose post consumption. Diets with a high GI and GL are also associated with numerous chronic diseases. Therefore, the aim was to examine foods assigned into NOVA categories by GI and GL. It was hypothesized that GI and GL would be lowest in minimally processed foods (MPF) compared to processed (PRF) and UPF (with no difference between PRF and UPF) for all food items and food groups. GI and GL values produced by healthy/normal individuals for 2,205 food items were collected from published sources. Food items were then coded by processing levels determined by the NOVA Classification. In addition, food items were coded into 8 groups (Beverages; Beans, Nuts, & Seeds [BNS]; Dairy; Fats & Sweets; Fruits & Fruit Juices; Grains; Meat Poultry & Fish; and Vegetables). A hierarchical linear model was used to determine significance with an alpha of 0.05. The effect of food processing on GI ($p<0.001$) and GL ($p<0.001$) was contrary to our hypothesis (i.e., the mean GI and GL were highest for minimally processed foods; MPF: 56a, PRF: 53b, UPF: 50b; values sharing same letter are not significantly different) and GL (MPF: 18a, PRF: 16b, UPF: 12c). Among food groups, there was no interaction between food processing and GI ($p=0.084$), but the interaction for GL was significant ($p<0.001$). Moreover, the direction of difference in GL was inconsistent among food groups: BNS (MPF: 6a, PRF: 9a,c, UPF: 10b,c), Dairy (MPF: 5a, PRF: 3a,c, UPF: 8b,c), and Grains (MPF: 23a, PRF: 21b, UPF: 13c). In conclusion, across all analyzed food items, UPF have a lower GI and GL compared to MPF and PRF (GL only), with mixed findings among food groups. Surprisingly, ultra-processing of grains may improve glycemic responses, perhaps by the addition of protein, fat, and sugars. These results suggest that the negative health outcomes associated with consumption of UPF are due to other unhealthful aspects (e.g., energy density, food additives, and increased palatability), not higher GI and GL.

Funding: AJB was awarded the 2021-2022 Arizona State University School of Life Sciences Completion Fellowship.

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P20 Effect of Macronutrient and Micronutrient Manipulation on Avian Blood Glucose Concentration: A Systematic Review

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With the high prevalence of diabetes worldwide, the animal kingdom may provide clues to improve human health. Birds are unique in their ability to prevent complications from their naturally high levels of blood glucose (e.g., glycation and oxidative stress), which makes them useful models to elicit potential strategies to prevent/treat diabetes-related complications in mammals. Since diet influences blood glucose and ultimately diabetes risk in mammals, the goal of this systematic review is to summarize the effects of nutrient (macro and micronutrient) manipulation on avian blood glucose. Three databases were reviewed (PubMed, SCOPUS, and Web of Science) with search terms ("Avian" OR "Bird" OR "Aves") AND ("Diet") AND ("Plasma Glucose" OR "Blood Glucose" OR "Serum Glucose") to find articles that met inclusion criteria: alter at least one nutrient and measure blood glucose in at least one avian species. The search yielded 91 articles that produced 128 data sets (i.e., one nutrient manipulation in one species). Across all macronutrient studies, most showed no change to blood glucose levels (62%). In addition, within the macronutrient groups (carbohydrate, lipid, protein, and mixed) most studies also showed no change in blood glucose (67%, 62%, 52%, and 86%, respectively). Across micronutrient studies, most showed no change in blood glucose (51%). While vitamin studies largely showed no change in blood glucose (62%), mineral studies had less consistent outcomes with 48% producing no change and 46% decreasing blood glucose. Chromium was the most studied micronutrient (n=24 data sets) with a majority of studies showing a decrease in blood glucose (67%). These results suggest that birds are able to consume diets of varying nutrient composition without altering blood glucose. It should be noted that the vast majority of included studies were conducted in poultry (macronutrient datasets: 86%; micronutrient datasets: 100%), thus further research in non-poultry is warranted.

Funding: AJB was awarded the 2021-2022 Arizona State University School of Life Sciences Completion Fellowship.

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P21 Effects of Cyanidin Chloride on the Human Mouth and Skin Microbiome

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This experiment was carried out to investigate the antioxidative properties of the anthocyanin, cyanidin chloride (cyc), on the human mouth and skin microbiome by examining protein concentration and reactive oxygen species (ROS). Working concentrations of cyc were prepared by obtaining 10 micrograms and 100 micrograms made in 1XPBS. Microbiome samples from the forearm skin and cheek were obtained under sterile conditions using sterile swabs. Two nutrient agar plates were obtained where Plate 1 was the experimental plate, divided into four sections for skin and mouth cyc concentrations. Plate 2 was the control plate with no cyc addition and was divided into two sections for skin and mouth. Each cyc concentration was spread onto the plate 1 and allowed to dry before the microbiome samples were streaked. Subsequently, an antioxidant analysis was carried out after 48 hours had elapsed. The microbiome plates were analyzed using CellROX Green Reagent (Sigma Aldrich) to detect reactive oxygen species (ROS). The manufacturer's protocol was used to detect ROS and microbiome cells analyzed using a Leica microscope. Following the antioxidant analysis, a BCA protein analysis was conducted after 24 hours of time. Single colonies from all sections of the microbiome plates were grown in nutrient broth for 24 hours at 370C. Cultures were then centrifuged and lysed using lysozyme. A BCA analysis (Pierce Thermo-Fisher) was performed according to manufacturer's instructions in duplicate. The ROS content considerably decreased in the mouth and skin microbiome with 100 micrograms concentration of cyc. The BCA assay results for the skin microbiome indicated an increased protein concentration in the 100 micrograms cyc treatment compared to control and 10 micrograms cyc. For the mouth microbiome BCA assay results indicated an increased protein concentration in the 10 micrograms cyc treatment compared to control and 100 micrograms cyc. The results from this study indicate that anthocyanins may increase antioxidant properties of the human microbiome along with increasing the microbiome protein concentrations. Further studies using more cyc concentrations and time intervals, need to be conducted to understand better the effects of cyc on the microbiome protein concentrations along with the antioxidative effects.

Funding: Research and Development Program in CSET

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P22 An Assessment of Recruitment of Minority Populations into Clinical Research Studies

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Racial and ethnic minorities make up roughly 38.7% of the United States population (Williams, 2018). After the NIH revitalisation act of 1993, the guidelines for NIH-funded research were changed to include women and minorities. Even though they are now included, the rate of inclusion of these minority groups in research studies is only between 2% and 16% (Williams, 2018). There are many health disparities observed in minority populations that have yet to be researched such as diabetes, cancer, and cardiovascular disease (Vega et al., 2009). In order to help underrepresented communities, we need to know what barriers there are in order to strategize our efforts to connect with them so they feel safe when participating in research. Thus, the purpose of this project was to identify barriers that could possibly deter members of underrepresented communities from participating in research. We performed a literature search in ScienceDirect and BiomedCentral using the following keywords: Hispanic community, underrepresentation in research, barriers, strategies, and successes in minority communities to identify relevant articles. The common barriers were: mistrust of the scientific community, economic and time constraints, and cultural barriers. Strategies to overcome these barriers included: increasing diversity of research personnel, flexibility of hours for participation, and incentives for participation. What was discovered after doing this literature search was that there was a multitude of barriers, but almost the same number of strategies to combat these barriers. What was also discovered is that it is also the researcher's responsibility to serve these communities through service, community engagement, and providing free services to build strong ties and relationships with the communities they want to engage.

Funding: National Institutes of Health

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P23 Sex, Age, and Region-Specific Changes in Astrocytes Following TBI in a Behaviourally Relevant Circuit

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Traumatic brain injury (TBI) survivors face long-term post-TBI morbidity and increased risk for neurodegeneration. Clinical studies report sex differences and neuroinflammation as a primary modulator for persisting pathophysiology. Astrocytes influence neuroprotection, neurorepair, and neuropathology. Longitudinal consequences in both sexes are unknown. The thalamocortical(whisker) circuit (WBC) in rodents underlies late-onset somatosensory hypersensitivity to whisker stimulation after TBI. Male and female Sprague Dawley rats(n=5-6/group) were subjected to sham surgery or midline fluid percussion injury (FPI). At 7, 56, and 168 days post-injury(dpi), brains were processed for immunohistochemical analyses to evaluate astrocyte activation and neuropathology in multiple brain regions. GFAP density and soma count increased as a function of FPI ($p > 0.0001$), DPI ($p > 0.05$) and FPI×DPI interaction ($p > 0.01$) for intensity in the thalamus. At 7dpi, GFAP was elevated (~45%) compared to sham and remained elevated at 168dpi. However, GFAP intensity increased between 56 and 168d in shams, such that GFAP levels in sham and FPI rats were similar 168d. Measures in the inhibitory nucleus mirrored the thalamus. In the cortex, GFAP intensity increased as a function of FPI ($p > 0.0001$), DPI ($p < 0.0001$), FPI×DPI ($p < 0.0001$), and approaches significance with Sex×FPI ($p=0.06$). GFAP pixel density and soma counts increased (82-100%) in FPI at 7dpi and decreased over time, where females were more like age-matched shams at 56dpi and males at 168dpi. Amino-cupric silver stain indicated neuropathology increased at 7dpi and decreased over time. These data indicate single mFPI results in prolonged neurodegeneration with a glial response that differs in sex, time, and region-dependent fashion. Age was a factor that influences gliosis independently over time. Assessment of astrocyte phenotypic plasticity could indicate if these sex, time, age, and region dependent effects demonstrate changes in neurotoxic or neuroprotective functionality.

