



Welcome to the 31st Annual Meeting of the Iowa Physiological Society

October 16 -17, 2026

Health Sciences Academic Building
302 South Grand Avenue
University of Iowa, Iowa City, IA

Organizers:

Jared McLendon, PhD
Clayton Peterson, PhD
Rasna Sabharwal, PhD
Anna Stanhewicz, PhD
Erin Talbert, PhD
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IPS 2026 Annual Meeting

Friday, October 16

- 1:30pm** **On Site Registration + Badge Pickup Open**
HSAB 1st Floor Lobby Outside Room 1501
- 2:00pm** **Welcome, Opening Remarks**
Anna Stanhewicz, PhD 2026 IPS President
HSAB 1501
- 2:15pm** **Keynote Lecture: Purpose, Practice, and Physiology: Designing Courses to Cultivate Expert Thinking**
Kathryn Smith, PharmD, BCACP
Associate Professor of Instruction, College of Pharmacy, University of Iowa
HSAB 1501
- 3:15pm** **Sponsor Talk – AD Instruments**
HSAB 1501
- 3:30pm** **Break and Panel Set Up**
- 3:45pm** **Panel Discussion: Teaching Real-World Skills in the Classroom/Curriculum**
Moderator: Clay Peterson, PhD
Associate Professor of Instruction, Department of Health, Sport, and Human Physiology, University of Iowa
Panelists:
***Kathryn Smith, PharmD, BCACP**, Associate Professor of Instruction, College of Pharmacy, University of Iowa*
***Jennifer Rogers, PhD**, Professor of Biomedical Sciences, Kansas College of Osteopathic Medicine*
***Sophie Gillett, PhD**, Assistant Professor in Biology, Cornell College*
HSAB 1501
- 5:00pm** **Adjourn**
- 5:30pm** **Social: ReUnion Brewery**
113 E. College Street, Iowa City
Heavy hors d'oeuvres, Cash Bar



Saturday, October 17

8:30am **Continental Breakfast**
On Site Registration + Badge Pickup Open
HSAB 1st Floor Lobby Outside Room 1501

9:00am **Keynote Lecture: Elucidating the Biochemical and Molecular Mechanisms that Underlie Various Forms of Muscular Dystrophy**
Kevin Campbell, PhD
Professor and Chair of Molecular Physiology and Biophysics,
Carver College of Medicine, University of Iowa
Sponsored by Novogene
HSAB 1501

10:00am **Sponsor talk – Novogene**
HSAB 1501

10:15am **Poster Session**
Even number posters will present 10:15 - 11:00am
Odd number posters will present 11:00 – 11:45am
HSAB 5th floor Lobby

11:45am **Lunch - Boxed Lunch Provided**
HSAB 1st Floor Lobby Outside Room 1501

12:45pm **Short Talks Selected from Submitted Abstracts Session I**
Moderators: Kanokwan Bunsawat, PhD, Assistant Professor
Jeremy Bigalke, PhD, Assistant Professor
Department of Health, Sport, and Human Physiology, University of Iowa
HSAB 1501

Sorbs2 regulates contraction and mechanotransduction responses in vascular smooth muscle cells
Kailey Said-Lathrum, University of Iowa

VEGF-A as a Molecular Determinant of Blood–Labyrinth Barrier Permeability in the Cochlea Following Cisplatin Treatment
Logan Cataldo, University of Iowa

Temporal Dynamics of Cerebral Blood Flow Reductions During Isocapnic Hyperoxia: The Role of Reactive Oxygen Species
Hedyeh Khademi Motlagh, University of Wisconsin

Testosterone deficiency contributes to chronic stress-induced cardiac dysfunction, senescence, oxidative stress and inflammation in a genetic mouse model of dilated cardiomyopathy
Wenddy W. D. Sougey, PhD, University of Iowa

1:45pm **Sponsor Talk – Moor Instruments**
HSAB 1501

2:00pm

Short Talks Selected from Submitted Abstracts Session II

Moderators: Kanokwan Bunsawat, PhD, Assistant Professor

Jeremy Bigalke, PhD, Assistant Professor

Department of Health, Sport, and Human Physiology, University of Iowa

HSAB 1501

Antihypertensive Mechanism Determines Retinal Hemodynamics in Isolated Systolic Hypertension

Breanna Pederson, PhD, University of Iowa

Acute experimental intermittent hypoxia and blood pressure in older adults

Dongnyeuck Seo, University of Iowa

Trauma Type and Cardiac Autonomic Function in Premenopausal Women with Post-traumatic Stress Disorder

Chasity Corbin, University of Minnesota

Cutaneous Microvascular Endothelial Function is Reduced with Advanced Maternal Age During Pregnancy but Not in Age-Matched Never-Pregnant Women

Ruda Lee, PhD, University of Iowa

3:00pm

Sponsor Talk – FujiFilm VisualSonics

HSAB 1501

3:15pm

Break

3:30pm

Integrating Exercise into Cancer Care: The Development and Impact of the Iowa Exercise Oncology Clinic

Jessica Gorzelitz, PhD, MS

Assistant Professor, Department of Health, Sport and Human Physiology, University of Iowa

HSAB 1501

4:30pm

Trainee AWARDS

HSAB 1501

5:00pm

IPS Business Meeting

HSAB 1501

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Short Talks Selected from Submitted Abstracts Session I

Sorbs2 regulates contraction and mechanotransduction responses in vascular smooth muscle cells

Kailey Said-Lathrum, Henry Lin, Ryan Boudreau, Kris DeMali, Isabella Grumbach, Kamal Rahmouni, Jared McLendon

Pharmaceutical Sciences and Experimental Therapeutics, University of Iowa

Sorbs2 is a cytoskeletal adapter protein highly expressed in vascular smooth muscle cells (VSMCs). Recent publications show Sorbs2 expression is dysregulated in cardiovascular disease (CVD), and that Sorbs2 interacts with actin and microtubules. We hypothesize that Sorbs2 regulates vascular tone by mediating cytoskeletal dynamics in VSMC contraction and mechanotransduction. To test if Sorbs2-KO is associated with CVD, we created a smooth muscle specific Sorbs2-KO (smKO) mouse. Blood pressure radio-telemeters were installed, and mice were treated with angiotensin-II for 10 days to induce hypertension. Sorbs2-smKOs showed a reduced change in mean arterial blood pressure after angiotensin-II administration. To test if Sorbs2-KO affects vascular tone, we performed wire myography. Sorbs2 smKO aortas showed increased contractility in response to thromboxane A2 agonist. In passive length-tension relationships, smKO aortas showed higher elasticity than WT. The higher contractility and elasticity of smKO aortas suggest Sorbs2 helps maintain the VSMC structural cytoskeleton. To assess Sorbs2's role regarding the VSMC cytoskeleton, primary WT or KO VSMCs were plated on elastic membranes at static conditions, or with 10% bicyclic stretch for 24 hours. Sorbs2-KO showed dysregulation of Calponin1 and Integrin beta-5 at a protein level and upregulation of phosphorylated ERK1/2 with no change in total ERK expression (n=6, p<0.05). RNA-seq of static KO vs WT showed an increase in contractile and focal adhesion pathways (Z=5.8, p<0.0001). Under stretch, KO VSMCs continued to show upregulation of genes associated in focal adhesion (Z=4.9, p<0.0001). Our results suggest Sorbs2 regulates vascular tone and VSMC mechanotransduction by regulating the VSMC structural cytoskeleton.

This work has been supported by an American Heart Association Career Development Award (23CDA1055147) and a Roy J Carver Charitable Trust Award granted to Dr. McLendon. Additional support from the Larry Schaaf Fellowship, Iowa Recruitment Fellowship, and Iowa Graduate College Summer Fellowship have been exceptionally helpful towards progressing in this work.

VEGF-A as a Molecular Determinant of Blood-Labyrinth Barrier Permeability in the Cochlea Following Cisplatin Treatment

Logan Cataldo, Kushal Raj Roy, Franz Gareza, Amanda Bonczkowski, Lisa Cunningham, and Cathy Yea Won Sung

Biology, University of Iowa

Cisplatin is a widely used and effective anticancer drug; however, it can cause permanent hearing loss in many patients. Cisplatin enters the cochlea through the blood-labyrinth barrier (BLB) within the stria vascularis and has been shown to increase the permeability of the BLB, however, the molecular determinants of this dysregulation are incompletely understood. Because VEGFA has been shown to increase vascular permeability in the blood-brain barrier, we focused on characterizing its expression following cisplatin treatment to establish its potential involvement in the cochlear response. Our cisplatin treatment protocol consists of three cycles; each being comprised of 4 days of cisplatin injections followed by 10 days of recovery. Single nucleus RNA sequencing (snRNA-seq) was performed, and the findings were further validated by RNA in situ hybridization (ISH) using a probe for VEGFA. Additionally, immunofluorescence staining for VEGFA was performed and imaged using confocal microscopy to assess changes in VEGFA protein expression at each treatment cycle. snRNA-seq data showed that VEGFA expression in the stria vascularis increased during Cycles 1 and 2 of cisplatin treatment and RNA ISH analysis showed increased VEGFA mRNA puncta in the stria vascularis following Cycles 1 and 2. Additionally, immunofluorescence analysis demonstrated a significant increase in VEGFA protein expression beginning in Cycle 1 and continuing to increase through Cycles 2 and 3. These findings suggest that VEGFA expression

is significantly increased following cisplatin treatment, identifying it as a potential mediator of cisplatin-induced vascular dysfunction and providing the basis for further investigation of its role in BLB regulation.

This work was supported by the National Institutes of Health under award number R00DC021198 and NIH/NCI under award number P30 CA086862. Data presented herein were obtained at the Carver Center for Imaging.

Temporal Dynamics of Cerebral Blood Flow Reductions During Isocapnic Hyperoxia: The Role of Reactive Oxygen Species

Hedyeh Khademi Motlagh, Logan J. Heenan, Andrés R. Ortiz, Kay A. Kakade, Kaylin D. Didier, Marlowe W. Eldridge, Kevin Johnson, Oliver Wieben, William G. Schrage
Kinesiology, University of Wisconsin-Madison

Background: Hyperoxia reduces cerebral blood flow (CBF), potentially through reactive oxygen species (ROS)-mediated vasoconstriction. However, the time course and mechanism of prolonged hyperoxia exposure remained poorly understood. We hypothesized that isocapnic hyperoxia would induce a time-dependent CBF decline and that acute antioxidant (AO) treatment would attenuate this response. **Methods:** 19 healthy adults (8F; 22±5 yr; BMI 22±2 kg/m²) completed a randomized, double-blind, placebo-controlled study. Participants received placebo (PLA) or AO (600 mg α-lipoic acid, 1000 mg vitamin C, 600 IU vitamin E) before pc ASL MRI. CBF was quantified during normoxia and isocapnic hyperoxia (~90% O₂) at ~5(H1), 10(H2), 25(H3), and 30 min (H4). **Results:** Mean arterial pressure remained stable (p>0.05). EtCO₂ was clamped at normoxic levels during AO (p>0.05) but increased ~1 mmHg during PLA (p<0.001). Under PLA, CBF declined from H1 (42±12) to H3 (36±11; p=0.025) and H4 (37±10 mL/100 g/min; p=0.033), with no difference from normoxia at H1. Under AO, CBF decreased from normoxia (45±13) to H2 (38±12; p=0.006), H3 (39±13; p=0.005), and H4 (38±13 mL/100 g/min; p=0.001). No between-condition differences occurred (all p>0.05). O₂ content increased ~10% in PLA (18±2 to 20±2) and 9–10% in AO (18±3 to 20±3 mL O₂/100 mL blood). Oxygen delivery decreased from H1 to H4 in PLA (61±12 to 57±11) and AO (65±11 to 57±12 mL O₂/min; p<0.05), despite increased O₂ content. **Conclusion:** Contrary to hypothesis, AO did not attenuate CBF reduction response to hyperoxia. This may reflect a complex ROS role; whereby scavenging ROS could disrupt ROS-mediated vasodilatory signaling."

This work was funded by National Heart, Lung, and Blood Institute Grant 5R01HL150361 to William G. Schrage with additional support in part by a core grant to the Waisman Center from the National Institute of Child Health. We thank the study participants and the staff of the Waisman Center for their assistance with data collection and MRI procedures.

