2015 APS Conference
Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender

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Harvard Univ.

Heddwen Brooks
Univ. of Arizona, Tucson

Kate M. Denton
Monash Univ., Australia

Rolando J. Ramirez
Univ. of Akron

Vera Regitz-Zagrosek
Charite Univ., Germany

Javier Salazar
Univ. of Murcia, Spain

Willis K. Samson
St. Louis Univ. Sch. Med.

Kathryn Sandberg
Georgetown Univ.

James R. Sowers
Univ. of Missouri Sch. Med.

Jennifer Sullivan
Georgia Regents Univ.

You-Lin Tain
Chang Gung Memorial Hosp., Taiwan

Rita Tostes
Univ. of São Paulo, Brazil

Acknowledgements

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

American Heart Association Council
Council on Hypertension
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<tr>
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<td>7:00 AM Registration</td>
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<tr>
<td>7:50—8:00 AM Welcome</td>
<td>8:00—10:00 AM Symposia V</td>
<td>8:00—10:00 AM Symposia VIII</td>
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<tr>
<td>S. Ananth Karumanchi</td>
<td>Developmental Programming of Cardiovascular, Renal and Metabolic Diseases: Roles of Gender/Sex</td>
<td>Pregnancy and Pre-eclampsia</td>
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<tr>
<td>8:00—10:00 AM Symposia I</td>
<td>Javier Salazar</td>
<td>Christine Marie-Bilkan</td>
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<td>Immune System and Regenerative Medicine—Impact of Gender/Sex</td>
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<td>Heddwen Brooks</td>
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<tr>
<td>10:00—10:30 AM Break</td>
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<tr>
<td>10:30 AM—12:30 PM Symposia II</td>
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<td>Non-reproductive Actions of Sex Hormones/Receptors—A</td>
<td>Non-reproductive Effects of Sex Hormones/Receptors—B</td>
<td>Population Studies—Gender/Sex in CVD, Renal Disease, and Metabolic Syndrome</td>
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<td>Rolando J. Ramirez</td>
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<tr>
<td>12:30—1:30 PM Lunch</td>
<td>12:30—1:30 PM Lunch</td>
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<td>11:35—11:45 AM Closing Remarks</td>
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<tr>
<td>1:30—2:30 PM Poster Session I</td>
<td>1:30—2:30 PM Poster Session II</td>
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<td>2:30—3:50 PM Symposia III</td>
<td>2:30—3:00 PM Plenary Lecture</td>
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<tr>
<td>Neuro Control of Cardiovascular, Renal and Metabolic Diseases: Impact of Gender/Sex</td>
<td>Kathryn Sandberg (Chair)</td>
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<td>Willis K. Samson</td>
<td>Janine Clayton (Speaker)</td>
<td>3:00—5:00 PM Symposia VII</td>
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<tr>
<td>3:55—4:30 Distinguished Investigator Award</td>
<td>Obesity, Metabolic Syndrome, Gender/Sex</td>
<td>James R. Sowers</td>
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<tr>
<td>Jennifer Sullivan, Chair</td>
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<tr>
<td>Chris Baylis, Speaker</td>
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<tr>
<td>6:30—8:30 PM Welcome and Opening Reception</td>
<td>5:00—6:00 PM Career Development Session</td>
<td>7:00—9:30 PM Banquet and Awards Ceremony</td>
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<tr>
<td>Jennifer Sasser</td>
<td>Erica Wehrwein</td>
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Location:
The 2015 APS Conference: Cardiovascular, Renal and Metabolic Diseases will be held November 17—20, 2015 at the Crowne Plaza Annapolis Hotel, 173 Jennifer Rd., Annapolis, MD 21401, USA, telephone (410) 266-3131, FAX: (410) 266-6247.

Onsite Registration Hours:
Tuesday, November 17………………3:00—8:00 PM
Wednesday, November 18………..7:00 AM—5:30 PM
Thursday, November 19…………..7:30 AM—5:30 PM
Friday, November 20………………7:30 —11:00 AM

On-Site Registration Fees:
APS Member……………………………………$650
APS Retired Member.................................$450
Nonmember ................................................................$800
Postdoctoral..............................................$500
Student................................................................$450

*Must have a ticket for entry.