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S1.1 Fibrillin-1 Mutation Accelerates Blood Brain Barrier Dysfunction and Cerebrovascular Aging, Leaving the Brain More Vulnerable to Traumatic Brain Injury

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Over 69 million traumatic brain injuries (TBIs) are reported annually worldwide, where the geriatric population are at greatest risk for prolonged morbidity and mortality. Cerebrovascular aging contributes to this increased vulnerability through extracellular matrix (ECM) impairment, vascular wall weakening and stiffening, blood-brain barrier (BBB) permeability, and exacerbated cytokine production, yet the mechanisms behind these contributions are minimally investigated. In order to study these targets efficiently and with minimal variability, an animal model presenting these cerebrovascular alterations is required. Fibrillin-1 (Fbn1) protein plays a role in elasticity and inflammation, and its mutation is known to lead to ECM impairment and vessel wall weakening induced by increased availability in transforming growth factor-beta (TGF-beta) and downstream production of matrix metalloproteinases (MMPs)-2/-9. In mice, this mutation induces vascular dysfunction by 6M of age.

In this study, a well-characterized transgenic mouse model (Fbn1+/-) was utilized to test the hypothesis that Fbn1 mutation would accelerate cerebrovascular rigidity, BBB permeability, and neurological alterations associated with aging, leaving the brain more vulnerable to diffuse TBI. In 6M-, 9M-, and 12M-old Fbn1+/- and C57BL/6 wildtype (WT) male and female mice, posterior cerebral artery (PCA) blood flow (n=6-10), PCA rupture point (N=3-5/group), BBB permeability (N=2-3/group), injury viability (N=5-8/group), and neurobehavioral severity scale (NSS) outcomes (N=10-11/group) were assessed.

Our data shows that 6M-old Fbn1+/- mice have decreased PCA blood flow ($p<0.05$), compromised PCA wall strength ($p<0.05$), increased BBB permeability ($p<0.05$), and elevated NSS scores ($p<0.05$) as compared to 6M-old WT, and similar to 12M-old WT mice. To investigate vulnerability to mild TBI (mTBI), varying pulse pressures (1.11-1.32atm) were applied to the brains of 6M-old WT (1.25-1.32atm) and Fbn1+/- (1.17-1.21atm) mice using midline fluid percussion injury, where Fbn1+/- mice required lower pressure to induce mTBI righting reflex times (4-6minutes).

These data support that cerebrovascular aging contributes to outcome after TBI. Furthermore, this study demonstrates that Fbn1 mutation plays a critical role in the vulnerability of the aged brain to mTBI. Using this novel approach of a transgenic animal model that isolates cerebrovascular aging allows for the mechanistic study of potential Fbn1 downstream pathways that could serve as a therapeutic target for prevention and management of symptoms in geriatric TBI patients.

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Graduate/Professional Student

S1.2 Effects of Postnatal Maturation on Muscarinic Acetylcholine Receptor Distribution in Hypoglossal Neurons

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Upper airway patency is decreased during rapid eye movement (REM) sleep due to loss of genioglossus (primary tongue protruder) tongue muscle tone. Hypoglossal motoneurons (XII MNs), which innervate the genioglossus muscle, receive less excitatory noradrenergic drive, and may be inhibited by activation of muscarinic acetylcholine receptors, during REM sleep. Indeed, preliminary data from intact adult rats during natural sleep implicated an inhibitory effect of muscarinic acetylcholine receptors on hypoglossal motoneurons. However, data using the rhythmic slice preparation from neonatal mice indicate that muscarine has a net excitatory effect on inspiratory burst amplitude at hypoglossal motoneurons. Our project examines the distribution of muscarinic acetylcholine receptors at XII MNs, and how that changes across postnatal maturation. We hypothesize there would be an increase in inhibitory (M2) and decrease in excitatory (M1, M3, M5) muscarinic receptors in XII MNs with postnatal maturation. We performed double-labeled immunofluorescence experiments on perfused 20µm transverse brainstem slices across six postnatal age groups under identical conditions: P0-P2, P3-P5, P6-P10, P11-P13, P14-P17, and adult against muscarinic targets M1, M2, M3, M5. Slices were co-labeled with choline acetyltransferase (ChAT) and 4',6-diamidino-2-phenylindole (DAPI). Images of the hypoglossal motor nucleus (HMN) were collected using a confocal microscope. ImageJ was used to determine the average HMN muscarine receptor subtype intensity across postnatal maturation. Preliminary data (n = 1) indicate that M1 receptors showed a consistent decrease in labeling intensity in the HMN across development (P1=100%, P13=80%, P17=67%, adult = 40%), whereas M3 (n = 1) (P5= 86%, P9=81%, P13 = 100%, adult = 45%) showed a transitory increases in expression before a final decrease into adulthood. M5 (n = 1) expression shows a bimodal distribution of labeling intensity (P1= 100%, P5= 58%, P9 = 70%, P13 = 58%, adult = 37%). In contrast, M2 receptor expression intensity remained relatively high with small fluctuations into adulthood (P1 = 92%, P5 = 100%, P9 = 91%, P13 = 78%, P17 = 88%, adult = 77%). These data partly support our hypothesis that there would be a decrease in expression intensity of excitatory M1, M3, and M5 receptor subtypes into adulthood. Contrary to our hypothesis, we observed minimal change in the expression intensity of inhibitory M2 receptors. The decrease in labeling intensity of excitatory muscarinic receptor subtypes supports the observed shift in muscarinic modulation from excitation to inhibition with postnatal maturation.

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Graduate/Professional Student

S1.3 Maternal Dietary Deficiencies in One-Carbon Metabolism During Early Neurodevelopment Results in Sex Differences in Stroke Outcome in Middle-Aged Male and Female Mice Offspring

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A maternal diet that provides adequate nutrition during pregnancy and lactation is vital to the neurodevelopment of offspring. Deficiencies in nutrients during fetal growth can lead to altered early life nutritional programming, such as spina bifida, a neural tube defect. One-carbon metabolism, which includes folic acid and choline, plays a vital role in the closure of the neural tube of the developing embryo; however the impact of maternal dietary deficiencies on offspring neurological function later in life remain unknown. Stroke is one of the leading causes of death globally, and its prevalence is expected to increase in younger age groups the future as the incidence of various risk factors for stroke increases. Furthermore, dietary deficiencies in one-carbon metabolism are a major risk factor for ischemic stroke. The aim of the study is to fill the literature gap regarding the impact of maternal dietary deficiency in folic acid or choline in adult offspring stroke outcomes. It is hypothesized that deficiencies in maternal nutrition during pregnancy will result in alterations in early life neuro programming that will ultimately affect stroke outcome. Female mice were placed on control, folic acid (FD), or choline deficient (ChDD) diets for a period of four weeks and then mated. After weaning, offspring were placed on a control diet and at 10-months of age female and male offspring underwent an ischemic stroke via photothrombosis targeting the sensorimotor cortex. Four weeks after damage to the sensorimotor cortex, we used the accelerating rotarod and forepaw placement tasks to measure stroke outcome of male and female offspring. After ischemic stroke, male offspring used their non-impaired forepaw more to explore the cylinder compared to female animals. The female offspring from FD and ChDD mothers preferentially used their impaired forepaw. Additionally, female mice were able to stay on the accelerating rotarod for longer and reach a higher speed compared to male offspring. The data from our study suggest that male middle-aged adult mice had worse stroke outcome compared to female offspring. We are currently assessing brain tissue from this study for neurodegeneration.