Testosterone deficiency contributes to chronic stress-induced cardiac dysfunction, senescence, oxidative stress and inflammation in a genetic mouse model of dilated cardiomyopathy

Wenddy W. D. Sougey, Liping Yang, Michelle Bader, Mikayla Weber, Robert M. Weiss, Rasna Sabharwal
Internal Medicine, University of Iowa

The prevalence of cardiovascular mortality and morbidity is higher in men than in age-matched young (premenopausal) women. Sex differences are strongly linked to circulating gonadal hormone levels and their cardio-specific actions. While chronic stress can actively suppress production of male sex hormone testosterone, the role of testosterone as a cardioprotective agent is incompletely understood. In this present study, our goal was to determine the role of testosterone on chronic stress-evoked cardiac function and the associated molecular underpinnings in sarcoglycan delta deficient (Sgcd^{-/-}) mouse model of dilated cardiomyopathy. Young adult (10-13 weeks) male wildtype (n=3-6) and Sgcd^{-/-} (n=3-7) mice were subdivided into sham and gonadectomized (GDX) subgroups. After a week of recovery, mice were exposed to a series of chronic unpredictable mild stressors (CUMS) for 14 days. Cardiac function was assessed by echocardiography before and after CUMS. Molecular gene expression of AT1R and MasR (renin-angiotensin system receptors), superoxide dismutase 2 (SOD2; oxidative stress marker), p21 (senescence marker), and IL-1b and IL-6 (inflammatory markers) were measured using RT-PCR. GDX+CUMS Sgcd^{-/-} mice exhibited

lower ejection fraction ($P=0.0065$), increased left ventricle thinning ($P=0.002$), increased end-diastolic and end-systolic volumes ($P=0.0209$) vs baseline (before CUMS) and WT GDX+CUMS. GDX+CUMS *Sgcd*^{-/-} mice also showed decreased cardiac masR ($P=0.0122$) and SOD2 ($p=0.003$), while increased p21 (0.0054) and IL6 ($P=0.07$) mRNA expression (vs WT GDX+CUMS). These initial results suggest that testosterone deficiency can accelerate onset of cardiomyopathy and contribute to increases in cardiac oxidative stress, inflammation and premature senescence in chronically stressed *Sgcd*^{-/-} mice.

NIH R01HL149677, R21AG070188

Short Talks Selected from Submitted Abstracts Session II

Antihypertensive Mechanism Determines Retinal Hemodynamics in Isolated Systolic Hypertension

Breanna Pederson, Amy Stroud, Matthew Armstrong, Randy Kardon, Gary Pierce
Health, Sport, and Human Physiology, University of Iowa

Isolated systolic hypertension (ISH) increases pulsatile pressure and flow, which damages the microvasculature of high-flow end organs such as the retina. We hypothesized that retinal arteriolar and venular flow hemodynamics would differ with central sympathetic inhibition (clonidine) versus volume depletion (hydrochlorothiazide, HCTZ), despite similar blood pressure reductions in ISH. Adults with ISH ($n=20$; age=40–84 yrs; systolic BP 138–173 mmHg) were randomized for 4 weeks to 0.2 mg/day clonidine ($n=8$), 37.5 mg HCTZ ($n=6$), or placebo ($n=6$) after a 7-day washout. Retinal flow hemodynamics were assessed at baseline and after 4 weeks using laser speckle flowgraphy. Primary outcomes were flow pulsatility index (PI), flow pulse amplitude, relative flow volume (RFV), and choroidal mean blur rate (blood flow velocity). Both agents produced equivalent systolic BP reductions (HCTZ -9.6% , $p=0.03$, clonidine -10.2% , $p=0.03$, between groups $p=1$). Clonidine increased arteriolar PI (7.0% , $p=0.02$) (between groups: vs HCTZ $p=0.067$; vs. placebo $p=0.40$). Arteriolar flow pulse amplitude did not change ($p>0.56$, between groups $p=1$). However, venous flow responses diverged: HCTZ significantly reduced PI (-30.4% , $p=0.031$) compared to both placebo and clonidine ($p<0.02$), and pulse amplitude (-33.9% , $p=0.031$) compared to clonidine ($p=0.02$). Clonidine produced no changes in primary venous flow outcomes (PI: $p=0.31$; pulse amplitude: $p=0.46$). Neither drug produced changes in choroidal flow ($p>0.31$) or relative flow volume (venules $p>0.38$; arterioles $p>0.55$). Equivalent BP reductions produced divergent retinal flow hemodynamic outcomes by antihypertensive mechanism, with HCTZ selectively reducing venous flow pulsatility and clonidine increasing arteriolar flow pulsatility in the absence of significant venous flow changes.

This project was funded by NIH grants R01 AG063790 (to GLP) and U54 TR001356 (to ICTS University of Iowa).

Acute experimental intermittent hypoxia and blood pressure in older adults

Dongnyeuck Seo, Jack E. Shelley, Andrew J. Feider, Darren P. Casey
Physical Therapy and Rehabilitation Science, University of Iowa

Intermittent hypoxia (IH) has emerged as a potential therapeutic strategy to improve BP and autonomic function. We tested the hypothesis that acute IH (4 min normoxia/6 min hypoxia x 5 cycles) would reduce resting brachial and aortic BPs, attenuate BP responsiveness to stress, and improve spontaneous cardiovagal baroreflex sensitivity (BRS) in older adults. Ten subjects (68 ± 7 yrs) completed three randomized study visits: 75% SpO₂ IH, 85% SpO₂ IH, and time control (TC). Before and after each trial 1) resting brachial and aortic BP, 2) peripheral BP responses to the cold pressor test (CPT), and 3) spontaneous cardiovagal BRS via sequence method were assessed. Brachial and aortic BPs increased following all three trials ($P<0.05$ for all). However, all post-intervention BPs were attenuated following 75% IH compared with TC (brachial systolic BP: 126 ± 15 vs. 130 ± 16 mmHg; brachial diastolic BP: 75 ± 5 vs. 78 ± 5 mmHg; mean arterial pressure: 92 ± 8 vs. 96 ± 8 mmHg, aortic systolic BP: 121 ± 15.3 vs. 125 ± 17 mmHg; aortic diastolic BP: 76 ± 5 vs. 79 ± 5 mmHg, $P<0.05$ for all). CPT induced peak increases in peripheral BP were unchanged following all three trials ($P>0.05$). Both IH protocols increased overall (75% IH; 9.1 ± 2.0 to 15.2 ± 6.7 , 85% IH; 10.1 ± 2.6 to 14.5 ± 4.0 ms/mmHg, $P<0.01$ for both) and down-sequence (75% IH; 9.7 ± 2.3 to 15.4 ± 5.2 , 85% IH; 10.9 ± 2.4 to 15.3 ± 3.9

ms/mmHg, $P < 0.001$ for both) spontaneous cardiovagal BRS gain. Our findings demonstrate acute IH attenuates the time-related increase in resting brachial and aortic BP and enhances spontaneous cardiovagal BRS but doesn't alter peripheral BP responsiveness to the CPT in older adults.

Trauma Type and Cardiac Autonomic Function in Premenopausal Women with Post-traumatic Stress Disorder

Chasity Corbin, Chowdhury Ibtida Tahmin, Ida Tchuisseu Fonkoue.

Department of Family Medicine and Community Health, University of Minnesota

Nearly half of women in the United States experience contact sexual violence. Further, sexual assault (SA) is recognized epidemiologically as a leading cause of post-traumatic stress disorder (PTSD) in women. While PTSD is known to impair autonomic control, the specific impact of SA on various cardiovascular biomarkers remains uncharacterized. Autonomic dysregulation, characterized by impaired baroreflex sensitivity (BRS), blunted heart rate variability (HRV), and elevated blood pressure variability (BPV), is an independent and powerful predictor of future cardiovascular disease. We investigated the effects of SA on HRV, BPV, and cardiovagal BRS in premenopausal women with PTSD. We hypothesized that SA (SA+, $n=23$, 28 ± 6 years) would be associated with lower BRS, blunted HRV and higher BPV compared to non-sexual trauma (SA-, $n=22$, 26 ± 8 years). All participants had a clinical diagnosis of PTSD prior to study enrollment. Demographics, anthropometric measures and resting hemodynamics were comparable between both groups. As hypothesized, the SA+ group showed lower time domains measures of HRV when compared to SA- [(SDRR, 48.6 ± 14.4 vs. 84.8 ± 14.4 ms, $p=0.002$), (RMSSD (40.1 ± 18.0 vs. 85.8 ± 61.9 ms, $p=.001$)). Contrary to our hypothesis, BRS was comparable between the groups and systolic BPV was lower in the SA+ group than the SA- group (1.5 ± 0.3 vs. 1.8 ± 0.5 mmHg, $p=.009$), with no difference in diastolic BPV. These findings suggest that SA in women may further blunt the lower resting HRV associated with PTSD. However, we found a divergent effect of SA on BPV, underscoring a critical gap in the understanding of impact of trauma type on cardiac autonomic control.

Cutaneous Microvascular Endothelial Function is Reduced with Advanced Maternal Age During Pregnancy but Not in Age-Matched Never-Pregnant Women

Ruda Lee, Gary Pierce, Anna Stanhewicz

Health, Sport, and Human Physiology, University of Iowa

Pregnancy at advanced maternal age (AMA, ≥ 35 years) is associated with increased risk of adverse pregnancy outcomes. We have demonstrated that pregnant women of AMA have reduced cutaneous microvascular endothelial function compared with younger pregnant women during the second trimester. However, whether this reduction is a primary effect of age or an interaction between pregnancy and age remains unclear. We enrolled 30 pregnant women (15 aged 18-30 years and 15 aged ≥ 35 years) and 26 never pregnant women (13 aged 18-30 years and 13 aged ≥ 35 years). Red blood cell flux was measured in the left ventral forearm using laser-Doppler flowmetry during local heating to 42°C . Brachial blood pressure was measured on the right arm, and cutaneous vascular conductance was calculated ($\text{CVC} = \text{laser-Doppler flux} / \text{mean arterial pressure}$) and normalized to maximum ($\%\text{CVC}_{\text{max}}$; local heat to 43°C). Pregnant women of AMA were older and had higher parity than younger pregnant women ($P \leq 0.01$), whereas AMA-aged matched never pregnant women were older and had higher diastolic blood pressure and mean arterial pressure than their younger counterparts ($P < 0.01$). Compared with younger pregnant women, pregnant women of AMA had reduced $\%\text{CVC}_{\text{max}}$ at the sensory-nerve mediated initial peak ($P < 0.001$) and endothelium-dependent plateau ($P = 0.046$). No group differences were observed between younger and AMA age-matched never pregnant women in any microvascular response ($P > 0.05$). These data suggest that altered vascular function may emerge specifically during pregnancy in women of AMA. This may contribute to the elevated risk of pregnancy complications in this cohort.

Poster Presentation Abstracts

Board#

1 **Transcriptomic and Metabolomic Profiling Identify Peroxisomal Dysregulation as a Potential Driver of Myosteatorsis in Pancreatic Cancer Cachexia**

Emanuella Parungao, Erin Talbert

Health, Sport, and Human Physiology, University of Iowa

Pancreatic ductal adenocarcinoma (PDAC) is associated with a high prevalence of cachexia, a muscle- and fat-wasting disease associated with muscle dysfunction and related to approximately 30% of all PDAC deaths. Similarly, PDAC patients frequently exhibit myosteatorsis, or lipid accumulation in muscle tissue. Myosteatorsis is hypothesized to contribute to cancer-mediated muscle dysfunction. However, mechanisms driving myosteatorsis in PDAC-associated cachexia are not well understood. Thus, to identify potential mechanism(s) of myosteatorsis, the skeletal muscle metabolome was analyzed using samples from 3 groups (n=10/group): weight-stable PDAC, cachectic PDAC, and non-cancer controls. The skeletal muscle transcriptome was also analyzed by comparing cachectic PDAC and non-cancer controls. Cachectic samples demonstrated an increase in triglycerides containing long (>18C), polyunsaturated fatty acids (FA) compared to non-cachectic or non-cancer controls. Downstream lipid products, such as short (<18C) triglycerides containing saturated FA, diglycerides, and phospholipids, were decreased in cachectic samples. Transcriptomics revealed that genes involved in peroxisomal fat metabolism were reduced in cachectic samples (log [RPKM+.01]): ACOX2 (-0.36), ABCD1 (-0.33), ABCD2 (-0.51), DECR2 (-0.29), CRAT (-0.20), ACAA1 (-0.24), SLC25A17 (-0.29), FABP4 (-0.51), and ALDH3A2 (-0.45). Additionally, relative expression decreased for genes involved in peroxisome maintenance, including PEX1 (-0.164), PEX5 (-0.23), PEX10 (-0.15), PEX12 (-0.17), PEX14 (-0.23), and PEX26 (-0.15). Peroxisome synthesis genes were also affected, including PEX16 (-0.46), PEX11A (-0.11), PEX11B (0.21), PPARG (-0.25), and PPARG (-0.48). These findings suggest that reduced peroxisomal biogenesis and fatty acid metabolism may contribute to abnormal lipid profiles in skeletal muscle and subsequently to muscle dysfunction in patients with cachexia.

This work was supported by a pilot grant from the Mayo Clinic Metabolomics Resource Core through grant number U24DK100469 from the National Institute of Diabetes and Digestive and Kidney Diseases, which originates from the National Institutes of Health Director's Common Fund.