Program Objective:
The role that sex steroids and gender play in the physiology and pathophysiology of cardiovascular and renal disease (CVRD) is becoming an increasingly more important area of research. The program will be balanced to include both basic science and clinical studies, ranging from the gene to the whole animal or human. The global aspect of the conference is to gather a critical mass of scientists with interests and expertise in the role of sex steroids and/or the gender differences in the physiology of CVRD, and to promote an exchange of ideas to foster collaboration that will further advance this important line of scientific investigation. In addition, this conference will be to increase the awareness of sex disparities in CVRD that need to be understood in order to ultimately improve clinical outcomes for men and women and promote individualized health care.

Target Audience:
The intended audience for this conference includes all levels of researchers working in the field of gender disparities in cardiovascular, renal and metabolic diseases. This conference will provide a diverse program that covers many of the organ systems in which sex steroids and gender have been shown to be important in cardiovascular diseases.

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

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

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

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

Photography is not permitted during the scientific sessions or in the poster room.

Don’t forget to join us at the Welcome and Opening Reception
Admiral’s Ballroom
Tuesday, November 17
6:30—8:30 PM
WEDNESDAY, NOVEMBER 18, 2015

Welcome 1.0

WELCOME ANNOUNCEMENT
Wednes., 7:50—8:00 AM, Wye Room.

Chairs:
Jane F. Reckelhoff, Univ. of Mississippi Med. Cir.

Symposia I 2.0

IMMUNE SYSTEM AND REGENERATIVE MEDICINE-IMPACT OF GENDER AND SEX
Wednes., 8:00—10:00 AM, Wye Room.

Chair:
Heddwyn Brooks, Univ. of Arizona, Tucson.

8:00 AM 2.1 Estrogen Receptor Alpha Enhances Loss of Tolerance to Nuclear Antigens and Immune Cell Activation Induced by the SLE Lupus Susceptibility Allele and is Responsible for the Sex Bias Associated with SLE. Karen Gould. Univ. of Nebraska, Omaha.

8:20 AM 2.2 Role of T Cells in Development of Cardiovascular Disease and Hypertension. Jennifer Sullivan, Georgia Regents Univ.


9:00 AM 2.4 Lower Levels of Interleukin-6 in Female Mice at Days 1 and 3 Post-myocardial Infarction Attenuate Neutrophil Infiltration, Rupture, and Left Ventricular Dilation. Kristine De Leon-Pennell. Univ. of Mississippi Med. Cir., Jackson. (5.11).

9:15 AM 2.5 The Effects of Testosterone and Oxidative Stress on Neuroinflammatory Signaling in Dopamine Neurons. Shaletha Holmes. Univ. of North Texas Hlth. Sci. Cir., Forth Worth. (14.6).


9:45 AM 2.7 Doxorubicin Reduces Proinflammatory Mediator Expression in Brain and Pial Arteries from Ovariectomized Female Rats. Rayna Gonzales. Univ. of Arizona, Phoenix. (14.7).

Symposia II 3.0

NON-REPRODUCTIVE ACTIONS OF SEX HORMONES AND RECEPTORS-A
Wednes., 10:30 AM—12:30 PM, Wye Room.

Chair:
Rolando J. Ramirez. Univ. of Akron.


10:50 AM 3.2 Differential Body Weight and Blood Pressure Responses to Normal Versus High-fat Diet in Melanocortin-4 Receptor-deficient Pregnant Rats. Frank Spradley. Univ. of Mississippi Med. Cir.

11:10 AM 3.3 GPER and Vascular Function. Sarah Lindsey. Tulane Univ.

11:30 AM 3.4 Contribution of the Nuclear Progesterone Receptor (nPR) to Breathing Stability and Hypocapnic Ventilatory Response in Adult Male Mice. Sofien Laouafa. Univ. of Laval, Quebec, Canada. (13.7).