Funding: AHA 20AIREA35050015

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S1.4 Age-Related Changes in the Retinoic Acid Synthesis Enzyme, ALDH1A2, in the **Zebra Finch Vocal Circuit**

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Vocal Learning is a complex learned behavior that occurs in zebra finches and humans. For humans it is the prerequisite trait to the acquisition of spoken language and understanding the associated brain mechanisms that underlie its use are important in understanding speech disorders. Like in humans, the neurological underpinnings of zebra finch vocalization is attributed to a cortical-striatal brain circuit. Interestingly, this circuit operates under the regulation of retinoic acid (vitamin A) signaling, a potent molecule that signals neuronal differentiation. When retinoic acid signaling is perturbed in the juvenile finch through vitamin A deficiency, its ability to learn song is affected. In this study we examine changes in the brain-specific retinoic acid synthesis enzyme, ALDH1A2, during the critical period for juvenile vocal learning. Previous research has identified ALDH1A2 gene expression in vocal nuclei HVC and LMAN, but the discovery of the ALDH1A2 protein in RA and striatal Area X, as well as the axons that connect the circuit, expands the targets of retinoic acid in this circuit. To characterize how this signaling changes over juvenile vocal development we measured ALDH1A2 in HVC, X and RA from male and female zebra finch brains collected at days 10, 15, 35, 50, and adulthood (>120 days). Slides were reacted by immunohistochemistry with an antibody to ALDH1A2, made visible with the Vector ABC system and a diaminobenzene precipitate. Brain structures were imaged at 20x with a Leica upright microscope and the images were analyzed for cell counts and signal densiometry in soma and neuropil using ImageJ. The ALDH1A2 signal was highest within the soma of cells within the HVC, when compared to tissue background. However, there were no significant changes to the densiometric concentration with age in HVC soma. This contrasts with a previous study that found the gene expression of ALDH1A2 in HVC increases with juvenile development. In our study we found that the ALDH1A2 enzyme increases in the neuropil of nucleus RA with a dramatic increase between 35 and 50 days. This developmental pattern did not occur in female brains however, consistent with the fact that females don't learn to sing. This supports a model of retinoic acid signaling that is controlled over a long distance in the brain and transmitted across the synapse. Furthermore, it suggests that autocrine signaling with HVC is not as imperative to the zebra finch's vocal learning. Given that human populations that experience vitamin A deficiency are estimated to number ~140 million globally, further studies on how this micronutrient plays a role in vocal learning and other forms of memory and brain function are important to improving human health.

Funding: MWU College of Graduate Studies Intramural Grant

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Postdoc/Research Associate

S2.1 Predicting and Preventing Outbreaks of Rocky Mountain Spotted Fever, the Deadliest Tick-borne Disease in the United States

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Beginning in 2003, an outbreak of Rocky Mountain Spotted Fever (RMSF) spread through Arizona. The number of cases in Arizona has grown year over year and now affects an area stretching across most of the Southwest United States and Northern Mexico. RMSF is a zoonotic disease that is spread from a canine host to humans through incidental contact with a tick vector. In the regions of the United States where RMSF is endemic, the bacteria is vectored primarily by *Dermacentor variabilis* and *Dermacentor andersoni* in the west, however neither of these species' ranges extend into the area associated with the current outbreak. As the deadliest tick-borne disease in the United States, RMSF outbreaks are always a public health concern, but what makes the Arizona outbreak of particular interest is the apparent rise of a novel vector, *Rhipicephalus sanguineus*, or the brown dog tick. Puzzlingly, the brown dog tick is a widely distributed species, being found in all states in the U.S., but reports of its capacity to vector RMSF seems to be limited to the Southwestern U.S. Here, we show that the rise of this unique vector and spread of RMSF in the Arizona region has been due to a combination of: (1) A unique population of ticks, (2) a unique strain of the causative bacteria *Rickettsia rickettsii*, (3) the variation in canine seroprevalence, and (4) the geographic distribution of climate. First, our analysis has shown that there are 3 genetically distinct clades of brown dog tick across the region with differential abilities to harbor *R. rickettsii*, with all three clades able to carry it. Second, we have shown that there is variation in the strain of *R. rickettsii* itself by sequencing less conserved intergenic regions of their genome. Third, by using immunofluorescence assay we have demonstrated that canine seroprevalence rates have risen in the region leading to spread of RMSF and we have identified seropositive dogs in regions that have previously not had any human cases. Even more concerning, 14 of 16 counties surveyed were at medium to high risk for human outbreak. Lastly, all of these factors were analyzed at a county level and correlated with geographic location and climate to determine areas of future spread. Together, these data help us in our efforts to predict and prevent future RMSF outbreaks, and decide where to deploy our limited preventative resources.

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S2.2 Myosin Heavy Chain mRNA Isoform Expression is Not Affected by Exercise or "Western-Type" Diet in Mice Models

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MHC isoform mRNA expression was evaluated in HFHS fed mice after 12 weeks of exercise training and return to a standard diet. 33 mice were studied during a 24-week period. A group of mice (n=9) were fed a HFHS diet (60% of calories from fat and high fructose (55%)/sucrose (45%) in drinking water) for the duration of the study. A HFHS control group (n=8) was fed the same diet as HFHS for the first 12 weeks, then fed a standard chow and water for the remaining 12 weeks of the study. A HFHS + exercise group (n=8) was treated as the HFHS group with the addition of exercise (30-minute bouts of treadmill running 5 days/week) for the last 12 weeks. A group (n= 8) was fed a standard chow and water for all 24 weeks and served as the lean control group (LN CON). Total RNA was extracted from gastrocnemius muscle, and isolated RNA was converted to cDNA. Real-time PCR was performed using TaqMan® gene assays to detect mRNA expression of MHC isoforms. Given that gastrocnemius includes predominantly fast twitch muscle, type II fibers, namely MYH 1 (type IIx), MYH 2 (type IIa), and MYH 4 (type IIb), became the focus of this study. mRNA expression was calculated through comparative CT analysis. The HFHS + exercise group shows decreased expression of MYH 2 mRNA compared to LN CON (0.52 ± 0.89 vs 1.00 ± 0.80; $P > 0.05$). When the HFHS + exercise group was compared to HFHS rather than the LN CON, MYH 2 mRNA expression was even less pronounced (0.44 ± 0.75 vs 1.00 ± 0.80; $P > 0.05$). No effects in mRNA expression of MYH 1 (type IIx) and MYH 4 (type IIb) were noted between groups ($P > 0.05$). Apart from a downward trend for MYH 2 (type IIa) expression seen with exercise training in the presence of HFHS diet, collectively these data show that MHC changes at the mRNA level are resistant to environmental factors under the experimental conditions of the study.

Funding: Midwestern-Arizona Alzheimer's Consortium

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Postdoc/Research Associate

S2.3 Decreased Aortic Smooth Muscle Contraction in The Mouse Model of Marfan Syndrome: Role of Nitric Oxide

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Marfan Syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue of the mammalian anatomy. It is caused by mutations in the Fibrillin-1 (Fbn1) gene encoding the Fbn1 glycoprotein, which forms the molecular scaffold for microfibrils in the extracellular matrix. The associated mutations induce aberrant elastic fiber organization and alignment, leading to aortic wall instability and increased stiffness. As a result, MFS patients, in addition to bone and skin abnormalities, frequently face cardiac and vascular complications, with the severe cases leading to eventual aortic dissection, rupture, and death. We have previously shown that MFS aortopathy is associated with endothelial dysfunction, which is highlighted by a significant decrease in endothelial nitic oxide (eNOS)-mediated nitric oxide (NO) production. These effects can be countered through aerobic exercise, which has been widely shown to promote NO production. In the current, study we examine the potential effects of exercise on vascular performance in 6-month-old MFS mice carrying Fbn1 mutation and age- and sex-matched C57BL/6 wildtype (WT) controls (male and females). At 4-6 weeks of age, MFS mice were subjected to daily treadmill exercise (at 55% of VO2max, 8m/min, 30min/day, 5days/week) for the duration of 5 months. At 6 months of age, 2mm descending aortic rings were collected and mounted in a small chamber myograph in order to measure the vascular reactivity in response to various pharmacological agents. Our results showed that MFS mice subjected to exercise had a higher rupture point compared to age-matched MFS sedentary mice. Furthermore, phenylephrine-induced contraction [50 µmol/ml] was lower in MFS mice compared to sedentary WT. Interestingly, exercise led to further drop in PE-induced contraction in MFS mice. In addition, using acetylcholine [1 µmol/ml] in the presence of either general inhibitor of NO production, N(G)-Nitro-L-arginine methyl ester (L-NAME) or the specific and potent inhibitor of inducible nitric oxide synthase (iNOS), 1400W, revealed that the observed decrease in aortic contraction in MFS mice is mainly due to increase NO production within the aortic wall mainly through increased iNOS activity. By blocking NO production within the aortic ring, we were able to restore PE-induced aortic contraction to a level similar to the one observed in healthy age-matched WT control mice. This study shows that MFS aortopathy is associated with an elevated level of basal NO production in the aortic wall mainly due to increase in iNOS activity. Our data also provide indications that NO uncoupling due to an increase in iNOS activity may contribute to the development of endothelial dysfunction during the progression of aortic aneurysm in MFS mice.