2 **PIEZO1 Activation Restores Ca²⁺-Sensitive nNOS and Redox Signaling during Skeletal Muscle Unloading**

Alhassan A. Abdalla, Namitha Bannimath, Noran A. Abdelaziz, Khaled Y. Kamal

Kinesiology and Health, Iowa State University

Background: Skeletal muscle relies on continuous mechanical stimulation to preserve mass and function. Disuse compromises mechanosensitive signaling networks, yet the mechanisms linking loss of mechanical input to skeletal muscle dysfunction remain incompletely understood. Piezo1 is a mechanically activated ion channel that converts physical forces into Ca²⁺-dependent intracellular signaling, but whether disruption of this pathway contributes to altered redox regulation during skeletal muscle unloading remains unclear. We hypothesized that mechanical unloading would suppress PIEZO1 and downstream Ca²⁺-sensitive signaling, leading to altered neuronal nitric oxide synthase (nNOS) localization and increased NOX2-associated redox signaling, whereas pharmacological PIEZO1 activation with Yoda1 would restore this mechanosensitive signaling network. Methods: 4-mo-old male Fischer-344 rats (n=6/group) were assigned to three groups: ambulatory control (CON), 14-day hindlimb unloading (HU), and hindlimb unloading with Yoda1 treatment (HUY; 1 mg/kg/day, i.p.). Gastrocnemius muscles were evaluated by Western blotting, subcellular fractionation, and immunofluorescence to quantify PIEZO1, CaMK phosphorylation, calcineurin, membrane and cytosolic nNOS localization, and NOX2. Results: HU reduced PIEZO1 abundance, whereas Yoda1 restored PIEZO1 in HUY compared with HU muscle (p=0.001). This response was accompanied by reduced p-CaMK/CaMK signaling and

calcineurin abundance during HU, both of which were restored toward control levels by Yoda1. HU also reduced membrane-associated nNOS with a corresponding increase in cytosolic nNOS, consistent with disrupted subcellular localization. Yoda1 restored membrane nNOS and reduced cytosolic accumulation, findings further supported by immunofluorescence. In parallel, current analysis of NOX2 abundance is predicted to show that HU increased NOX2 abundance, whereas Yoda1 attenuated this response despite continued unloading. Conclusion: Mechanical unloading disrupts a coordinated PIEZO1-associated signaling network involving Ca^{2+} -sensitive CaMK/calcineurin signaling, nNOS localization, and NOX2-associated redox regulation. Pharmacological PIEZO1 activation restores these responses despite continued unloading, identifying PIEZO1 as a potential therapeutic target for preserving mechanosensitive signaling during skeletal muscle disuse.

This work was supported by the NASA EPSCoR Research Building Seed (RBS) Program under Award No. 80NSSC22M0031 and by the FightDMD Association.

3 Piezo1 Activation Modulates Site-Specific Bone Remodelling During Mechanical Unloading

Namitha Bannimath^{1*}, Noran Abdelaziz¹, Alhassan A. Abdalla¹, Kim C. Mansky², Khaled Y. Kamal¹

¹Department of Kinesiology and Health, Iowa State University, Ames, IA 50011, USA.

²Division of Orthodontics, Department of Developmental and Surgical Sciences, University of Minnesota School of Dentistry, Minneapolis, MN 55455, USA

Introduction: Mechanical loading is essential for maintaining bone structure and normal remodelling. Reduced mechanical loading disrupts bone mechanosensing and can produce site-specific changes in bone mass and microarchitecture. PIEZO1 is a mechanosensitive ion channel that allows bone cells to sense and respond to mechanical forces. We hypothesized that pharmacological activation of PIEZO1 with Yoda1 would modify the skeletal response to mechanical unloading. Methods: Male Fischer 344 rats were assigned to control (CON), hindlimb unloading (HU), or hindlimb unloading with Yoda1 (HUY; 1 mg/kg/day, i.p.). HU and HUY rats underwent 14 days of pelvic harness suspension. Whole-body and hindlimb bone mineral density (BMD) and bone mineral content (BMC) were measured by DXA. Micro-CT assessed proximal and distal trabecular architecture and mid-shaft cortical bone. SOST/sclerostin, RUNX2, RANKL, OPG, and the RANKL ratio are currently being assessed. Results: DXA showed higher whole-body and hindlimb BMD and whole-body BMC in HUY compared with HU, although differences were not significant. Micro-CT demonstrated site-specific responses. Proximally, HUY had the highest BV/TV, while trabecular thickness was greater in HU and HUY than CON. Distally, HU showed higher BV/TV and trabecular number and lower trabecular thickness than CON, while HUY values shifted toward CON. At the mid-shaft, HUY showed greater cortical bone fraction and thickness than HU, although differences were not significant. Conclusion: Mechanical unloading produced site-specific changes in bone microarchitecture, and Yoda1 modified several of these responses, supporting a role for PIEZO1 in skeletal adaptation to reduced mechanical loading.

This work was supported by the NASA EPSCoR Research Building Seed (RBS) Program under Award No. 80NSSC22M0031 and by the FightDMD Association.

4 Using Patient Cells and Tissues to Investigate VEGF Signaling in Pulmonary Lymphangioliomyomatosis

Sahana Nagarajan, Emily C. Liu, Amy L. Ryan
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Lymphangioliomyomatosis (LAM) is a rare cystic lung disease driven by loss-of-function mutations in the tumor suppressor TSC2, resulting in constitutive mTOR activation and proliferation of abnormal smooth muscle-like cells. Although elevated VEGF-D is a well-established biomarker of LAM, the role of VEGFs in LAM progression is still understudied. To define VEGF-associated signaling pathways in LAM, patient lung tissue was analyzed by immunofluorescence for localization of the LAM cell marker PMEL with phosphorylated AKT, ERK, and focal adhesion kinase (FAK). Signaling activity was further examined

in TSC2-positive and TSC2-deficient angiomyolipoma (AML) cell lines by immunoblotting. Functional effects of VEGF signaling on primary lymphatic endothelial cells (LECs) were assessed using electrical impedance measurements following VEGF-C or VEGF-D stimulation. Phosphorylated AKT and ERK colocalized with PMEL-positive LAM cells within lung nodules, indicating activation of pro-survival and proliferative signaling pathways. In contrast, phosphorylated FAK was primarily detected adjacent to PMEL-positive regions, suggesting activation within the surrounding microenvironment. Immunoblot analyses confirmed activation of AKT and ERK signaling in AML cells, whereas FAK activation was not detected despite preservation of total FAK expression. VEGF-C and VEGF-D treatment induced concentration-dependent changes in LEC resistance measurements, consistent with altered endothelial barrier and adhesive properties. Collectively, these findings support a model in which VEGF signaling promotes bidirectional communication between TSC2-deficient LAM cells and neighboring lymphatic endothelium through activation of AKT and ERK pathways. The distinct spatial distribution of FAK activation further suggests microenvironment-specific signaling mechanisms that may facilitate lymphatic remodeling and disease progression.

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5 Unimodal Finite Mixture Models: Potential Distribution Model for Biological Data Sets

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Many biological phenomenon consist of multiple stages or processes which could represent multiple distributions. We have previously studied the unimodal finite mixture model (UFMM) as a potential model for biological data sets. Finite mixture models are weight sums of two or more distributions that can be unimodal, bimodal, or multimodal, yet UFMMs can appear as single distributions. We have shown that shifting a distribution or data set by multiplying the distribution by a variate dependent weight can yield different curves for a UFMM as compared to single distributions (normal, lognormal, gamma, or Weibull). Single distributions are unimodal and remain unimodal after shifting, but a UFMM can demonstrate a unimodal, bimodal, or multimodal distribution when shifted. The objective of our work is to develop methods by which it can be determined whether a data set is best represented by a single distribution or a UFMM. Previously we only focused on the mode of the original distribution and shifted distribution. However, very few if any statistics that are based on the mode. Here we present recent work where we examine the shifted weights, means, and variances to develop statistical methods for assessing whether a data set is more likely represented by a single distribution or a UFMM. Additionally, when shifted the means and variances of a UFMM are different from those of single distributions. We will present theoretical rationale and resulting analysis of published data to demonstrate the relevance of this work.

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6 DNA-PK-Mediated Akt Activation Controls Centriole Amplification and Club Cell Progression During MCIDAS-Driven Multiciliogenesis

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Mucociliary clearance is a critical airway defense, driven by multiciliated cells, and is impaired in diseases like COPD, cystic fibrosis, and asthma. Multiciliated cells are essential for effective mucociliary transport, and the transcriptional co-activator MCIDAS drives multiciliogenesis via the EDM (E2F4/5-DP1-MCIDAS) complex. However, the expression of MCIDAS is context dependent. To identify

signals enabling MCIDAS function, we developed an inducible human airway basal cell model and examined its interaction with Notch signaling. Transcriptomic profiling revealed that robust activation of core ciliogenesis genes, including FOXJ1, CCDC20B, and DRC1, occurred only when MCIDAS induction was combined with Notch-inhibition, identifying Notch suppression as a prerequisite for establishing multiciliogenic competence. Pathway analyses identified PI3K-Akt signaling as a key regulator of this process. Mechanistic studies demonstrated that following specification of basal cell-derived club cell intermediates, continued differentiation into mature multiciliated and goblet cells requires Akt activation during early window of first 48 hours of differentiation. During this period, it supports centriole amplification and lineage progression. DNA-PK inhibition disrupted Akt-phosphorylation and impaired multiciliated cell differentiation, while pharmacologic Akt activation restored differentiation despite DNA-PK blockade, establishing Akt as a critical downstream effector of DNA-PK signaling. Together, these findings define a DNA-PK-Akt-MCIDAS signaling axis that coordinates early cell fate decisions and mucociliary differentiation. We propose a model where Notch inhibition licenses MCIDAS-dependent ciliogenesis, while DNA-PK-mediated Akt activation enables centriole amplification and progression from club-cell intermediates to mature mucociliary phenotypes. This framework offers insight into airway regeneration and identifies potential targets to restore mucociliary function in chronic airway disease.

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7 TRPV4-mediated AP-1/NFATC2 signaling axis drives squamous reprogramming of airway basal cells

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Airway basal stem cells (BCs) are the resident stem cell population of the proximal airway epithelium, responsible for maintaining epithelial homeostasis through their capacity for long-term self-renewal and multilineage differentiation. Aberrant airway remodeling is implicated in the pathogenesis of airway diseases such as chronic obstructive pulmonary disease (COPD), asthma and Cystic Fibrosis (CF), where BCs respond to persistent injury with squamous differentiation that promote pathological airway repair over functional regeneration. Although phenotypic and structural alterations of the epithelium are well documented in these diseases, a significant knowledge gap remains in our mechanistic understanding of how BCs sense their niche and translate these signals to either promote functional regeneration or pathological remodeling. We have identified transient receptor potential vanilloid 4 (TRPV4) as a key Ca^{2+} -permeable multimodal stress sensing ion channel in primary human BCs. TRPV4 expression was enriched within lamellipodia, consistent with a role in BC migration. TRPV4 inhibition using selective antagonist HC-067047 delayed BC migration, determined by time-lapse microscopy. Sustained TRPV4 activation using GSK1016790A drives squamous reprogramming in BCs. Motif analysis via ATAC-sequencing identified AP-1 as the dominant enriched gene and revealed significant enrichment of NFAT: AP-1 composite motifs. NFATC2 is another highly induced transcript in our RNASeq analysis, suggesting a central role for calcium-responsive transcriptional machinery. Overall, our study has identified dual roles of TRPV4 in the context of BC regeneration. While initial TRPV4 activation is required for effective mechano-sensing and epithelial repair, sustained channel activation promotes squamous reprogramming by activating AP-1/NFATC2 gene programs, leading to pathological airway remodeling.

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8 Endothelial Gene Dysregulation Across the Kidney-Brain Axis in an Adenine-Induced Rat Model of Chronic Kidney Disease

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Chronic kidney disease (CKD) affects more than 1 in 7 adults in the United States and is associated with vascular dysfunction, blood-brain barrier (BBB) disruption, and neurobehavioral abnormalities. However, the extent to which endothelial alterations occur across the kidney-brain axis remains unclear. We previously showed that male rats exposed to a 21-day adenine diet combined with unilateral nephrectomy develop severe CKD, confirmed by elevated serum creatinine, reduced glomerular filtration rate, and increased renal fibrosis markers. These animals also exhibited increased behavioral emotionality and hippocampal upregulation of angiopoietin-2 (Angpt2) and vascular endothelial growth factor A (Vegfa), regulators of endothelial stability, angiogenesis, and vascular permeability. We hypothesized that CKD would be accompanied by endothelial transcriptomic alterations in kidney and brain, representing a vascular component of kidney-brain crosstalk. We examined endothelial and vascular-associated genes in renal cortex and hippocampus using RNA-seq datasets from control and CKD animals. In the kidney, most genes meeting differential-expression criteria (adjusted $p < 0.05$ and $|\log_2 \text{fold change}| > 0.58$) were downregulated, including genes involved in endothelial identity, vascular homeostasis, angiogenic signaling, and barrier function. In the hippocampus, three genes, Angpt2, von Willebrand factor (Vwf), and Vegfa, were significantly upregulated using the same criteria. Notably, Angpt2 was upregulated in both tissues, whereas Vwf and Vegfa were upregulated in hippocampus but downregulated in renal cortex. This divergent regulation suggests tissue-specific endothelial responses to CKD, with renal endothelial dysfunction alongside vascular activation and remodeling in the brain. These findings identify distinct but overlapping endothelial responses across the kidney-brain axis that may contribute to BBB disruption and behavioral abnormalities.