11:45 AM 3.5 Functional and Structural Changes in Internal Pedal Arteries Underlie Erectile Dysfunction Induced by Androgen Deprivation. Rheu Lopes. Univ. of São Paulo, Brazil. (4.8).

12:00 Noon 3.6 6p-Hydroxysterosterone, A Cytochrome P450 1B1-Derived Metabolite of Testosterone Plays an Important Role in Renal Dysfunction Associated with Angiotensin II-Induced Hypertension in Male Mice. Ajeeh Pingili. Univ. of Tennessee Hlth. Sci. Cir., Memphis. (7.13).


Poster Session I 4.0

CARDIOVASCULAR DISEASE
Wednes., 1:30—2:30 PM, Rhode/Severn Room.

Poster Board 1

1. 4.1 Matrix Metalloproteinase-9 is Critical for 2-Methoxyestradiol Mediated Angiotensin Type 1 Receptor Down-Regulation. B. Ogola, Y. Zang, and T. Thekkumkara Texas Tech Univ. Hlth. Sci. Cir. Sch. of Pharmacy, Amarillo, TX.


5. 4.5 A Study of the Potential Risk Factors of Cardiovascular Diseases in Young Saudi females. L. Al-Asoom. Univ. of Dammam, Saudi Arabia.

6. 4.6 Assessment of Gender and Age-dependent Patterns of Cardiovascular Remodeling in Spontaneously Hypertensive Rats (SHR). S. Ruginsk, J. Antunes, L. Ramalho, F. Carneiro, and R. Tostes. Univ. of São Paulo, Ribeirao Prto, Brazil.

7. 4.7 Indices of Cardiovascular Function Derived from Peripheral Pulse Wave Analysis Using Radial Applanation Tonometry in HIV Positive Patients from Mthatha District of South Africa. K. Awodetu, R. Erasmus, A. Awodetu, and A. Namugowa. Walter Sisulu Univ., Mthatha, South Africa; Univ. of Stellenbosch, Cape Town, South Africa.

8. 4.8 Functional and Structural Changes in Internal Pedal Arteries Underlie Erectile Dysfunction Induced by Androgen Deprivation. R. Lopes, K. Neves, M. Barbosa, V. Oliva, S. Ruginski, J. Antunes, L. Ramalho, F. Carneiro, and R. Tostes. Univ. of São Paulo, Ribeirao Prto, Brazil.

Photography is not permitted during the scientific sessions or in the poster session room.


DAILY SCHEDULE

POSTER SESSION II

5.0 CARDIAC

Wednes., 1:30—2:30 PM, Rhode/Severn Room.

Poster Board


5.2 Haemostatic and Rheologic Factorials as Determinants of Acute Myocardial Infections in Nigerians. E. Nwall, and O. Ajayi. Univ. of Benin, Benin City, Nigeria.


5.4 Indices of Cardiac Sympathetic Activity During Lower Body Negative Pressure in Men and Women Throughout the Menstrual Cycle. H. Edgell, and R. Hughson. York Univ., Toronto, Canada, and Univ. of Waterloo, Canada.


5.6 Angiotensin II Modulates Sex Steroid Metabolizing Enzyme and Receptor Expression in Cardiac Fibroblasts From Male and Female Rats. L. Madhavpeddi, R. Gonzales, and T. Hale. Univ. of Arizona, Phoenix.

5.7 Cardiac Remodeling in Female Hearts by Kv11.2 Subunit. J. Tur, K. Chapalamadugu, T. Padawer, and S. Tipparaju. Univ. of South Florida.


6.0 METABOLISM AND DIABETES

Wednes., 1:30—2:30 PM, Rhode/Severn Room.

Poster Board


6.3 Withdrawn.


6.8 High Fructose Intake Exacerbates the Impairment of Mesenteric Arterial Function Compared to Glucose in Female Rats: Possible Involvement of EDRF Contribution in Modulating Vascular Reactivity. S. Shaligram, G. Sangiésa, F. Akther, M. Alegret, J. C. Laguna, and R. Rahimian. Univ. of the Pacific, and Univ. of Barcelona, Spain.