Funding: National Institutes of Health

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S2.4 Microbiome and Metabolome Profiles of High Screen Time in a Cohort of College Students

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Screen time, or the time spent using a device such as a computer, television, or games console, is a matter of increasing public and scientific interest. As screens are progressively integrated into every facet of modern life, there is growing concern over the potential effects of high screen time. Previous studies have largely analyzed self-report data on mood and behavior, and no molecular theory has yet been developed. In this study, we explored the fecal microbiome and metabolome of a diverse group of 60 college students classified by high (≥75 min/day; n = 46) or low (0-75 min/day; n = 14) self-reported screen time using 16S amplicon sequencing, targeted liquid chromatography-tandem mass spectrometry (MS/MS), and targeted detection of short-chain fatty acids using gas chromatography-MS. PICRUSt analysis predicted differential functional changes in more than 50 biologically relevant enzymes ($1.39e\text{-}4 \leq q \leq 0.049$), whereas enzyme enrichment analysis of metabolomic data predicted significant dysfunction in 22 enzymes ($0.003 \leq p \leq 0.045$). Taxon set enrichment analysis showed subjects in the high screen time group had significant increases in taxon sets related to Crohn's disease ($q = 0.001$), type I diabetes ($q = 0.003$), having an overweight/obese mother ($q = 0.003$), and myocardial infarction ($q = 0.008$); high screen time users also had significant increases in taxa related to consumption of red wine ($q = 0.007$) and coffee ($q = 0.025$). Conversely, the low screen time group had significant increases in taxon sets related to liver cirrhosis ($q = 0.001$), autism ($q = 0.006$), as well as consumption of a high-fat diet ($q = 0.047$). Furthermore, fecal metabolites associated with eight disease signatures were significantly increased in the high screen time group: celiac disease ($p < 0.001$), inflammatory bowel disease ($p = 0.001$), treated celiac disease ($p = 0.008$), obesity ($p = 0.016$), asymptomatic diverticulitis ($p = 0.031$), diverticular disease ($p = 0.031$), symptomatic uncomplicated diverticular disease ($p = 0.031$), and chronic fatigue syndrome ($p = 0.043$). We integrated 16S and MS/MS data using neural networks to perform microbe-metabolite interaction analysis: *Collinsella*, *Lactobacillales*, *Ruminococcus*, cc115 (family Erysipelotrichaceae), and *Turicibacter* had a high probability of co-occurring with isoleucine, L-alloisoleucine/leucine/norleucine, valine, proline, and phenylalanine. We synthesized our findings to articulate an integrated hypothesis describing widespread mitochondrial dysfunction and aberrant amino acid metabolism. To the best of our knowledge, this is the first-ever study to report the effects of high screen time at the molecular level.

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S3.1 Reproducibility of a High Fat Diet Induced Weight Gain Over Independent Years

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The purpose of this study is to assess the reproducibility of a high fat diet (HFD) over 3 independent, consecutive years (18-20). Male Sprague-Dawley rats (140-160g) had ad libitum access to water and either a lard based HFD (5.24 kcal/g) or a standard 'CHOW' diet (3.1 kcal/g) for an 8-week period, after an acclimation period of 3-weeks (CHOW). Animal weights were obtained daily. Fresh portions of food were provided each day and the weight of non-ingested pellets were recorded for caloric intake calculations. Cumulative (peak) data showed HFD-fed rats had increased weight gain and energy intake, within years, when compared to control. However, periodic (weekly) evaluation expressed significance in the first two weeks only. Additionally, significant growth rate curves between CHOW and HFD ($p=0.001$ and <0.0001 respectively) exposed two phases (insignificant between years); an early rapid phase followed by a late slow phase with an ~50% reduction of weight gain from fast to slow. Multiple comparison of means showed insignificance for each phase of each diet, significance between diets, and no significance in mean weight gain. Isolated periodic responses for peak weight gain between diets expressed significance in week 1 for all years, week 2 of year 18, and insignificance in subsequent weeks. Rodents were further identified into upper and lower tertiles where the upper tertile was defined as obesity prone (OP) and the lower as obesity resistant (OR). OP rats expressed higher weight gain and energy intake. Cumulative values expressed significance; however periodic values indicated the OP phenotype was defined within the first week. Between years, both periodic and cumulative data suggested no significance between a HFD and CHOW diet in addition to OP and OR. Conversely, energy intake of HFD rats was significant at all intervals. Feeding efficiency (FE) was insignificant between years, however, each year FE was higher in OP rats when compared to OR. In conclusion, cumulative values for weight gain and energy intake are suggestive of reproducible data, however periodic evaluation of this data is not suggestive of similar patterns. Additionally, the appearance of obesity results from analysis of cumulative weights for HFD and CHOW in all weeks, however weekly data reveals that weight gain (and/or hyperphagia) is limited to the first or second week. Finally, energy intake does not entirely explain weight gain thus indicating an alternative response such as an increased FE, rather than caloric intake, as a possible explanation of weight gain.

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S3.2 Impact of an Exercise Training Intervention on DNA Methylation in Skeletal Muscle

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Human skeletal muscle is dynamically regulated by the physical demands of the body and environmental stimuli. The plasticity of muscle is constantly altered in response to activities imposed, such as exercise training, which ultimately changes physiological processes, including metabolism and gene expression. DNA methylation is an epigenetic mechanism used by cells to control gene expression, where changes in DNA methylation predispose individuals to obesity and other related metabolic syndromes. Significant research has been conducted to analyze the association between obesity and DNA methylation. However, our goal is to understand the mechanisms and genes involved in DNA methylation before and after an exercise training program. Thirteen sedentary participants (5 men and 8 women, aged 34.6 ± 3.1 years, BMI 30.7 ± 2.1 kg/m2) were placed on a supervised eight-week exercise regimen to analyze training effects on glucose and insulin metabolism, peak aerobic activity (VO2), and differentially methylated cytosines (DMCs). Participants underwent a euglycemic hyperinsulinemic clamp to measure insulin action on glucose utilization pre and post 8-weeks of exercise training. We showed that exercise training significantly increased peak aerobic capacity (pre: 31.7 ± 1.1 to post: 36.6 ± 1.5 ml per Kg FFM per minute, P = 0.000034). Moreover, exercise training significantly decreased fasting serum insulin (pre: 8.5 ± 2.5 versus post: 2.4 ± 0.9 uIU/mL, P = 0.00065) and increased insulin-stimulated glucose disposal (pre: 8.5 ± 1.2 versus post: 9.0 ± 1.3 mg per Kg FFM per minute, P = 0.01). There were no changes in fasting plasma glucose and rates of glucose appearance in the pre- versus post-training. Exercise training resulted in 13 increased, and 90 decreased DMCs post-exercise training. Of the 13 increasers, 2 were assigned to the following genes, FSTL3 and RP11-624M8.1. Of the 90 decreasers, 9 were assigned to the following genes, CNGA1, FCGR2A, KIF21A, MEIS1, NT5DC1, OR4D1, PRPF4B, SLC26A7, and ZNF280C. The results from this study conclude that physical and environmental factors cause modifications in DNA methylation.

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S3.3 High-Resistance Breathing Training Enhances Respiratory Strength and Endurance and Blunts Cardiac Response to Exercise

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Low respiratory strength and endurance are independent risk factors for myocardial infarction and cardiovascular disease death. High-resistance, low-volume Inspiratory muscle strength training (IMST) can substantially lower blood pressure in as few as three weeks, and also has the potential to enhance inspiratory muscle strength and endurance. However, the relationship between IMST and inspiratory muscle strength and endurance has not been adequately explored. Further, the cardiac response to IMST has not been characterized. The purpose of this study was to assess the effects of 6 weeks of inspiratory muscle strength training on inspiratory muscle strength and endurance, as well as the cardiac response, during a constant-load respiratory test in recreationally active men and women (n=9; 21.1 ± 2.5 years). Maximal inspiratory pressure was assessed with a two-way non-rebreathing valve against near-infinite resistance at baseline and weekly thereafter to ensure exercise intensity was maintained week-to-week. Inspiratory endurance was assessed by continuous breathing via a constant-load circuit at 65% of subjects' maximal inspiratory pressure until failure. Blood pressure and heart rate were assessed continually during the endurance task with an automated finger cuff pressure transducer. Subjects performed high-resistance IMST 5 minutes/day, 5 days/week, for 6 weeks (5 sets of 6 breaths at 75% of maximal inspiratory pressure). 6 weeks of IMST resulted in a decrease in systolic and diastolic blood pressure (-5.8 ± 4.1 and -5.2 ± 5.2 mmHg, respectively) and an increase in inspiratory muscle strength (65.2 ± 46.5%), as well as in inspiratory work (67.9 ± 63.9%) and time-to-failure (302 ± 219 s) during the endurance task. Change in inspiratory muscle strength and endurance were modestly associated, but not significantly (r=0.476, p=0.195). In addition, blood pressure and heart rate responses during the endurance task were depressed following the intervention. IMST is an effective tool to reduce cardiovascular disease risk through reductions in blood pressure and improvements in inspiratory strength and endurance in healthy young adults. Further, the cardiac response to constant-load inspiratory work was depressed, despite large increases in test duration and total workload, suggesting repressed sympathetic activity. In conclusion, high-resistance, low-volume IMST is a time- and cost-efficient exercise with the potential to be a highly-effective tool to combat cardiovascular disease.