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9 Molecular and Functional Mapping of Inputs to Aldosterone-Sensitive HSD2 Neurons that Regulate Sodium Appetite

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HSD2 neurons in the nucleus of the solitary tract (NTS) are the primary aldosterone sensors in the brain and are essential for sodium appetite. However, the afferents that act in concert with aldosterone to stimulate HSD2 neurons during hypovolemia or suppress their activity to prevent excess sodium intake have not been systematically investigated. We examined presynaptic regulation of HSD2 neurons across distinct sodium balance states. Optogenetic circuit mapping in acute brain slices demonstrated that excitatory afferents from the hypothalamus are generally weak, although inputs from the paraventricular hypothalamus (PVH) showed modest enhancement during sodium deficiency. In contrast, GABAergic afferents from the NTS and central amygdala (CeA) produced dense connectivity, large currents, and potent inhibition of HSD2 neurons. Consistent with this, chemogenetic activation of NTS-projecting CeA neurons suppressed aldosterone-induced saline ingestion. However, these results conflict with prior reports that CeA lesions abolish salt intake. Resolving this paradox, we confirm that CeA ablation severely impairs sodium intake, whereas selective ablation of NTS-projecting CeA neurons leaves appetite intact, suggesting distinct CeA populations exert opposing effects on sodium consumption. Guided by molecular profiling of NTS-projecting CeA neurons, we identify CeA Tac1 neurons as a major source of GABAergic synaptic input to HSD2 neurons. Together, our results demonstrate prominent inhibitory control of aldosterone-sensing HSD2 neurons and identify functionally opposing CeA populations that control sodium appetite.

10 ITGA6-Dependent Adhesion Signaling Coordinates Cytoskeletal Organization, Epithelial Dynamics, and Regenerative Competence in Airway Basal Cells

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Airway basal cells (BCs) are resident stem cells of the proximal airway that maintain epithelial homeostasis and drive tissue repair, yet how cell-matrix adhesion regulates cytoskeletal organization and coordinated epithelial behavior to support these functions remains incompletely understood. Although integrin $\alpha 6$ (ITGA6/CD49f) is widely used as a marker of airway BC identity, its functional role in epithelial organization and regeneration remains unclear. To address this question, we generated CRISPR-mediated ITGA6 knockout, genetic rescue, or overexpression models in primary human BCs from multiple donors. Using live-cell imaging, ultrastructural analyses, electric cell-substrate impedance sensing (ECIS), and differentiation models, we evaluated epithelial organization, barrier assembly, and cell fate. Loss of ITGA6 disrupted cytoskeletal organization, resulting in altered F-actin architecture, reduced cellular anisotropy and alignment, and abnormal epithelial ultrastructure. Live-cell imaging revealed impaired collective cell migration, delayed epithelial self-organization, and prolonged tissue assembly dynamics in ITGA6-deficient BCs, whereas ITGA6 rescue in knockout cells shifted these behaviors back toward wild-type patterns. Consistent with these defects, ITGA6 loss impaired barrier formation and maturation, and ITGA6 overexpression enhanced epithelial resistance across multiple donors. Across serial passages, ITGA6-deficient BCs progressively lost proliferative and organizational capacity, consistent with diminished regenerative competence, whereas ITGA6 re-expression partially preserved these functions. ITGA6-deficient BCs failed to differentiate into a functional pseudostratified mucociliary epithelium and instead acquired a KRT13-associated squamous-like phenotype; this pathogenic differentiation was rescued by restoration of ITGA6 expression. Collectively, these findings identify ITGA6 as a critical regulator of BC stemness and function, establishing a critical role beyond its application in BC identity.

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11 Implications for CFTR Expression during Early Pancreatic Development

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Exocrine pancreatic insufficiency (EPI) is a prevalent comorbidity in cystic fibrosis (CF), affecting approximately 85% of CF infants within the first year of life. The precise role of CF transmembrane conductance regulator (CFTR) in pancreatic development and the mechanisms by which CFTR mutations contribute to EPI remain incompletely understood. Using a ferret model of embryonic pancreatic development, we observed increasing levels of CFTR expression in multipotent pancreatic progenitors (PP). This study tests the hypothesis that CFTR expression and/or function influences the differentiation and maturation of PP cells. Patient-specific, human-derived iPSCs from people with (pwCF) and without CF were differentiated into PP cells. We found the differentiation efficiency in iPSC from pwCF to be significantly lower than the control iPSC. At the PP stage, CF cells exhibited significantly reduced NKX6.1 transcript in comparison to WT cells, supporting a reduced efficiency in early pancreatic development. Pharmacological inhibition of CFTR in WT cells led to a marked decrease in NKX6.1 and PDX1 protein, mirroring the phenotype observed in CF-PP cells along with an increase in differentiation efficiency observed in the presence of CFTR modulators. Our findings demonstrate that CF-PP cells exhibit impaired differentiation efficiency from the primitive gut tube stage of differentiation, a defect recapitulated by pharmacologic CFTR inhibition in non-CF iPSCs. These results support a previously unrecognized role of CFTR in pancreatic development, requiring further investigation of the cellular mechanisms impacted by attenuated CFTR expression/function. The data highlights the need to consider early intervention to restore complete pancreatic function in CF.

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12 Dynamamin-Related Protein 1 in Leptin Receptor Neurons Regulates Metabolic Homeostasis and Cardiovascular Function

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Leptin receptor (LepRb) signaling in the brain plays a pivotal role in the regulation of metabolism and blood pressure. Mitochondria dysfunction is implicated in many diseases including obesity and cardiovascular diseases. Dynamamin-related protein 1 (DRP1) which plays essential role for mitochondria fission/fusion has been implicated in mitochondria dysfunction. However, the role of DRP1 in LepRb neurons in the regulation of metabolic and cardiovascular functions is unknown. Here, we investigated whether loss of DRP1 in LepRb-expressing neurons affects metabolic and cardiovascular homeostasis. For this, we crossed female mice harboring floxed alleles of the *Drp1* gene (*Drp1^{fl/fl}*) with male mice expressing Cre recombinase in LepRb (*LepRbCre*) cells. Using immunofluorescence staining, we confirmed that DRP1 is expressed in the LepRb+ cells of the hypothalamus and that conditional knockout (CKO) mice have selective loss of DRP1 protein expression in the LepRb+ cells. LepRb+ cells of the CKO mice exhibited significantly elongated mitochondria by electron microscopy. Next, we found that both male and female CKO mice fed normal chow diet have similar body weight compared to control littermates. However, fat mass was significantly higher in both male (5.9 ± 0.9 vs 3.6 ± 0.6 g) and female (3.1 ± 0.4 vs 2.0 ± 0.3 g) CKO mice compared to controls. Of note, both male and female CKO mice displayed impaired insulin sensitivity compared to control animals, whereas glucose tolerance was similar between the two groups. Striking, CKO mice were sensitized to diet-induced obesity. Indeed, body weight of male and female CKO mice fed high-fat high-sucrose diet (HFHSD) was significantly increased compared to controls (47.4 ± 1.6 vs 40.4 ± 2.1 g for males, and 40.8 ± 2.6 vs 34 ± 1.6 g for females). This excess weight gain was primary due to increased fat mass whereas lean mass was not altered. Decreased brown adipose tissue sympathetic activity indicates that reduced energy expenditure may contribute to the development of obesity in CKO mice fed HFHSD. Female, but not male, CKO mice fed HFHSD displayed insulin intolerance, but no change in glucose tolerance. Surprisingly, telemetry systolic blood pressure of male CKO mice fed normal chow diet was significantly lower relative to controls (107.9 ± 5.9 vs 116.6 ± 2.6 mmHg). Renal sympathetic nerve activity was also significantly lower in male CKO mice compared to controls under normal chow diet (75 ± 2.5 vs 93.4 ± 5.1 spike/sec) or HFHSD (67.2 ± 8.3 vs 102.5 ± 6.8 spike/sec), suggesting that reduced renal sympathetic nerve activity may contribute to lower blood pressure in CKO mice. We are currently testing blood pressure in mice fed HFHSD. These results demonstrate that DRP1 in leptin receptor-expressing cells regulate body weight, glucose homeostasis and blood pressure.

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13 Muscle strengthening activity guideline adherence is associated with reduced microvascular function in women after pregnancy: an exploratory analysis

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Women with a history of gestational diabetes mellitus (GDM) have a greater risk of developing cardiometabolic disease compared to healthy control (HC) women who had an uncomplicated pregnancy. Microvascular endothelial dysfunction, mediated in part by reduced nitric oxide (NO)- and exaggerated endothelin-1 (ET-1)-dependent mechanisms, persists after GDM and likely contributes to chronic disease progression. Muscle strengthening activity (MSA) is associated with improved vascular function, reduced ET-1 synthesis, and reduced cardiometabolic disease risk. We hypothesized that MSA guideline adherence (≥ 2 days MSA/week) would be associated with microvascular endothelium- and

NO-dependent dilation and the change in these outcomes with ET-1 receptor antagonism. 24 women (n=12/group) underwent intradermal microdialysis for the delivery of lactated Ringer's (control) or 500nM BQ-123 (ETA receptor antagonist) during a local heating protocol (42°C; 0.1°C·s⁻¹) with 15mM NG-nitro-L-arginine methyl ester (NO-synthase inhibitor) to quantify NO-dependent dilation. Red blood cell flux was measured by laser-Doppler flowmetry (LDF). Cutaneous vascular conductance was calculated (CVC=LDF/MAP) and normalized to maximum (28mM sodium nitroprusside, 43°C). MSA adherence was assessed via questionnaire. 5 HC and 2 GDM participants met MSA guidelines. Two-way ANOVA revealed that endothelium- (p=0.04) and NO-dependent (p=0.03) dilation were attenuated in GDM vs. HC. MSA adherence was associated with lower endothelium (p=0.03)- and NO-dependent dilation (p=0.04). GDM history was associated with a greater positive change in endothelium- (p=0.02) and NO-dependent dilation (p=0.01) with BQ-123 vs. HC. These exploratory results suggest that MSA adherence is associated with reduced microvascular function after pregnancy.

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14 CRISPR-Mediated Enhancer Deletion Alters Transcription in Post-Traumatic Stress Disorder

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PTSD is a mental health condition that develops after experiencing or witnessing an extremely stressful or traumatic event. Genome-wide association studies have identified risk loci for many neuropsychiatric disorders, including PTSD, with many of these variants lying within noncoding regions of the genome. One important type of noncoding regulatory element is an enhancer, which increases the transcription of target genes. However, the specific enhancer regions that regulate genes associated with PTSD have not been extensively characterized. In this study, we investigated how a candidate enhancer region regulates the expression of a PTSD-associated gene, TSNARE1, in SH-SY5Y neuroblastoma cell lines. Using CRISPR-mediated deletion, we removed the enhancer region and hypothesized that its deletion would result in decreased expression of TSNARE1. We confirmed successful deletion of the enhancer using polymerase chain reaction (PCR) and gel electrophoresis, and quantified changes in gene expression using quantitative PCR. Gel analysis confirmed that the full length fragment was found in both the control and guide samples while the guide samples also exhibited an additional band, consistent with a heterogeneous cell population containing the deletion. Disruption of the target enhancer unexpectedly led to a 3.46-fold increase in gene expression, suggesting the deleted region may function instead as a silencer. This implies that noncoding regions associated with PTSD can act as regulatory elements, potentially functioning as silencers rather than traditional enhancers, and highlights the complex role of these regions in gene regulation.

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15 Selective Kidney-Brain Gene Pathway Responses in an Adenine-Induced Rat Model of Chronic Kidney Disease

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Chronic kidney disease (CKD) is a common and progressive systemic disorder affecting more than 1 in 7 adults in the United States and is associated with neurological and behavioral complications. Our previous work identified selective hippocampal endothelial gene dysregulation in CKD, including increased Angpt2 and Vegfa expression, suggesting that vascular pathways may contribute to kidney-brain crosstalk. However, whether these brain abnormalities reflect generalized activation of disease-associated pathways or selective kidney-brain signaling remains unclear. We previously showed that male rats exposed to a 21-day adenine diet combined with unilateral nephrectomy develop severe CKD,

characterized by elevated serum creatinine, reduced glomerular filtration rate, increased renal fibrosis markers, and increased behavioral emotionality. We hypothesized that hippocampal abnormalities in CKD result from selective kidney-brain signaling rather than generalized activation of renal injury, inflammatory, and fibrotic pathways in the brain. To test this hypothesis, we compared RNA-seq expression of gene panels associated with injury, inflammation, and fibrosis in renal cortex and hippocampus from control and CKD animals. In the kidney, all 22 genes examined met differential-expression criteria (adjusted $p < 0.05$ and $|\log_2 \text{fold change}| > 0.58$) and were upregulated, including markers of tissue injury, inflammatory signaling, immune activation, extracellular matrix remodeling, and fibrosis. In contrast, none of the corresponding detectable genes in the hippocampus met the same criteria; *Havcr1* and *Il6* were not detected. These findings show that marked renal injury, inflammatory, and fibrotic transcriptional responses are not paralleled in the hippocampus. Together with the selective endothelial changes, these findings support kidney-brain signaling mechanisms rather than a generalized disease response.