6.10 Alterations in Fatty Acid Signaling Pathways Differentially Affect Fat Intake in Male and Female Mice. T. Gilbertson, M. Pillmore, N. Dahir, and D. Minaya. Utah State Univ., and Conn. of Florida, Gainesville.

Poster presenters…don’t forget that your poster is displayed only on the day you present.

Please remove your poster at the end of your presentation day. Unclaimed posters will be removed and stored by APS until the conclusion of the conference. Any unclaimed posters will be recycled.
**Poster Session IV**

**Renal**

**Poster Board 32**

6.11 Withdrawn.


6.13 Do Women Need to Lose More Weight than Men to Increase circulating Adiponectin? X. Wang, Univ. of South Carolina, Columbia.


6.15 Increasing Leptin Sensitivity with Protein Tyrosine Phosphatase 1B Deletion Leads to More Severe Cardiac Alterations in Female than Male Mice. A-C. Huby, and E. J. Belin de Chanteseme. Georgia Regents Univ.

6.16 Sex Differences in Renal Sodium Handling in Mice on High-fructose and High-salt Diet. A. Roug, L. Fan, B. Swar, and C. Waterruoacha. Oklahoma State Univ., Tulsa.


7.0 RENAL

Wednes., 1:30—2:30 PM, Rhode/Severn Room.

**Poster Board 47**

7.5 Withdrawn.


7.7 Progestosterone Synergizes Estradiol-Induced Natriuresis in Response to Increased Dietary Sodium Intake. E. Koh and D. M. Pollock. Univ. of Alabama at Birmingham.

7.8 Withdrawn.

7.9 High Salt Alters Cellular Transcriptional Milieu And Human Angiotensinogen Expression in a Gender-Dependent Manner: An Effect Exacerbated by a Risk Haplo-type. M. Kav, N. Puri, and A. Kumar. Univ. of Toledo Hlth. Sci.


7.12 Multiple Estrogen Receptor Subtypes Selectively Influence Fluid Intake in Female Rats. J. Santollo, and D. Daniels. Univ. at Buffalo.


8.0 Neuro Control of Cardiovascular, Renal and Metabolic Diseases: Impact of Gender and Sex

Wednes., 2:30—3:30 PM, Wye Room.

Chair: Willis K. Samson, St Louis Univ.

8.1 Autonomic Regulation of Blood Pressure in Adult Humans: Effects of Sex and Age. Michael Joyner, Mayo Clinic, Rochester, MN.

8.2 Sex Differences in Desensitization of the Dipsogenic Effect of Angiotensin II. Derek Daniels. Univ. of Buffalo, SUNY.


8.4 Characterizing the Gender Differences of Multidrug-resistance Peptide (MRP) Transporter Expression in Mouse Blood-brain Interfaces. Katrina Flores. Univ. of Connecticut (143).

**Join us for the Opening Reception on Tuesday, November 17, 2015 from 6:30—8:30 PM**
### Daily Schedule

#### Plenary Lecture

**DISTINGUISHED INVESTIGATOR AWARD**

**Chair:** Jennifer Sullivan, Georgia Regents Univ.

**Time:** 3:55 PM

**Details:** The Enigma of the Maternal Plasma Volume Expansion During Normal Pregnancy. *Chris Baylis, Univ. of Florida, Gainesville.*

#### Career Session

**CAREER DEVELOPMENT SESSION**

**Chair:** Jennifer Sasser, Univ. of Mississippi Med. Ctr., Jackson.

**Time:** 8:00 AM

**Details:** Unraveling the Complexity of Reproductive Hormones and Metabolic Disease. *Erica Wehrwein, Michigan State Univ.*