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S3.4 Marfan Syndrome-Associated Aortic Aneurysm: the Role of Nitric Oxide

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Marfan Syndrome (MFS) is an autosomal-dominant connective tissue disorder caused by missense mutations in the gene that encodes for Fibrillin-1 (FBN1). FBN1 is a glycoprotein in the extracellular matrix (ECM) that functions as a scaffolding protein during the formation and maturation of elastic fibers. The mechanism underlying MFS pathogenesis stems from a crosstalk between the Angiotensin-II (AngII) pathway and over activation of transforming growth factor-beta (TGF-b) signaling. There are several clinical manifestations seen in MFS, but the most serious and life-threatening is the aortic aneurysm due to degradation and fragmentation of aortic wall elastin fibers. If left untreated, aortic aneurysm progression may lead to dissection and rupture. Previous studies in the MFS mouse model have shown that the progression of aortic aneurysm is associated with a significant decline in endothelial function and nitric oxide (NO) production in the aortic wall, and that overexpression of endothelial nitric oxide synthase (eNOS) could delay the progression of aortic root aneurysm in MFS mice. A recent study in our laboratory has also shown that mild aerobic exercise can block aortic aneurysm in MFS mice. It is well established that exercise can improve endothelial function mainly through an increase in eNOS-mediated NO production. Therefore, we tested the hypothesis that mild aerobic exercise prevents aortic aneurysm progression in the mouse model of MFS mainly through increasing the production of NO within the aortic wall. To test this hypothesis, C57BL/6 WT and MFS mice were subjected to daily treadmill exercise (at 55% of VO2max, starting at 4 weeks of age) in the absence or presence of the general inhibitor of NO production, N(G)-Nitro-L-arginine methyl ester (L-NAME) at 0.05 g per 100 mL of drinking water. At 6-months of age, in vivo imaging of the aortic root diameter and pulse wave velocity (PWV) as an index of wall stiffness, was performed using the high resolution Vevo2100 ultrasound system. The aortic root diameter at the sinus of Valsalva, and pulse wave velocity were both increased in MFS mice compared to WT, however MFS mice subjected to treadmill exercise had significantly decreased aortic root diameter and pulse wave velocity compared to sedentary MFS mice. In situ analysis of aortic wall integrity was analyzed at 6 months by Van Geison staining. Our results revealed that MFS mice had an increase in elastin fragment count and a decrease in elastin fiber length compared to WT. Interestingly, MFS mice subjected to exercise had fewer elastin fragment count and an increase in elastin fiber length compared to sedentary MFS mice. Current ultrasound analysis and in situ analysis of 6-month sedentary MFS mice and 6-month exercise MFS mice subjected to L-NAME treatment is ongoing and will be compared to exercise MFS and WT. This study provides preliminary evidence that mild aerobic exercise blocks the progression of aortic root dilation in MFS mice through increasing the production of NO within the aortic wall, and further emphasizes the value of increased physical activity in aneurysm population.

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S3.5 Calcium Exchange with Troponin C in Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a complex genetic disorder of the cardiac sarcomere affecting 1/500 individuals worldwide. HCM is typically characterized by variable cardiac remodeling, impaired myocardial relaxation, altered calcium homeostasis, and in some cases sudden cardiac death; however, phenotypes for patients with HCM are now known to vary from mutation to mutation. An interesting example of this heterogeneity occurs with mutations in cardiac troponin T (cTnT), a protein component of the cardiac thin filament (CTF). cTnT is part of the heterotrimeric cardiac troponin (cTn) complex responsible for conferring calcium regulation to muscle contraction, and, when mutated, it often causes HCM. This study focuses on six HCM-causing, highly penetrant point mutations located within the cTnT N-terminus (R94H/C, R92L/W/Q, and I79N) which are each associated with distinct phenotypes and disease severities in human patients. The goal of this study was to determine the effects of HCM-causing mutations in cTnT on the calcium-based regulation of muscle activation. Using fluorescently labeled, bacterially expressed, recombinant human protein, we measured in vitro calcium exchange (sensitivity and kinetics) of human cTn and CTF complexes in the presence and absence of these disease-associated mutations. Calcium sensitivity was measured by titrating calcium into cTn or CTF complexes, and kinetics of calcium dissociation and/or association were measured via stopped-flow. Introducing disease-causing HCM mutations into cTn complexes alone resulted in no significant changes in either calcium sensitivity or calcium dissociation kinetics compared to wild-type (WT) controls. Of note, this was not the case in the CTF; in this system, every mutation significantly sensitized TnC to calcium. These results indicate that actin and tropomyosin are necessary to observe the effects of mutations on CTF activation. Although all mutations significantly increased calcium sensitivity of CTFs, only four mutations (R92L/Q and R94H/C) significantly decreased the rate of calcium dissociation, whereas two mutations significantly accelerated calcium dissociation. Three mutations significantly accelerated calcium association (R92W, I79N, and R94C) while a fourth trended with a slight acceleration (R94H). Thus, the calcium sensitization reported here for each mutation is accomplished via mutation-specific changes to the kinetics of calcium exchange with TnC. Furthermore, these results suggest that the kinetics of calcium exchange with TnC in the CTF system afford high resolution mechanistic insight into altered myofilament calcium sensitivity.

Funding: NIH HL075619, ARCS Foundation

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S3.6 Is Prohibitin a Mediator of Cardiac Fibroblast Activation?

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Identification of novel molecular targets to regulate cardiac fibroblast (CF) activation in the diseased heart is a viable therapeutic approach for treating heart failure. During cardiac injury-induced fibrotic remodeling, CFs become activated and secrete extracellular matrix. Characteristics of an activated fibroblast include increased proliferation rate, increased fibrogenic gene expression, and resistance to cell death. In cancer cells, prohibitin (PHB) increases proliferation, apoptotic resistance, and mitochondrial function. However, little is known about PHB in the heart. CFs isolated from hypertensive rats (SHR) transiently treated with an angiotensin converting enzyme inhibitor (ACEi) exhibit reduced inflammatory and fibrogenic phenotypes. This shift is associated with a reduction in gene expression for PHB and other mitochondrial proteins indicating metabolic reprogramming. The aim of this study is to investigate the role of PHB in activated CFs and determine whether PHB may be a novel target for anti-fibrotic therapy. PHB and markers of CF activation were evaluated in fibroblasts following activation in vivo (myocardial infarction) or in vitro (TGF-β stimulation). To determine whether decreased CF PHB persists after injury in SHRs previously treated with an ACEi, myocardial infarction was induced in vivo by coronary artery ligation. Primary CFs were isolated from the infarct region of the left ventricle 3 days post-MI. Protein expression of PHB and periostin, a marker of CF activation, was lower in CFs from SHRs previously treated with an ACEi compared to control. Moreover, PHB expression positively correlated with periostin in CFs post-MI suggesting a mechanistic link between CF activation and PHB. To interrogate the impact of reduced PHB on fibroblast activation, PHB was knocked down in vitro using siRNA (siPHB) in RAT2 fibroblasts which were then treated with TGF-β (a potent activator of fibroblasts, 10 ng/ml) or vehicle for 48 hr. PHB siRNA significantly reduced PHB and prevented TGF-β-induced elevations in PHB expression. PHB siRNA also attenuated fibroblast proliferation and decreased Col1a1 gene expression in response to TGF-β. The propensity for fibroblasts to undergo apoptosis was assessed by the ratio of BAX/BCL-2, which was elevated in siPHB fibroblasts suggesting that PHB may confer apoptotic resistance. Together, these data indicate that PHB modulates activation and survival of fibroblasts. Thus, targeted depletion of PHB may reduce the abundance of activated CFs, thereby limiting fibrotic remodeling. Future studies will evaluate the impact of PHB on mitochondrial function and metabolic flux of activated fibroblasts.