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16 Regulation of Skeletal Muscle Cell Proliferation and Differentiation by MEK inhibition

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Myogenesis, the coordinated proliferation, differentiation, and fusion of muscle progenitor cells, is driven by myogenic regulatory factors (MRFs), including MyoD and MyoG, as well as fusogenic protein Myomaker. Mitogen-activated protein kinase kinase (MAP2K/MEK)- extracellular signal-regulated kinase (ERK) signaling coordinates this process by promoting myoblast proliferation and regulating progression through differentiation. MEK inhibitors (MEKi) are widely used as anti-cancer therapies, particularly in cancers with RAS or RAF mutations. Because the MEK/ERK pathway interacts with transcriptional programs governing myogenesis, we hypothesized that MEK inhibition would alter MRF expression and affect muscle cell differentiation. To test this, cells were treated with multiple MEKi across a range of concentrations, and proliferation, differentiation, and regenerative capacity were assessed. In a previous study of tumor-bearing mice, MEK inhibition did not increase the amount of centrally located nuclei, or embryonic myosin heavy chain (eMHC)-positive fibers, suggesting no enhancement of regeneration. Likewise, dose-escalation studies showed no increase in muscle cell proliferation, while reduced proliferation was observed but only at concentrations substantially exceeding clinically relevant doses. In contrast, MEKi treatment altered the temporal expression of MRFs, with the greatest differences observed on day 3 of differentiation, suggesting an effect on the timing of myogenic progression. Together, these findings indicate that MEK inhibition does not enhance muscle cell proliferation or regeneration but may influence the differentiation timing during a discrete window of myogenesis. Further studies are needed to determine the functional significance of these transcriptional changes.

17 Behavioral Effects of Post-Injury 17 β -Estradiol Following Repetitive Mild Traumatic Brain Injury in Male Mice

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Mild traumatic brain injury (mTBI) is the most common form of neurotrauma, frequently occurring in contact sports, vehicle accidents, combat, and falls. Although mTBI is often associated with transient cognitive and behavioral changes, repetitive mTBI (rmTBI) may produce more persistent consequences, and the mechanisms underlying these effects remain poorly understood. Previous work in our lab indicates that male mice may be particularly vulnerable to cognitive impairment following mTBI, raising the possibility that sex-related biological factors influence the response to injury. Estrogen, particularly 17 β -estradiol (E2), has been implicated in behavioral and cellular responses following traumatic brain injury, but its effects following repetitive mild injury in males remain less understood. To examine this

question, we investigated the effects of post-injury E2 administration on behavioral outcomes following rmTBI in male mice. Twenty-four male mice underwent a repetitive mild head-injury paradigm and received either E2 or vehicle treatment following injury. Behavioral outcomes were assessed using a rewarded T-maze, elevated plus maze, and novel object recognition task to examine spatial working memory, anxiety-like behavior, and object recognition memory. Preliminary findings suggest that E2 may influence task retention in the rewarded T-maze and attenuate differences in anxiety-like behavior between sham and rmTBI animals, while no clear treatment-associated differences were observed in novel object recognition. These findings suggest that post-injury E2 may have domain-specific effects following rmTBI.

18 Time-Dependent Inflammatory Response of Whole Blood to High Sodium

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Diets high in sodium are common in developed countries and increase risk for high blood pressure and cardiovascular disease. High sodium consumption has been associated with chronic inflammation, which may contribute to the progression of cardiovascular disease in people who consume high-sodium diets. We hypothesized that acute high-sodium treatment would induce an inflammatory response in whole blood samples collected from healthy, normotensive, young adults. Whole blood samples were collected via venipuncture, treated with 0mM (control), 25mM, or 50mM sodium chloride (NaCl), and incubated at 37°C/5%CO₂ for 4 and 8 hours. Following incubation, plasma samples were collected and stored at -80°C until further analysis. Plasma concentrations of inflammatory cytokine TNF-α were assessed via ELISA to quantify inflammatory responses to NaCl. There was no effect of treatment on TNF-α concentrations at the 4-hour time point (all $p > 0.05$). TNF-α concentrations were greater for 50mM NaCl treatment compared to control (control: 14.4±5.2pg/ml, vs. 50mM: 21.1±7.7pg/ml; $p = 0.09$) and 25mM NaCl (25mM: 12.8±5.9pg/ml vs. 50mM: 21.1±7.7pg/ml; $p = 0.05$) at the 8-hour time point. There was a significant effect of time on TNF-α concentrations in the control samples (4 hrs: 17.16±5.35pg/ml vs. 8 hrs: 14.43±5.21pg/ml; $p = 0.05$) but not the treated samples (all $p > 0.05$). These data suggest that inflammation may be a mechanism by which high sodium diets contribute to elevated cardiovascular disease risk in young adults.

19 Sex Specific Biomarkers for Right Ventricular Dysfunction in Animal Models of Pulmonary Hypertension

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Introduction: Pulmonary hypertension (PH) is an incurable cardiopulmonary disease. Sex differences exist in prevalence and prognosis of right heart failure, however, the mechanisms underlying the differences are largely unknown. The aims were to study a link of sex-specific genes in hypoxic PH animal models and their relation to right ventricular hypertrophy and cardiac remodeling. **Conclusions:** Males show more RV hypertrophy in Hypoxic and Sugen/Hypoxic PH with higher RV:LV cavity ratios. ID3 and HMGB1 genes reflect sex-specific changes that preserve the female heart while negatively affecting the male heart leading to RH failure. Therefore, sex gender could be as a risk factor for developing PH. **Results:** RVP, RVSP, and mPAP measurements showed induced PH was present in Hypoxic and Sugen/Hypoxic mice. FI showed that male mice develop RV hypertrophy in Hypoxic and Sugen/Hypoxic conditions whereas female mice maintained their cardiac physiology under Hypoxia but affected in Hypoxic-Sugen conditions. Morphologically, RV:LV cavity ratios as an indicator of dilation were significantly increased in Sugen/Hypoxia versus Normoxia ($P = 0.011$) and Hypoxia ($P = 0.033$) in males but not observed in females. ID3 gene expression in the RV tissue, was significantly decreased in Hypoxia ($P < 0.001$) and Hypoxic-sugen ($P < 0.001$) in females but not observed in males. This correlation is linked

to RV hypertrophy in hypoxic male mice. Gene expression for HMGB1 was significantly increased in male Hypoxia ($P=0.038$) only and in female Sugen/Hypoxia ($P=0.004$). Moreover, Lipocalin-2 was significantly increased ($P=0.022$) in females versus males in Normoxic mice group only. No similar change was seen in LV tissue. We would like to correlate this to RV hypertrophy found in males. Methods: C57BL/6J wild-type mice were exposed to normal air (21% O_2) or chronic hypoxia (10% O_2) and Sugen5416/hypoxia (10% O_2 plus Sugen5416 20mg/kg, i.p., weekly) for 6 weeks to induce PH. Right Heart Catheterization (RHC) was used to assess PH phenotype. RV hypertrophy was measured using Fulton index (FI) (RV weight: LV + Septum weight). Mouse hearts were harvested, left (LV) and right ventricular (RV) excision for qPCR (Sex-specific genes: Lipocalin-2, HMGB1, and ID3) and western blotting. H&E and Masson trichrome staining were used on cross sectional areas of the heart to measure the morphology of LV and RV structures and remodeling.

20 **TGF- β 1 Lipid Accumulation is Reduced by NAD⁺ and NAC Supplementation**

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Myosteatosis, categorized by an accumulation of lipid inside of skeletal muscle, is prevalent in patients with cancer and a marker for poor prognosis. Muscle of mice bearing C-26 tumors demonstrate both increased lipid accumulation and an increase in Transforming Growth Factor-Beta1 (TGF- β 1), leading us to seek a better understanding of the mechanism behind the association. Furthermore, worsening myosteatosis is associated with higher circulating levels of TGF- β 1 in people with pancreatic cancer. To determine if TGF- β 1 was sufficient to induce lipid accumulation in muscle cells, C2C12 myotubes were treated with 10 ng/mL of TGF- β 1 or vehicle. When the media was supplemented with fatty acids, TGF- β 1 induced an approximately 25% increase in Bodipy 493/503, demonstrating increased intracellular lipid content. Although the pathways behind the increased lipid accumulation are not well understood, and therefore, difficult to reverse or prevent, our data demonstrated reduced NAD⁺ and hallmarks of oxidative stress. Therefore, we tested if supplementation with either an NAD⁺ precursor or a glutathione donor could reduce lipid accumulation. Half of cells were treated with 10 ng/mL of TGF- β 1 in low glucose media and half of treated and untreated TGF- β 1 cells were given either NMN or N-acetylcysteine (NAC). Supplementing either NMN or NAC decreased the lipid accumulation, while the combination of the two did not provide additional protection. This data suggests an NAD⁺ or glutathione supplementation may decrease lipid accumulation in muscle cells under stress. Increasing the antioxidant capacity or NAD⁺ supplementation of the myotubes may provide the cell with a greater ability to combat lipid accumulation.

21 **Mucosal melanoma microbiomes differ from cutaneous melanoma and site-matched squamous cell carcinoma**

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Significance: Mucosal melanoma (MM) patients have drastically shorter survival outcomes compared to those with cutaneous melanoma (CM). MMs display limited responses to immunotherapy and originate in locations with rich microbial compositions, but how the microbiome may contribute to tumor progression is unknown. This study utilizes human biospecimens and 16S metagenomic analyses to compare the MM microbiome to CM and site-matched squamous cell carcinoma (SCC). The identified enriched taxa will be tested in gnotobiotic zebrafish MM models. Hypotheses: MM microbiomes differ from CM and site-matched SCC. Some bacteria enriched in MM may contribute to its adverse outcomes. Methods: Metagenomic analyses with QIIME2 were used to identify taxa enriched in human MMs compared to CMs and site-matched SCCs. Germ-free zebrafish larvae were inoculated with MM-enriched or -depleted species by immersion and assessed for colonization with culture and qPCR. Results: MMs have lower alpha diversity than site-matched SCCs, and their beta diversity differs by diagnosis and location. Differential abundance analysis determined several taxa significantly enriched in site-matched MM vs SCC. Several aerotolerant bacteria colonize the zebrafish comparably to

literature-reported bacterial loads, but lower levels of colonization were observed with other MM- and SCC-associated bacteria. Many anaerobic species tested do not colonize zebrafish with current delivery methods, although ongoing work involves utilization of microgavage to deliver bacteria. Impact: We have identified bacteria enriched in human MMs and established zebrafish models for investigating their effects on MM progression. In the future, microbiome-targeted interventions may improve immunotherapy responses and survival outcomes in MM patients.

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22 Aortic Load-Dependent Stiffness is Associated with Estimated Glomerular Filtration Rate Among Healthy Adults: A Cross-Sectional Study

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Background: Total aortic stiffness, measured by carotid–femoral pulse wave velocity (cfPWV), comprises load-dependent (LD-cfPWV) and structural (S-cfPWV) components and is associated with kidney function across adulthood. While load dependent and structural carotid stiffness mechanisms are not associated with estimated glomerular filtration rate (eGFR), whether these components of central aortic stiffness are associated with eGFR remains unknown. We hypothesized that load-dependent and structural aortic stiffness are associated with kidney function among healthy adults. Methods: Healthy participants ($n = 176$, female $n = 79$; age 46.3 ± 17.4 ; range 18–84 yrs) with no history of cardiovascular disease had blood pressure (BP) and cfPWV measured with non-invasive tonometry. LD-cfPWV, and S-cfPWV were calculated with participant specific exponential models using standardized BP. Serum creatinine, age, and sex were used to calculate eGFR. Results: LD-cfPWV was significantly associated with reduced eGFR independent of age, sex, and body mass index (BMI) (95% CI, -9.41 to -1.02 ; $p = 0.015$). cfPWV and S-cfPWV were not significantly associated with eGFR after age, sex, and BMI adjustment, with BP included for cfPWV (95% CI, -1.12 to 2.05 ; $p = 0.56$; 95% CI, -0.61 to 2.31 ; $p = 0.25$, respectively). Conclusion: Load dependent, but not structural, aortic stiffness is associated with lower eGFR among healthy adults, suggesting that lowering BP may preserve kidney function through modifying aortic stiffness among healthy adults. The mechanisms by which load-dependent aortic stiffness may contribute to lower kidney function require further investigation.

23 Longitudinal Changes in Load-Dependent Arterial Stiffness During Pregnancy: No Relation with Preeclampsia Diagnosis

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Arterial stiffness is a biomarker of cardiovascular risk and undergoes adaptation during pregnancy. Total arterial stiffness measurements conflate structural (i.e., elastin/collagen/wall thickness/diameter) and load-dependent (LD) (i.e., blood pressure-related) contributions, which may follow distinct trajectories across gestation. We hypothesized that longitudinal changes in LD, but not structural, arterial stiffness would be distinct between women with a healthy vs. preeclamptic pregnancy. A total of 141 pregnant women (127 healthy, 14 preeclampsia; age 30.6 ± 4.0 years) completed assessments across three trimesters (T1, T2, T3). Total carotid-femoral (aortic) and carotid PWV (cfPWV and carPWV, respectively) were decomposed into structural and LD components using pressure-standardized reference values. Longitudinal stiffness changes were assessed via linear mixed-effects models (including trimester, age, BMI, random participant intercept). Sensitivity analysis confirmed that preeclampsia status (9% of cohort) did not alter trimester trajectories, supporting a pooled analysis. Total cfPWV decreased from T1 to T2 ($\beta = -0.422$, $p < 0.001$) and remained lower at T3 vs T1 ($\beta = -0.392$, $p < 0.001$). Structural cfPWV

declined through gestation, whereas LD cfPWV showed a mid-gestational (T2) reduction that returned toward baseline by T3. LD carPWV followed a comparable trajectory to LD cfPWV (T2 vs T1: $\beta = -0.225$, $p < 0.001$; T3 vs T1: $\beta = -0.034$, $p = 0.426$). Pregnancy is characterized by a transient mid-gestational reduction in LD arterial stiffness distinct from progressive decreases in structural stiffness, with preeclampsia diagnosis unaffected by these longitudinal trajectories. Therefore, arterial stiffness adaptation appears to be consistent across healthy and preeclamptic pregnancies.

24 CRISPR-Cas9 Investigation of NLGN1 Regulation in Relation to Suicide Risk

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Suicide is a major public health concern and is among the leading causes of death worldwide. While genetic factors are known to contribute to suicide risk with heritability estimates of 30-50%, much of the genetic basis remains unknown. In this research, we investigated the role of a putative enhancer region predicted to influence the expression of NLGN1, a gene involved in neuronal development and synaptic function that has been associated with suicide risk and psychiatric disorders. CRISPR-Cas9 was used to remove the targeted regulatory region in a human neuroblastoma cell line, SH-SY5Y. The removal of the targeted region was confirmed using PCR and gel electrophoresis. Changes in NLGN1 expression were then measured using qPCR to determine whether removal of the regulatory region altered gene expression. We observed a decrease in NLGN1 expression following removal of the region, consistent with our hypothesis that the region functions as an enhancer. These findings provide insight into the potential regulatory mechanisms influencing NLGN1 expression and its possible relationship to suicide risk. Future research should investigate the transcriptome-wide effects of removing this regulatory region and examine whether changes in NLGN1 expression contribute to neuronal or behavioral phenotypes associated with suicide risk.

25 Glomerular Filtration Rate and the Renal Function Reserve Response to Oral Protein Load in Healthy Young Adults

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Renal functional reserve (RFR), the capacity of the kidneys to increase glomerular filtration rate (GFR) in response to an acute stimulus, may provide a method for identifying early changes in kidney function before traditional clinical markers detect kidney damage or disease. However, normative RFR responses in healthy young adults and potential sex differences remain poorly characterized. We sought to measure RFR in healthy young men and women and determine whether the magnitude of the response to an acute protein load differs by sex. Participants underwent a fasted baseline assessment followed by ingestion of whey protein (1.2 g/kg body weight). GFR was estimated by timed creatinine clearance (CrCl) normalized to body surface area at baseline and 75- and 150-min following protein ingestion. RFR was defined as the change from baseline to peak post-protein CrCl ($\Delta RFR = \text{peak CrCl} - \text{baseline CrCl}$). Preliminary data were collected from nine healthy young adults (6 female, 3 male). Mean ΔRFR was $8.14 \pm 33.45 \text{ mL/min/1.73 m}^2$ in females compared with $-31.47 \pm 20.68 \text{ mL/min/1.73 m}^2$ in males. The difference between sexes approached statistical significance ($p=0.054$). These preliminary findings demonstrate substantial inter-individual variability in RFR and suggest a potential sex difference in the renal response to acute protein ingestion, with females exhibiting a greater positive change in CrCl with protein loading compared to males.

26 Diabetes is Independently Associated with Impaired Vascular Function in Individuals with Stage 3 CKD

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Diabetes remains the most common cause of chronic kidney disease (CKD). Both CKD and diabetes are associated with increased risk of cardiovascular disease (CVD). Still, diabetes remains an independent risk factor for CVD in CKD patients. Endothelial dysfunction is a mediator of CVD and noted in both diabetes and CKD. We hypothesized that in patients with CKD, those with diabetes will have significantly worse endothelial function than those without diabetes. We utilized data from a prior clinical trial where we evaluated if allopurinol improves endothelial function in 80 patients with stage 3 CKD and hyperuricemia. 48(61%) of the participants had diabetes. We compared clinical characteristics, measures of vascular function, and biomarkers of inflammation and oxidative stress between those with diabetes and without diabetes using non-parametric T-test. Endothelium-dependent dilation (EDD) was measured via brachial artery flow-mediated dilation (BA-FMD) and endothelium-independent dilation via nitroglycerin-mediated dilation (NMD). We found that BA-FMD was significantly lower in diabetes vs no diabetes (mean (SD) BA-FMD 3.86 vs 6.23 %Δ, respectively, $p=0.029$). Similarly, NMD was significantly lower in diabetics vs non-diabetics (mean (SD) NMD 14.9(6.1) vs 24.1(11.0) %Δ, respectively, $p=0.0002$). There were no significant differences in age, sex, systolic and diastolic blood pressure, kidney function, or biomarkers of inflammation and oxidative stress between those with diabetes and without diabetes. Diabetes is independently associated with impaired EDD and EID in CKD. The exact mechanisms underlying these findings warrant further study.

27 **Bioinformatic and Biophysical Characterization of Estrogen Receptors in *Xenopus laevis***

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Previously, our lab observed that 17- β -estradiol (E2) and bisphenol-A (BPA) suppress compound action potentials (CAPs) in isolated *Xenopus laevis* sciatic nerves; however, the molecular mechanism behind this response remains unknown. To investigate this, we used in-silico approaches to identify and characterize estrogen receptors within *Xenopus* sciatic nerves. Amino acid sequences of two proteins, GPER1.L and ESR1, were retrieved using UniProt, representing estrogen receptors GPER1 and ER α , respectively. We used AlphaFold to predict 3D structures and assessed functional binding potential using InterPro, which identified conserved residues within the ligand-binding pockets of each receptor. A docking analysis was performed using SwissDock to evaluate ligand-receptor interactions between both E2 and BPA. These in-silico analyses suggested that both GPER1 and ER α are potentially present in *Xenopus* sciatic axons and can bind both E2 and BPA. Consistent with findings from other species, both receptors exhibited a higher binding affinity for E2 as compared to BPA. ER α also demonstrated higher binding affinity for both ligands when compared to GPER1; however, the rapid onset of action potential suppression in situ suggests an initial GPER1-mediated non-genomic signaling event. The sustained CAP suppression following washout suggests that ER α involvement cannot be ruled out. Preliminary SDS-PAGE results indicate the presence of both ER α and GPER1 in *Xenopus* sciatic nerve lysate. We continue to refine Western blot protocols to confirm receptor presence using commercially available antibodies that recognize the putative *Xenopus* ER α and GPER1 isoforms identified through in-silico analyses with immunohistochemistry to confirm the localization of receptors in the nerves.

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28 **Effects of BPA and Estrogen on Compound Action Potential Amplitude and Conduction Velocity in Myelinated *Xenopus* Sciatic Nerve**

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Environmental exposure to endocrine disrupting chemicals (EDCs) is ubiquitous and can lead to metabolic, developmental, and neurological changes primarily by binding estrogen receptors and mimicking estrogen. The few studies that have investigated the effects of EDCs on amphibian peripheral nervous system found that bisphenol A (BPA) or estradiol (E2) exposure suppressed compound action potential (CAP) amplitude in *Rana* sciatic nerve without affecting threshold. Rat cardiac muscle exposed to BPA showed decreased myocardial conduction velocities, whereas smooth muscle exposure resulted in rapid concentration-dependent relaxation. Despite the effects seen in smooth and cardiac muscle, effects on skeletal muscle contraction remain largely unexplored. We studied CAP threshold, amplitude, and conduction velocity in sciatic nerves from *Xenopus laevis*. Using concentrations found to be effective in *Rana*, we found that incubation in 0.5 mM BPA or 0.05 mM 17- β -estradiol did not affect threshold, but both solutions decreased the maximum CAP amplitude, with greater suppression by BPA. The effects of BPA were not fully reversed following wash-out with amphibian Ringer's, whereas E2 exposed nerves recovered almost entirely. Sciatic nerve conduction velocity was significantly slower in nerves incubated in BPA but faster in those exposed to E2. To examine if the effects seen in the sciatic nerve translate to changes in muscle contraction, we ran a trial experiment to test muscle function following nerve exposure to E2, BPA, or Ringer's. Our pilot study suggests BPA, but not E2 or Ringer's, suppress muscle contraction amplitude, but refinement of the procedure is needed to draw conclusive results.

All procedures were reviewed and approved by Drake IACUC (IACUC approvals 091126-DC-01, 091126-DC-02, 091126-DC-03).

29 **Changes in Cerebral Blood Flow Following Gender-Affirming Hormone Therapy: Case Report**

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Background: Gender-affirming hormone therapy (GAHT) is life-saving therapy associated with reduced psychological distress and improved quality of life. However, the cerebrovascular effects of GAHT have not been well studied. Sex steroids regulate cerebral blood flow (CBF), with estrogen promoting vasodilation and testosterone promoting vasoconstriction. We examined the impact of initiating testosterone-based GAHT on global and regional CBF in a nonbinary adult, hypothesizing that CBF would decrease with the switch from estrogen to testosterone. **Methods:** One nonbinary adult (25 years; BMI, 21 kg/m²; assigned female at birth) completed MRI visits before and after 4 months of clinician-managed GAHT (50 mg testosterone gel daily). CBF was quantified using 3T pseudo-continuous arterial spin labeling, and pre- and post-GAHT measures were compared. **Results:** CBF decreased globally and across lobes. Whole-brain CBF decreased from 42 to 30 mL/100 g/min (−28%), with reductions in gray matter (−19%) and white matter (−43%). CBF reductions occurred in the frontal (−15%), temporal (−5%), parietal (−13%), and occipital (−32%) lobes, subcortical regions (−16%), and brainstem/cerebellum (−24%). Among regions of interest, CBF decreased most in the anterior cingulate gyrus (−26%) and anterior insula (−14%), whereas the hippocampus (+5%) and amygdala (+3%) changed little. Gray and white matter volumes were stable (+0.3%, +1%), indicating reductions were not due to tissue loss. **Discussion:** Testosterone-based GAHT reduced CBF, consistent with increased androgen exposure and/or reduced ovarian sex-steroid signaling in cisgender individuals. Regional differences suggest region-dependent effects on CBF. These findings highlight the need for larger studies of GAHT's cerebrovascular effects.

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30 **STAT3 increases endothelial-to-mesenchymal transition to promote vascular permeability in hypoxia-induced pulmonary hypertension**

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Introduction: Pulmonary hypertension (PH) is a progressive and life-threatening disease. Pulmonary vascular remodeling partially due to the increased lung vascular endothelial cell (EC) proliferation is a major cause for the elevated pulmonary arterial pressure in patients with PH. Endothelial-to-mesenchymal transition (EndMT) is biological process that converts EC into mesenchymal cells with the increased proliferative capacity. Signal transducer and activator of transcription 3 (STAT3) is an important for EC homeostasis but its role in the development of EndMT and PH is unknown. We hypothesized that STAT3 induces EndMT and vascular permeability to contribute to EC dysfunction in PH. **Methods:** Human lung EC were exposed to normoxia (21% O₂) or hypoxia (3% O₂) for 72 hours to induce EndMT. C57BL/6J wild-type or EC-specific STAT3-KO mice were exposed to normal air (21% O₂) or hypoxia (10% O₂) for 6 weeks to induce PH. EndMT profile was measured by expression of specific EC markers or mesenchymal markers using qPCR, Western blotting, and immunostaining. Vascular permeability was determined by FITC-dextran assay in vitro or in vivo. PH phenotype was assessed by hemodynamic measurements, right ventricular hypertrophy and morphological analysis of H&E-stained lung tissues. Normal EC were transfected with STAT3 siRNA followed by exposure to hypoxia or normoxia. In addition, EndMT and STAT3 signaling were estimated in lung tissues from healthy donors and patients with hypoxia-associated Group 3 PH. **Results:** Mice with hypoxia-induced PH exhibit enhanced pulmonary vascular remodeling, EndMT and vascular permeability. Upregulated SNAI1/2 and enhanced EndMT are correlated with activated STAT3 signaling in hypoxic human lung EC or hypoxic mice. Hypoxia also increased EC survival and monolayer permeability, while disrupting cell-cell junctions. Knockdown of STAT3 abolished hypoxia-induced EndMT and restored EC barrier function in vitro. EC-specific STAT3 deletion significantly improved PH phenotype, reduced vascular leakage, EndMT, and right ventricular hypertrophy in mice under hypoxic conditions. Immunostaining of lung tissues from Group 3 PH patients showed increased expression of SNAI1-mediated EndMT and p-STAT3 compared with controls. **Conclusions:** STAT3 induces EC dysfunction, vascular leakage, and pulmonary vascular remodeling through SNAI-mediated EndMT in hypoxia-induced PH. Targeting this pathway may offer a novel therapeutic strategy to treat PH patients.