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S3.7 Transient ACE Inhibition Sex-Selectively Impacts Angiotensin II-Induced Fibrogenic Responses

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Hypertensive heart disease is characterized by cardiac fibrosis in the left ventricle (LV). Angiotensin II (Ang II) promotes cardiac fibrosis through direct actions on cardiac fibroblasts. Inhibition of Ang II production with angiotensin converting enzyme (ACE) inhibitors has been shown to reduce interstitial collagen deposition in the LV. We have previously shown that transient treatment of male spontaneously hypertensive rats (SHRs) with an ACE inhibitor persistently suppresses the fibrogenic capacity of cardiac fibroblasts. In this study, the goal was to investigate the impact of transient ACE inhibition on subsequent Ang II-induced fibrogenic responses in the LV of male and female SHR. Male and female SHR (11-week-old) were treated with an ACE inhibitor (enalapril, 30mg/kg/day) or vehicle for 2 weeks followed by a 2-week washout period. At the end of the washout, rats were given Ang II (400ng/kg/min, s.c.) or vehicle for 2 weeks (n=8-11 per group per sex). Collagen I, III, and IV gene expression was assessed via RT-qPCR and immunoblotting for LOX and Postn was performed. In males, the Ang II-induced increase in collagen gene expression (i.e. Col1a1, Col3a1, and Col4a1) was significantly attenuated in SHR previously treated with enalapril. In female rats, Ang II significantly increased the expression of Col1a1 and Col3a1 similarly, regardless of prior enalapril treatment. We found a positive correlation between the degree of increase in Col1a1 and Col3a1 as well as with Col1a1 and Col4a1 in male Control + Ang II rats. However, in male Enalapril + Ang II rats, there was a negative correlation between Col1a1 and Col3a1 and no correlation between changes in Col1a1 and Col4a1. In female rats, there were significant positive correlations in all cases regardless of prior ACE inhibition. Additionally, in both male and female rats infused with Ang II, cross-linking proteins Postn and LOX showed decreased expression with prior ACE inhibition. These data reveal that even after stopping treatment, ACE inhibition produces persistent changes in the myocardium that render it resistant to fibrotic effects of Ang II in male, but not female, SHR. Moreover, cross-linking proteins involved in the fibrogenic response are affected in both males and females. The opposing effects seen in females suggests a possible dysregulation between collagen production and extracellular matrix cross-linking events following ACE inhibition. Future studies will elucidate the mechanisms underlying the sex-specific response to ACE inhibition and the long-term protective effect in male LV, with a goal of identifying novel therapeutic targets.

Funding: NIH HL141165 (TMH), AHA 19AIREA34460000 (TMH)

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S4.1 TBI-Induced and Age-Related Neuroinflammation Intersect at 6-Months Post-Injury

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Traumatic brain injury (TBI) affects over 69 million people every year worldwide. The development of persisting neurological deficits implicates neuroinflammation. Our lab previously identified a time course for structural, molecular, and functional mechanisms contributing to lateonset persisting hypersensitive somatosensation mediated through the whisker barrel circuit (WBC) in rats. We hypothesize that TBI leads to neurodegeneration that causes a persistent and sex dependent neuroinflammatory response in behaviorally relevant brain circuitry mediating somatosensory hypersensitivity. Young adult, age-matched male and female, Sprague-Dawley rats underwent a midline fluid percussion injury (FPI) or sham surgery (n=64). At 7, 56, and 168 days post injury (DPI), we evaluated the neuroinflammatory response in the thalamic relay of the WBC by counting Iba-1 stained cells to assess microglial infiltration and quantify morphological character-stics to estimate average branch length/cell and endpoints/cell. We found increased numbers of Iba-1 stained cells with shorter branches and fewer endpoints, indicating microglial-mediated neuroinflammatory response as a function of FPI ($p<0.0001$) & DPI ($p<0.05$). Microglial activation declined over time after FPI, but age-related microglial activation increased in shams such that microglial morphology and cell counts were similar between sham and injured groups by 168DPI ($FPI^{x}DPI$; $p<0.01$). A triple interaction between $FPI^{x}DPI^{x}$Sex approached significance ($p=0.059$) for the number of endpoints/cells whereby FPI more robustly impacted males at 7DPI than females. Additionally, the time course of activation in GFAP-stained astrocytes correlated with microglial activation, explaining a similar interaction between $FPI^{x}DPI$ ($p<0.01$). These data indicate both injury and age can influence the neuroinflammatory response. Sex may be a variable that can influence the magnitude of response at 7DPI. Persisting neuroinflammation can modify brain circuitry and accelerate age-related neuroinflammation and may provide a temporal profile critical to identifying mechanisms mediating persistent neurological deficits.

Funding: NIH-R01NS100793; Phoenix Children's Hospital Mission Support

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S4.2 Impact of Doxorubicin and Metformin on Cardiac Mitochondrial Electron Transport Chain Proteins

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Doxorubicin (DOX) has proven to be an effective chemotherapeutic treatment for childhood leukemia; however, it has adverse effects like cardiotoxicity, which has been proposed to be mediated in part by impairing mitochondrial function. Metformin has been shown to protect the heart against Doxorubicin-induced cardiotoxicity. The present study investigated the impact of doxorubicin in the presence and absence of metformin on the expression of mitochondrial proteins. Four-week old male Sprague Dawley rats were given four bi-weekly doses of DOX (4mg/kg), or vehicle [saline]. A separate group of four-week-old rats were administered MET [250mg/kg per day] in the drinking water with and without DOX. Rats were euthanized 24-30 hours after final injection of DOX. Western blots were performed to measure the expression of electron transport chain proteins CI-NDUFB8, CII-SDHB, CIII-MTCO1, CIV-UQCRC2, and CV-ATP5A in mitochondria isolated from cardiac tissue. Dox significantly reduced the body weight of rats, which was not impacted by concomitant treatment with MET. Upon gross inspection, DOX rats had noticeably enlarged, pale livers and presence of ascites in 7/8 rats. One out of four MET rats showed enlarged pale liver, and one out of four DOX+MET rat liver has fused lobes. LV to tibial weight was increased in MET compared to VEH and to DOX rats. Neither Metformin nor DOX significantly altered expression of electron transport chain proteins. The DOX treatment protocol produced marked changes in liver pathology and weight loss that was mitigated by MET. There were no significant changes in expression of mitochondrial electron transport chain proteins. Future studies are underway to evaluate the degree to which DOX and MET alter the activity of these proteins. MET has shown to provide cardio-protection. A better understanding of these mechanisms through which this occurs will have a beneficial effect on those exposed to Doxorubicin.

Funding: Valley Research Partnership; NIH; Undergraduate Biology Research Program/Native American Cancer Prevention Program at the University of Arizona; University of Arizona - College of Medicine Phoenix

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S4.3 Can Astaxanthin Improve Redox Signaling in Older Adults?

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Previous work from our laboratory has demonstrated that older individuals have an impaired redox signaling response to acute exercise compared to young. Furthermore, we have shown that this is due to chronically elevated basal levels of oxidative stress resulting in attenuated ability to respond to acute physiological stimulus. The aim of the present pilot study is to test whether redox signaling can be enhanced using a phytochemical antioxidant intervention. Astaxanthin (AX) is a caretenoid that has been shown to have significant antioxidant effects. Importantly, AX acts directly on the mitochondria where the majority of basal production of reactive oxygen species occurs. We hypothesized that a 2-week AX supplementation would improve the cellular response to an ex vivo oxidative stimulus. The study cohort consist of men and women over the age of 55y, (target n=15). The participants completed a screening visit that included health history, lifetime physical activity questionnaire, anthropometric measures, and resting blood pressure. Baseline blood draw after an overnight fast was taken and again after 14-days of AX supplementation. Peripheral blood mononuclear cells (PBMCs) were isolated and redox signaling was induced by stimulating the sample with H2O2 (low dose: 25 µM, high dose: 500 µM) and DMSO as control. The samples were incubated with the respective treatment in media at 37ºC for 10 minutes. Changes in gene expression of genes associated with redox cell signaling response were measured in response to the treatments and the AX intervention using RT-qPCR. Additionally, stimulated samples were labeled with infrared maleimide dye to detect global thiol oxidation using Western blotting. To date we have 3 men and 8 women (mean age: 61y ± 3) that have either completed or have started the intervention, with recruitment still in process. Compliance to the supplementation is 98.8%. Preliminary gene expression results show minimal changes under non-stimulated conditions (DMSO) from pre to post AX intervention. The supplementation increased the stimulated response as shown by increased Trx1 by 1.6-fold ±0.3 and NQO1 by 1.8-fold ±0.6 to the low dose H2O2. High dose stimulation increased Trx1 by 4.1-fold ±2.9, NQO1 by 1.6-fold ±0.7, and HO1 by 2.4-fold ±1.2. Preliminary western blot data show decreased non-stimulated global thiol oxidation after the intervention but no effect of the H2O2 stimulation. These early results indicate that astaxanthin supplementation may be able to improve basal redox balance in older adults and improve cell signaling response, however, additional data are needed and are in progress.