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31 Sex Dismorphic Mechanisms Underlie Disuse-Induced Muscle Atrophy

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Disuse-induced skeletal muscle atrophy is a prevalent condition involving progressive myofiber size loss and impaired muscle function. Despite being very common, potential sex-specific differences in the mechanisms involved remain poorly understood, hindering the development of optimal personalized therapies. In males, disuse drives proteolytic pathways like the autophagy-lysosome system and decreases protein synthesis, both of which can be modulated by UNC-51-like kinase 1 and 2 (ULK1/2), leading to atrophy. Therefore, we aim to mechanistically explore a potential sex-dimorphic role of ULK1/2 in the modulation of disuse-induced muscle atrophy. Wild type (WT) and skeletal muscle-specific ULK1/2 (Ulk1/2 skmDKO) female and male mice underwent unilateral hindlimb immobilization (3 and 7 days). Tibialis anterior (TA) muscles were analyzed for muscle mass, fiber type, diameter, protein synthesis rate, muscle force, autophagic flux, and select RNA and protein levels by immunoblotting. Loss of Ulk1/2 protected males against muscle atrophy as indicated by total TA mass (WT -18% vs skmDKO -10%, $p < 0.01$) and attenuated fiber size reduction across MyHC IIa, IIx, and IIb

fibers. Induction of autophagy was attenuated in both male and female Ulk1/2 skmDKO. However, only in males, this protection was associated with attenuated decreases in protein synthesis rate (WT –38.6% vs skmDKO –17.3%, $p=0.05$). Mechanistically, the partially preserved protein synthesis was associated with higher phosphorylation levels of mTORC1, P70S6K, and RPS6, suggesting that loss of ULK1/2 enhances anabolic signaling pathways during disuse in male muscles. These results suggest that there are different mechanisms for disuse-induced skeletal muscle atrophy in males and females. While ULK1/2 play a crucial role in preserving protein synthesis in male muscles, further studies are needed to clarify the mechanisms involved in disuse-induced atrophy in female muscles.

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32 Beyond Pain Relief: Aspirin's Role in Immune Function and Muscle Maintenance in *Drosophila melanogaster*

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Maintaining tissues is an essential task for ensuring organismal survival. Muscle cells contain unique structures required for contraction and generation of force to enable muscle functions such as running or flight. Therefore, muscle function is very sensitive to changes in cellular organization. Fruit flies provide an incredible opportunity to ‘screen’ individual genes and proteins for potential involvement in muscle maintenance. Previous work in the Green lab at Cornell has looked at the role of prostaglandins in regulating muscle development. Prostaglandins are short range cellular signals synthesized by the cyclooxygenase (COX) enzyme. The average person might recognize prostaglandins for their role in promoting inflammation, which can be mediated by NSAIDs, such as aspirin, to reduce prostaglandin signaling. Recently, we fed muscle mutants aspirin and compared the progression of muscle damage to mutants without aspirin treatment. Preliminary data showed that aspirin treatment resulted in less damaged muscle tissue, suggesting a ‘protective effect’ by aspirin. While short term inflammation is helpful, many studies show prolonged inflammation can accelerate tissue damage, including in *Drosophila* muscle (Green et al., 2018). This led us to hypothesize that activation of the immune system could be contributing to the progression of muscle disease. In combination with previously collected muscle structure and function data, we show that aspirin produces complex, dosage-dependent effects in both immune and muscle tissue. Future work will continue to explore the mechanism of aspirin in these tissues to better understand the ‘double-edged’ sword of aspirin benefits and side effects observed in different tissues.

33 Effects of Semaglutide on Body Composition and Skeletal Muscle in Older Adult Mice

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Sarcopenia and obesity are highly prevalent conditions in older adults, impacting life expectancy, quality of life, and independence. GLP-1 receptor agonists, such as semaglutide, prevent and treat obesity; however, their impact on skeletal muscle health and function in older adults remains unknown. Therefore, we examined the effects of semaglutide on body composition and skeletal muscle function in older adult mice. Twenty-month-old male and female C57BL/6N mice were fed a high-fat diet for 7–8 weeks to reach an overweight state. Those mice were then assigned to semaglutide, pair-feeding (PF), or control groups for 3 weeks. Muscle contractile function and body composition were assessed via in vivo percutaneous stimulation and nuclear magnetic resonance, respectively. After treatment, semaglutide and PF groups lost body weight (–13.1%, $p<0.0001$, and –12.3%, $p<0.001$), body fat (–10.2%, $p=0.0002$ and –8.9%, $p=0.0008$), and lean mass (–4.7%, $p=0.0082$ and –2.4%, $p=0.2207$) compared to controls, and both improved the total % of lean mass related to their body weight (11.9%, $p=0.0072$ and 13.6%, $p=0.0017$). Interestingly, semaglutide treatment led to a significant improvement in glucose tolerance in relation to both PF ($p=0.0036$) and controls ($p=0.0073$). Additionally, preliminary analysis

suggests that semaglutide and PF do not compromise maximal force. These initial findings indicate that most outcomes of semaglutide can be mimicked by calorie restriction, and do not greatly affect muscle force when male and female mice are evaluated jointly. We are currently investigating the muscular and molecular mechanisms underlying potential sex-specific differences.

34 The cardiomyocyte ncMTOC scaffolding protein PCM1 could influence perinuclear proteasomes and worsen heart failure

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Centrosomes are known to anchor the microtubule network and interact with the ubiquitin-proteasome system (UPS). As cardiomyocytes mature, they lose canonical centrosomes through centrosome reduction, where centrosomal proteins reorganize into a perinuclear cage-like non-canonical microtubule organizing center (ncMTOC). We analyzed cardiac/cardiomyocyte expression, perinuclear localization, and disease association for a broad group of centrosomal genes to identify candidates that relocated to the ncMTOC and are associated with heart failure. PCM1, a centrosomal scaffolding protein, stood out. PCM1 bulk gene expression is high in hearts, and in cardiomyocytes specifically according to single cell data. Moreover, PCM1 is associated with atrial fibrillation/flutter, shows prolonged QRS duration and RR intervals, and is upregulated in human ischemic and dilated cardiomyopathy. Additionally, PCM1 interacts with numerous UPS-related proteins. We hypothesize PCM1 loss disrupts the ncMTOC and perinuclear proteasome localization, impairing cardiomyocyte contractility and UPS function, contributing to heart failure. To knockout PCM1, eight CRISPR guides targeting an out-of-frame exon were cloned and their cutting efficiency validated in HT22 cells using PCR. The best guide pair was packaged into AAV and injected into transgenic aMHC-Cas9 mice for cardiomyocyte-specific PCM1-KO. Doses of 5E10vg/g(vs. 2.5E10) were determined to be sufficient. Knockout was confirmed by IF, western blot, and qPCR. In our initial KO cohorts, no significant EKG, gravimetric or nuclei characteristic differences were found. However, future cohorts will examine KO-heart function over greater periods of time, along with response to induced heart failure. Altogether, PCM1 is a promising mechanistic link between centrosomal biology and cytoskeletal/proteostatic dysfunction under cardiac stress.

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35 History of Gestational Diabetes Mellitus Does Not Influence Cerebral Hemodynamics and Cerebrovascular Reactivity to Hypercapnia

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Individuals with a history of gestational diabetes mellitus (GDM) have an increased risk of dementia, which may be due to impaired cerebral blood flow regulation. We have previously demonstrated that individuals with a history of GDM have reduced microvascular endothelial function, compared with women with a history of uncomplicated pregnancy; yet it is unknown if individuals with a history of GDM have similar deficits in cerebrovascular function. We recruited 9 individuals with a history of GDM and 7 individuals with a history of uncomplicated pregnancy. All participants were within 5 years postpartum and free of current cardiometabolic disease. Middle cerebral artery velocity (MCAv), pulsatility index (PI; $PI = \frac{MCAv_{systolic} - MCAv_{diastolic}}{MCAv_{mean}}$), mean arterial pressure (MAP), cerebrovascular conductance index (CVCi, $CVCi = \frac{MCAv}{MAP}$), and end-tidal CO₂ (ETCO₂) were continuously recorded at rest and in response to stepped hypercapnia (4% and 6% CO₂). Reactivity was calculated as the slope

of the relation between MCAv or CVCi and ETCO₂. There were no differences in MCAv ($p=0.07$), CVCi ($p=0.76$), or PI ($p=0.18$) between groups at rest. Similarly, there were no differences in absolute changes of MCAv ($p=0.78$), CVCi ($p=0.98$), or PI ($p=0.45$) from rest to 6% CO₂. Finally, MCAv reactivity ($p=0.21$) and CVCi reactivity ($p=0.79$) were similar between groups. Cerebral hemodynamics and cerebrovascular reactivity were not different between individuals with a history of GDM and uncomplicated pregnancy. Future studies should evaluate cerebrovascular function in postmenopausal women with a history of GDM, as impairments in cerebral hemodynamics or cerebrovascular reactivity may not be present until after the menopausal transition.

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36 Regulation of Airway Surface Liquid by the PGE₂ Response in Secretory Cells and Ionocytes

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Objective: Airway surface liquid (ASL) volume is determined by the balance between liquid absorption and secretion rates. Many pulmonary diseases disrupt ASL volume. We recently discovered that two airway cell types perform opposing functions: ionocytes contribute to ASL absorption, while secretory cells secrete. Both cell types require cystic fibrosis transmembrane conductance regulator (CFTR) channels to regulate ASL volume. However, it remains unclear how airway epithelia balance the contributions of two neighboring cell types that perform opposing functions through the same apical channel. Understanding how airway epithelia balance absorption and secretion is crucial in developing treatments to restore physiological ASL volume. **Materials and Methods:** Airway epithelia were cultured at the air-liquid interface from human lung donors. To test CFTR activity, we studied CFTR-mediated Cl⁻ currents using the transepithelial voltage-clamp technique and the CFTR inhibitor CFTRinh-172. To evaluate CFTR and receptor expression, we analyzed single-cell RNA datasets obtained from LungMap and cultured epithelia. **Results:** Exposing human airway epithelia to 1 μ M PGE₂ increased CFTR-mediated secretion by secretory cells. However, PGE₂ simultaneously inhibited CFTR-mediated absorption by ionocytes. Single-cell RNA sequencing analysis revealed that airway epithelia express the prostaglandin receptors EP₂, EP₃, and EP₄. EP₂ and EP₄ were expressed by all epithelial cells except ionocytes, whereas EP₃ was expressed solely on ionocytes. Activating EP₃ with its specific agonist sulprostone recapitulated the inhibition of CFTR activity in ionocytes by PGE₂, but did not alter secretory currents. **Conclusion:** PGE₂ serves as a key ligand that simultaneously increases CFTR activity in secretory cells and decreases CFTR activity in ionocytes. Thus, PGE₂ serves to balance ASL secretion and absorption.

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37 Renal hemodynamic and tissue oxygenation responses to hypoxic stress in a preclinical model of PMOS

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Polyendocrine metabolic ovarian syndrome (PMOS) is the most common endocrine disorder affecting reproductive-aged women and is associated with numerous metabolic, reproductive, and cardiovascular consequences including renal dysfunction. Renal manifestations of PMOS include glomerular hyperfiltration, hyperuricemia, and endothelial dysfunction. These abnormalities may be driven by the hormonal dysregulation, insulin resistance, dyslipidemia, and systemic inflammation associated with PMOS. In this study, we sought to characterize the renal hemodynamic responsiveness to acute hypoxic challenge which may be altered in a rodent model of PMOS. We predicted that PMOS induction would reduce the kidney's ability to withstand ischemic insults due to acute hypoxic challenges. Eight female Sprague-Dawley rats underwent a 4-week DHEA protocol for PMOS induction

and were compared to 8 placebo-treated controls. Following induction, all rats were subjected to 10 acute hypoxic episodes followed by hypoxic dose-response challenges at fractional inspired oxygen (FiO₂) levels of 5%, 10%, and 15%. Transit time flow and tissue oxygen probes were used to continuously monitor cardiac (HR and RR interval) as well as renovascular hemodynamic (mRBF, sRBF, dRBF, cPO₂, pulse flow, and RRI) metrics during the hypoxic episodes. Our findings suggest that renal responses during AIH remain similar across the episodes between groups. However, both the recovery and dose response differed between groups. This indicates that, in this model, treatment alters the kidney's response to hypoxic challenges and may affect its capacity to recover from repeated episodes, potentially increasing susceptibility to renal dysfunction in PMOS.

38 NBCE1-mediated Bicarbonate Transport in Lung Epithelial Cells

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Objective: CFTR provides an apical pathway for HCO₃⁻ secretion into the airway surface liquid (ASL) and increases ASL pH. In cystic fibrosis, loss of CFTR-mediated HCO₃⁻ secretion results in an acidic ASL that impairs host defenses. Understanding the cellular mechanisms underlying CFTR-mediated secretion could help restore pH-dependent host defenses in CF and other airway diseases. The basolateral transporter NBCe1 plays an important role in HCO₃⁻ transport in epithelia. We hypothesize that NBCe1 may pair with CFTR in the same cells in airway epithelia. Materials and Methods: Cell types containing NBCe1 or CFTR were identified by analyzing single cell RNA sequencing data on human airway epithelial cells and expressed splice variants were determined by performing PCR with splice variant-specific primers. To study NBCe1 function in intact human airway epithelia, the NBCe1-encoding SLC4A4 gene was disrupted using CRISPR/Cas9 and changes in mRNA expression measured using RT-qPCR. CFTR-mediated HCO₃⁻ secretion was measured in control and NBCe1-knockdown (NBCe1-KD) epithelia using the short-circuit technique and ASL pH was measured with SNARF-dextran. Results: NBCe1 co-localizes to a secretory cell type. NBCe1-B and NBCe1-C were the dominant isoforms expressed. NBCe1-KD decreased NBCe1 expression to 27.6% ± 20.7% of controls (p=0.0266; n = 3). Unexpectedly, NBCe1-KD increase HCO₃⁻ secretion. Conclusion: The data suggest that NBCe1 expression limits HCO₃⁻ secretion. Testable hypotheses include, NBCe1 operates with a renal-like 1:3 stoichiometry in airway epithelia, or that eliminating NBCe1 alters the expression of other acid-base transporters.

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39 ABC Transporter Network Adaptation During the Development of Paclitaxel Resistance in Ovarian Cancer

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Acquired chemoresistance impedes durable treatment response in ovarian cancer. Although ATP-binding cassette (ABC) transporters can reduce intracellular drug exposure, the limited clinical success of strategies targeting ABCB1 suggests that resistance may involve broader transporter networks. We hypothesized that paclitaxel exposure drives dynamic remodeling of ABC transporters and that selected transporters contribute functionally to acquired resistance. Paclitaxel-resistant OV90 and OVCAR8 ovarian cancer cells were generated through repeated drug exposure, recovery, and dose escalation. Resistance was confirmed by rightward shifts in paclitaxel concentration-response curves. To distinguish acute drug responses from stable resistance-associated changes, temporal RNA-seq compared untreated sensitive cells, sensitive cells after 6 or 48 hours of paclitaxel exposure and established resistant cells before and after paclitaxel rechallenge. ABC transporter expression showed extensive remodeling between sensitive and resistant states, with distinct profiles across cell models. In OV90 cells, resistance was associated with enrichment of xenobiotic and glutathione-conjugate

transport programs involving ABCB1, ABCC2, and ABCC3. ABCC3 displayed a progressive increase from 6 hours ($\log_2\text{FC}=0.302$) to 48 hours ($\log_2\text{FC}=0.732$) and established resistance ($\log_2\text{FC}=2.368$, $\text{padj}=1.0\times 10^{-6}$), with increased expression independently confirmed by RT-qPCR. Ongoing siRNA-mediated knockdown studies are testing whether resistance-associated transporters are functionally required for the paclitaxel-resistant phenotype. These findings support progressive, model-dependent remodeling of ABC transporter networks during acquired paclitaxel resistance and identify candidate resistance-associated vulnerabilities for functional validation.

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40 Acute Increase in Sympathetic Nerve Activity is Associated with Different Large Central Artery Stiffness Responses in Adults with and Without Hypertension

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Increased central artery stiffness is associated with higher systolic blood pressure, contributing to the development of hypertension and cardiovascular disease with aging. Acute increases in sympathetic nerve activity (SNA) in the absence of changes in blood pressure (BP) are associated with increased central artery stiffness in adults without hypertension. However, it is unknown if acute increase in SNA results in changes in large central artery stiffness in adults with hypertension. We examined whether lower body negative pressure (LBNP)-induced elevations in SNA increase aortic stiffness (carotid-femoral pulse wave velocity, cfPWV) and carotid compliance (CC) in normotensive young (N-YG, $n=15$, age=19–43 yrs), normotensive middle-aged/older (N-MA/O, $n=13$, age=46–73 yrs), and hypertensive middle-aged/older (H-MA/O, $n=26$, age=45–84 yrs) adults. As previously reported, LBNP causes significant increases in cfPWV among N-YG (+21%, $p<0.001$) and N-MA/O (+12%, $n=12$, $p=0.007$), and decreases in calculated CC among N-YG (-18%, $p<0.001$), but not in N-MA/O (+5.6%, $n=13$, $p=0.75$) suggesting lack of responsiveness of carotid arteries in MA/O. In contrast, cfPWV did not significantly change in H-MA/O (+2.9%, $n=16$, $p=0.78$) but CC decreases in H-MA/O (-11%, $n=24$, $p=0.023$) to LBNP, suggesting divergent effects with hypertension present. Although average BP did not change during LBNP, individual changes in cfPWV were correlated with changes in mean arterial pressure only in H-MA/O ($n=13$, $p=0.032$). These findings indicate acute increases in SNA differently affect aortic vs carotid stiffness among normotensive and hypertensive adults, and acute changes in aortic stiffness may be explained partially by changes in MAP in the presence of hypertension.

41 Chronic kidney disease induces a depressive-like phenotype and alters hippocampal Angpt2 and VEGF expression involved in blood-brain barrier integrity

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Chronic kidney disease (CKD) is associated with structural and functional alterations in limbic brain regions and an increased risk of anxiety and depression; however, the underlying neurobiological mechanisms remain poorly understood. This study sought to identify novel limbic biomarkers and cellular pathways that contribute to depression-like behaviors associated with CKD. Genome-wide RNA sequencing was performed on hippocampal tissue from male rats subjected to a 21-day adenine diet combined with unilateral nephrectomy, a model of severe CKD. Bioinformatic analyses, followed by quantitative PCR validation, revealed significant dysregulation of genes involved in blood-brain barrier (BBB) integrity, oxidative stress, and neuroprotection. Notably, expression of angiopoietin-2 (Angpt2), vascular endothelial growth factor (VEGF), and FMS-like tyrosine kinase 1 (FLT1/VEGFR1), key regulators of vascular homeostasis and BBB function, was significantly increased in the hippocampus of CKD animals exhibiting heightened behavioral emotionality. These findings suggest that impaired BBB

integrity may represent a critical pathophysiological mechanism linking renal dysfunction to behavioral disturbances. To assess the translational relevance of these findings, differentially expressed genes (DEGs) identified in the CKD model were compared with DEGs previously reported in postmortem hippocampal subregions (dentate gyrus and CA1) from individuals with major depressive disorder (MDD). Subsequent qPCR validation demonstrated dysregulation of overlapping genes associated with neurotrophic signaling (BDNF, MKP-1, IGF-2, galanin), BBB integrity (VEGF, FLT1, MMP9, NOTCH4), and neuroinflammation/oxidative stress (AURKB, IMMP2L). Collectively, these results indicate that CKD induces molecular alterations resembling those observed in human depression and identify potential therapeutic targets for neuropsychiatric comorbidities associated with kidney disease.

42 Lipocalin-2 (Lcn2) upregulation across limbic brain regions identifies a potential biomarker of chronic pain-induced affective disturbances

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Chronic pain is frequently accompanied by depression and other affective disorders, yet the neurobiological mechanisms linking persistent pain to negative emotional states remain poorly understood. To identify molecular substrates/biomarkers associated with vulnerability or resilience to pain-induced affective disturbances, we examined transcriptional changes within key limbic brain regions of rats exposed to chronic inflammatory pain. Behavioral assessments were used to classify pain-exposed animals as either susceptible or resilient to the development of enhanced emotionality and depressive-like behaviors. Genome-wide RNA sequencing of the prefrontal cortex (PFC), combined with bioinformatic analyses and qPCR validation, revealed significant dysregulation of genes involved in neuroinflammatory signaling, oxidative stress responses, and neuroplasticity. Notably, expression of *S100a9*, *Fmod*, and *CD74* (neuroinflammation), as well as *Fos*, *Lox*, *GSTM2*, *Nupr1*, and *MGST1* (oxidative stress) differed between susceptible and resilient phenotypes, implicating these pathways in the affective consequences of chronic pain. In parallel, analyses of limbic pain-processing circuits identified robust upregulation of lipocalin-2 (*Lcn2*), an iron-binding glycoprotein implicated in innate immune function, neuronal plasticity, and emotional regulation. Chronic pain produced consistent and robust increases in *Lcn2* mRNA expression within the hippocampus, prefrontal cortex, and anterior cingulate cortex of male rats, with similar hippocampal upregulation observed in females. Collectively, these findings highlight convergent neuroinflammatory and oxidative stress-related molecular adaptations across limbic networks and identify *Lcn2* and related immune-regulatory pathways as potential biomarkers and therapeutic targets for mood disorders that frequently accompany chronic pain.

43 Characterization of renal hemodynamics and tissue PO₂ in a pre-clinical model of PCOS

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Polycystic ovary syndrome (PCOS) is a chronic disorder often manifesting as irregular menstrual cycles, hirsutism, acne, and female-pattern alopecia. Affecting 10% of females, symptoms arise between the ages 18 and 39, although diagnosis and care are often delayed. Patients with PCOS also face higher risks for reproductive, metabolic, cardiovascular, renal, and psychological abnormalities- most notably infertility. Despite the high prevalence and broad spectrum of co-morbidities, the pathophysiology is not entirely understood, causing the treatment to be both delayed and limited to targeting the symptoms. Specifically, one of the understudied co-morbidities of PCOS is chronic kidney disease (CKD). We hypothesized that hyperandrogenism-induced hormonal dysregulation in PCOS compromises renal hemodynamics and tissue oxygenation. To evaluate this, female Sprague-Dawley rats (n=8) were subcutaneously implanted with DHEA-releasing pellets for 28 days to establish a rodent model of PCOS and compared against placebo-implanted control rats (n=8) with cycle staging via vaginal swabbing and

several parameters that measure renal function. These parameters included renal blood flow (RBF), cortical partial pressure of oxygen (cPO₂), heart rate, pulse flow, cardiac R-R interval, and renal resistive index (RRI). There were no significant differences between the groups for any of the parameters measured, suggesting renal perfusion may be resilient to the short-term DHEA model. This may also suggest that renal responses in PCOS may develop downstream of secondary changes rather than early hormonal dysregulation alone. Future investigations should evaluate whether prolonged using a DHEA model impairs renal function.

44 Beyond Mean Flow: Cardiac Cycle-Dependent Divergence in Renal Blood Flow During Hypoxic Stress

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Chronic intermittent hypoxia (CIH), a major consequence of obstructive sleep apnea, alters renal blood flow (RBF) and tissue oxygenation. However, mean RBF may not fully reflect changes in renal perfusion across the cardiac cycle. We hypothesized that systolic and diastolic RBF responses diverge during acute hypoxic stress and are altered by prior CIH conditioning. Adult female Sprague-Dawley rats were exposed to CIH (n=6; 60 s at 10% O₂ followed by 120 s at 21% O₂) or normoxic air (AIR; n=6) for 8 h/day for 14 days. Following conditioning, RBF was measured under anesthesia using a transit-time flow probe at baseline and during acute intermittent asphyxia (IA; 10 cycles of 30 s at 10% O₂ + 3% CO₂ followed by 60 s at 21% O₂). RBF waveforms were analyzed to quantify mean, systolic, and diastolic flow, pulse amplitude, and renal resistive index (RRI). In AIR animals, IA increased systolic flow while decreasing diastolic flow, widening the RBF pulse. These responses were significantly attenuated in CIH animals (p<0.05). RRI was also significantly lower in CIH compared with AIR animals (p<0.05), despite no difference in mean RBF between groups (p>0.05). These findings indicate that CIH alters the pulsatile organization of renal perfusion during hypoxic stress and that systolic and diastolic flow analysis can reveal changes in renal vascular regulation not apparent from mean RBF alone.

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