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S4.4 Neuroprotective Effects of an Over-The-Counter Curcumin Supplement Against Rotenone Induced Toxicity

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In cell culture and animal models, curcumin has demonstrated neuroprotective effects against cellular changes associated with Alzheimer's disease (AD), however in clinical trials it has exhibited poor bioavailability due to limited absorption, rapid metabolism, and rapid elimination. Longvida, an over-the-counter dietary supplement (OTC), encapsulates curcumin within solid lipid particles supposedly to improve bioavailability through enhanced gastrointestinal absorption. The study presented here was done to determine if the modifications to the OTC curcumin altered or decreased its neuroprotective effects compared to pure curcumin. Since mitochondrial dysfunction and oxidative stress have been implicated in the pathogenesis of AD SH-SY5Y cells, a human neuroblastoma cell line, was exposed to rotenone. This induces cytotoxic effects by accumulation of reactive oxygen species (ROS) by blocking complex I in the electron transport chain. Cells were pretreated before rotenone exposure with varying concentrations of Longvida or curcumin for a 2-hour period. Following pretreatment, a 24-hour treatment with rotenone was performed. Cell viability was assessed using an MTT assay, which measures metabolic activity. Statistical analysis comparing cells that received pre-treatment compared to those that were not, was performed using one-way ANOVAs followed by Bonferroni corrections. Similar to previously published studies, it was found that curcumin pretreatment significantly reduced rotenone induced cell death. Additionally, our results demonstrate that the OTC supplement Longvida significantly reduced cell death to a similar extent as curcumin. Thus far our results have found similar neuroprotective effects between purified curcumin and an OTC curcumin supplement. Currently there is no cure for AD and few treatments. Substantial neuronal cell loss occurs prior to the onset of symptoms, which makes identifying possible preventative protective measures important. The findings presented here indicate that further investigation into the potential therapeutic value of OTC curcumin is warranted.

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S4.5 Differential Expression Profiles of S1PR Types 1-5 Following Hypoxia Plus Glucose Deprivation in Human Cerebrovascular Cells

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Sphingosine-1-phosphate receptors (S1PRs) and their signaling pathways play an important role in mediating vascular health and function. Upon ligand activation, S1PR types 1-5 couple with diverse heterotrimeric G-protein subunits (Gαi, Gαq/11, Gα12/13), initiating multimodal downstream signaling pathways. S1PRs exhibit overlapping or selective expression patterns in various cell types and tissues such as lymphoid tissue and the nervous system. However, S1PR1-5 expression profile in the brain vasculature has not yet been investigated. Therefore, the present study aimed to screen for S1PR types in human brain microvascular endothelial cells (ECs) and brain vascular smooth muscle cells (VSMCs) following ischemic-like injury. Male ECs and VSMCs were exposed to either hypoxia plus glucose deprivation (HGD; 1% O2) or normoxia (21% O2) for 3h. RT-PCR was used to examine S1PR gene expression, concomitantly with western blot and ICC to examine protein levels. At the mRNA level, VSMCs expressed all S1PR types whereas we were only able to detect S1PR types 1, 2, and 3 in the ECs. Under normoxic conditions, we observed that gene expression of S1PR types 1 and 3 were most prominent relative to the other S1PR types in both the ECs and VSMCs. In ECs, HGD did not alter the mRNA levels of S1PR types 1, 2, and 3. However, we observed that HGD increased type 1 S1PR protein expression in ECs but did not alter types 2 and 3 S1PR protein levels. In the VSMCs, HGD increased both gene expression and protein levels of type 2 but did not alter the gene expression and protein levels of types 1 and 3. In conclusion, HGD appears to differentially regulate S1PRs in VSMCs and ECs; HGD increases S1PR2 expression at the transcriptional level in VSMCs and increases S1PR1 expression at the translational level in ECs. The differential expression in the various S1PR types both basally and following HGD exposure may suggest different signaling mechanisms at play during normoxia and HGD, highlighting the pathophysiology of ischemic injury at the cerebrovascular level. Furthermore, downstream mediators and proteins of S1PR signaling may be integral to the EC and VSMC cellular response to ischemic injury. Further investigation will be necessary to determine the signaling pathways of S1PR types and their impact on cerebrovascular cell function following ischemic injury.

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S5.1 Unveiling a Detrimental Role for Oxldl/LOX-1 During Occlusive Stroke: Targeting Endothelial Health and Function

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Acute ischemic stroke (AIS) triggers endothelial activation that disrupts vascular integrity, induces cerebrovascular inflammation, and increases hemorrhagic transformation (HMT) leading to worsened stroke outcomes. A critical factor mediating injury is elevated levels of oxidized low-density lipoprotein (oxLDL). Via the lectin-like oxLDL receptor 1 (LOX-1), oxLDL further contributes to cerebrovascular dysfunction and inflammation, exacerbating occlusive stroke. The impact of oxLDL/LOX-1 on cerebrovascular endothelial dysfunction and inflammation in the setting of AIS remains to be elucidated. The aim of this study is to investigate the potential of the LOX-1 receptor as a therapeutic target for acute cerebrovascular ischemic injury. Here we employed an in vitro HGD (hypoxia plus glucose deprivation) human brain endothelial cell model as well as a thromboembolic rat stroke model. In the in vivo experimental stroke studies, male Wistar rats underwent a right middle cerebral artery or sham luminal thrombin injection. Recombinant tissue-type plasminogen activator (rt-PA; 1mg/mL) or rt-PA in combination with the selective LOX-1 inhibitor, BI-0115, was administered at 4h after stroke onset and HMT was evaluated after 24h post injury via MRI. We observed an increase in HMT following thromboembolic stroke and rt-PA infusion in comparison to sham, and this response was significantly reduced by LOX-1 inhibition. In the dish, endothelial cells were conditioned with human oxLDL (50μg/dL; 18h) using a clinically detrimental serum dose reported in AIS patients. At 12h cells were treated with BI-0115 (10μM) or vehicle (<0.1% DMSO) and then exposed to HGD (1% O2) or normoxia (21% O2) for 6h in the continued presence of oxLDL and LOX-1 inhibition. HBMEC barrier, adhesion molecule, and inflammatory protein levels and localization were examined using FIJI mediated immunocytochemical analysis. HGD decreased ZO-1 levels, and with the addition of oxLDL these levels were increased independently of LOX-1 inhibition. Concomitantly, HGD increased VCAM-1 levels, however LOX-1 inhibition did not alter this response. HGD or HGD+oxLDL increased inflammatory mediator levels, IL-1β and iNOS, and these responses was attenuated by LOX-1 inhibition. In conclusion, the beneficial effect of BI-0115 on HMT, cerebrovascular permeability, and inflammation via inhibition of LOX-1 suggests that this may be a novel, viable therapeutic target in the treatment of AIS. The precise stage and mechanisms(s) by which oxLDL and LOX-1 regulate endothelial barrier function and inflammation during stroke merits further investigation.

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S5.2 Therapeutic Potential of Novel Rexinoids in Prevention and Treatment of Alzheimer's Disease

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Alzheimer's disease (AD) is the most prevalent form of dementia distinguished by synaptic dysfunction, memory loss, neuroinflammation, and neuronal cell death. AD is accompanied by aggregation, accumulation, and impaired degradation of β-amyloid (Aβ) in the brain. After decades of research to find a cure for AD, current therapeutic strategies involve predominately alleviating patient symptoms whilst the disease continues to progress within the brain. More recently bexarotene, an FDA-approved therapeutic used in the treatment of cutaneous T-cell lymphoma (CTCL), has shown promise to reverse neurodegeneration, improve cognition and decrease levels of amyloid-β in transgenic mice expressing familial AD mutations. While the mechanism of these effects is not fully understood, bexarotene is a high affinity ligand for the retinoid X receptor (RXR) which heterodimerizes with the liver-X-receptors (LXR) and with peroxisome proliferator-activated receptor-gamma (PPARγ) to control cholesterol efflux, inflammation, and transcriptionally upregulates the production of apolipoprotein (ApoE) in the brain. Enhanced ApoE expression may promote clearance of soluble Aβ peptides from the brain and reduce Aβ plaques, thus resolving both amyloid pathology and cognitive deficits. In the present study, we assessed the potential of bexarotene and a group of 23 novel rexinoids to bind RXR using a mammalian two-hybrid system (M2H). RXRE-mediated reporter assays were also employed to test transcriptional activation of these compounds. Moreover, LXRE-mediated luciferase assays were performed to analyze the ability of our novel analogs to activate LXRE-directed transcription, and to induce ApoE mRNA in U87 glial cells. Results from these multiple assays indicate that our panel of RXR ligands contains compounds with a range of activities, with some analogs capable of binding to RXR with higher affinity than others, and in some cases upregulating ApoE expression to a greater extent than bexarotene. Our data suggest that minor modifications to the bexarotene core chemical structure may yield novel analogs possessing an equal or greater capacity to activate RXR and may be useful as therapeutic agents against Alzheimer's disease.

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S5.3 Post-Menopausal Impairment in Brain Arteriolar Endothelial K^+ Channel Function in a Mouse Model of Alzheimer's Disease

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Cognitive decline, as seen in Alzheimer's disease (AD), is a growing public health concern and is linked to decreased cerebral blood flow, particularly in women after menopause. Impaired cerebrovascular function precedes the onset of AD, likely due to reduced endothelial function, such as observed during menopause, although exact mechanisms remain elusive. Endothelial K^+ channels, including Ca^{2+}-activated K^+ channels (SKCa/IKCa) and inwardly-rectifying K^+ channels (KIR2), play a key role in mediating cerebral microvascular dilation via endothelium-dependent hyperpolarization downstream from K^+ efflux. Thus, alterations in endothelial K+ channels can have a dire impact on cerebral microvascular function and may underlie the increased risk of cognitive decline in menopausal females. The goal of this study was to determine whether menopause impairs endothelial K^+ channel function in cerebral arterioles of the 5x-FAD mouse model of AD. Menopause was induced by the 4-vinylcyclohexene diepoxide (VCD) model, which induces gradual ovarian failure. Cerebral parenchymal arterioles were isolated and studied by pressure myography. Data are means ± SEM. Using tail-cuff plethysmography we observed that menopause did not affect mean arterial pressure in 5x-FAD females (98 ± 5.8 vs. 108.7 ± 7.9 mmHg, 5x-FAD vehicle n=5 vs. 5x-FAD VCD n=3; p=0.34). Although there was no significant difference in myogenic tone (% myogenic tone: 23.49 ± 2.2 vs. 28 ± 3.2, 5x-FAD vehicle n=10 vs. 5x-FAD VCD n=7), there was a significant decrease in resting lumen diameter in the menopausal 5x-FAD mice (39.16 ± 2.6 vs. 27.79 ± 2.0 µm, 5x-FAD vehicle n=9 vs. 5x-FAD VCD n=7; p=0.003). We then tested the function of endothelial K^+ channels. Arterioles from menopausal 5x-FAD mice showed a significantly blunted response to a SKCa/ IKCa activator NS-309, as shown by a cumulative concentration-response curve (at 1 µM, %vasodilation: 14.96 ± 2.9 vs. 9.42 ± 1.4, 5x-FAD vehicle n=7 vs. 5x-FAD VCD n=4; p=0.001), without differences in KIR2 function (%vasodilation: 16.02 ± 1.3 vs. 13.69 ± 2.3, 5x-FAD vehicle n=9 vs. 5x-FAD VCD n=6). In conclusion, we found that menopause leads to SKCa/IKCa channel dysfunction in 5x-FAD mice independent of alterations in KIR2 function. These findings may help identify mechanisms of microvascular dysfunction underlying cognitive decline in AD.

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S5.4 Investigating Muscarinic Receptor Subtype Roles on Inspiratory Bursting at Hypoglossal Motoneurons of Neonatal Mice

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A loss of airway patency during sleeping conditions, controlled in part by the genioglossus muscle of the tongue, has been shown to be causally implicated in obstructive sleep apnea (OSA). Decreased excitability of hypoglossal (XII) motor neurons that innervate the genioglossus muscle may be due to activation of muscarinic acetylcholine receptors acting through G-protein coupled signal transduction pathways. There are five types of muscarinic acetylcholine receptors that can be broadly categorized as excitatory or inhibitory. M1, M3, and M5 receptors are excitatory receptors coupled to Gq, whereas M2 and M4 receptors are inhibitory receptors coupled to Gi. XII MNs express M1, M2, and M5 subtypes of muscarinic receptors, but the specific mechanisms of how cholinergic signaling modulates excitability of XII motor neurons are not well understood. We tested the hypothesis that M1 and M5 receptors contribute to an excitatory component of inspiratory bursting, whereas M2 receptors contribute to an inhibitory component of inspiratory bursting in XII motor neurons. Using medullary rhythmic slice preparations from neonatal CD1 mice (postnatal day P0-5) local application of muscarine (30s, 100μM) to the XII motor nucleus increased inspiratory burst amplitude to 175 ± 7% [n = 21]. Blocking M1 receptors with pirenzepine (10 μM & 100 μM), decreased the muscarine mediated potentiation of inspiratory bursting to 87 ± 15% and 73 ± 17% of control muscarine response [n = 4]. Activating M1 receptors with cevimeline at 1000 μM for 30s and 60s increased burst amplitude to 114 ± 8% and 115 ± 8% of control muscarine response [n = 6]. Blocking M2 receptors with AF-DX 116 (1μM & 10 μM), the muscarine mediated effect was 104 ± 8% [n = 4] and 98 ± 20% [n = 5] of control muscarine-mediated excitation. Modulating M5 receptors with VU 0238429 (20μM and 1000μM) increased burst amplitude to 116% ± 8% and 116 ± 7% of control muscarine-mediated excitation [n = 6]. Our data partially support a role of M1 receptors contributing to the muscarinic potentiation of inspiratory bursting in XII motor neurons. Future research will evaluate other muscarinic receptor agonists and antagonists, as well as determine how the muscarinic modulation of inspiratory bursting changes with postnatal maturation.

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S5.5 Alcohol Effects on Dopamine Signaling in the Zebra Finch Vocal Circuit

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Slurred speech is one of the most common and stereotypical signs of alcohol intoxication, however the neurological mechanisms of this effect is poorly understood. Unlike other drugs of abuse, alcohol lacks a clear molecular pathway in which it may affect the brain. Alcohol is generally known as a depressant of the nervous system, however this does not fully explain the pleasure-associated role of alcohol or its effects on motor activation. Alcohol may induce changes in dopamine (DA) signaling, which from the ventral tegmental area (VTA) would be associated with the pleasure associated with drinking, and from the substantia nigra (SN) which is associated with changes in motor control. In the zebra finch, learned song is controlled by an anterior forebrain pathway that is influenced by DA inputs from SN. When finches consume alcohol it affects both amplitude and entropy of the song produced, and overall leads to a less variable song. This suggests that the striatal portion of the finch vocal circuit is a potential target of alcohol. To investigate how alcohol may affect DA signaling in the vocal circuit we exposed 35-day old zebra finches (n=18) to 5% alcohol in their drinking water or water alone over a 10-day drinking period, then measured the expression of DA-associated genes in the anterior forebrain pathway. Specifically we are investigating DA-related signaling in Area X, SN, and VTA for DA synthesis and packaging enzymes, Dopa decarboxylase and alpha synuclein, the DA degradation enzymes, MAO and COMT, as well as two dopamine receptors, D2 and D5 that are enriched in Area X. Brain tissue was harvested and sectioned at 10 μm thin sections in the coronal plane with a freezing cryostat. Utilizing in situ hybridization we then measured mRNA in key brain structures for these genes. All brains were hybridized with antisense riboprobes within the same experiment under uniform conditions for each gene, and mRNA signal was visualized with a NBT/BCIP immunoprecipitation assay. Signal was imaged with a Leica DM4000 and images were analyzed for the densiometric signal using ImageJ. We found high MAO expression in striatal Area X in a thinly dispersed cell type. The effect of alcohol on MAO expression did not differ when compared to the control group, suggesting that alcohol does not change DA degradation rates in this brain circuit. Further analysis of the remaining genes involved in DA signaling will be completed to achieve a fully comprehensive understanding of alcohol effects in this vocal-motor control circuit. In songbirds, DA levels vary in Area X during different social contexts: during female-directed song, DA released from the VTA and SN increases leading to a less variable song. Thus, future studies on the role of alcohol on DA signaling in Area X during these different social contexts may shed light on how alcohol affects speech in humans during different social drinking encounters.

Funding: MWU faculty start up to CRO

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