#### Thursday, November 19, 2015

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<th>Symposia V</th>
<th><strong>DEVELOPMENTAL PROGRAMMING OF CARDIOVASCULAR, RENAL AND METABOLIC DISEASES: ROLES OF GENDER AND SEX</strong></th>
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<tr>
<td><strong>Chair:</strong></td>
<td>Javier Salazar, Univ. of Murcia, Spain.</td>
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<tr>
<td><strong>Time:</strong> 8:00 AM</td>
<td>11.1 Effect of Estrogen in Gender-dependent Fetal Programming of Adult Cardiovascular Dysfunction. <em>Duliao Xiao, Loma Linda Univ. Sch. of Med.</em></td>
</tr>
<tr>
<td>8:20 AM</td>
<td>11.2 Sex Differences in Cardiovascular and Metabolic Risks Due to Early Life Stress. <em>Analia Loria, Univ. of Kentucky, Lexington.</em></td>
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<tr>
<td>8:40 AM</td>
<td>11.3 Maternal Undernutrition Significantly Impacts Ovarian Follicle Number and Increases Ovarian Oxidative Stress in Adult Rat Offspring. <em>Deborah Slaboda, McMaster Univ., Hamilton, Canada.</em></td>
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<tr>
<td>9:00 AM</td>
<td>11.4 Reduced Sleep Time During Pregnancy-Effects on Renal Morphology and Function of Female Offspring. <em>Guimar M. Gomes, Univ. of São Paulo, Brazil.</em></td>
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<tr>
<td>9:15 AM</td>
<td>11.5 Delayed Effects of Perinatal Hypoxia on Adult Rats Pulmonary Vessels Structure and Reactivity. <em>Martin Vizek, Charles Univ., Prague, Czech Rep.</em></td>
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<td>9:30 AM</td>
<td>11.6 Sex Difference in Sensitization of Angiotensin I (Ang I)-elicited Hypertension in Female Hypertensive Pregnant Rats. <em>Baojian Xue, Univ. of Iowa.</em></td>
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<td>9:45 AM</td>
<td>11.7 Sex Differences in Cardiovascular Responses to Stress in Adult Rats Prenatally Exposed to Desamethasone. <em>Taben Hale, Univ. of Arizona, Phoenix.</em></td>
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#### Symposia VI

**NON-REPRODUCTIVE EFFECTS OF SEX HORMONES AND RECEPTORS-B**

**Chair:** Kate M. Denton, Monash Univ., Melbourne, Australia.

**Time:** 10:30 AM

**Details:** 12.1 Androgen Effects on Endothelial Function in Women with Polycystic Ovary Syndrome. *Nina Stachenfeld, Yale Univ.*

**Time:** 10:50 AM

**Details:** 12.2 Mechanisms Involved in Cardioprotection in Females: Role of Estrogen and Estrogen Receptors (ERs). *Elizabeth Murphy, NIH, NHLBI.*

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<tr>
<td>10:10 AM</td>
<td>12.3 Sex and Sex Hormone Effects in Cardiovascular Pathophysiology. <em>Vera Regitz-Zagrosek, Charite Univ., Berlin, Germany.</em></td>
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<td>11:30 AM</td>
<td>12.4 Effects of Aerobic Exercise Training on Renin-angiotensin System Components in Hypertensive Women. <em>Aline Jarrete, Campinas State Univ., Brazil.</em></td>
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<tr>
<td>11:45 AM</td>
<td>12.5 Gender and Circulating Vascular MicroRNAs in Middle-Aged Adults. <em>Jamie Hjimans, Univ. of Colorado, Boulder.</em></td>
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<td>12:15 PM</td>
<td>12.7 Effects of Menopause and Acute Exercise on Brachial Artery Flow Mediated Dilatation and Plasma Endothelial Microparticles. <em>Corinna Serviente, Univ. of Massachusetts, Amherst.</em></td>
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#### Poster Session II

**RESPIRATORY**

**Chair:** Thurs., 1:30—2:30 PM, Rhode/Severn Room.

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<td>13.3 Estrogen Prevents Cardiopulmonary Dysfunctions Induced by Chronic Intermittent Hypoxia in Females. <em>S. Laouafa, F. Marcouiller, D. Roussel, A. Bairam, and V. Joseph, Univ. of Laval, Quebec, Canada, and Univ. Claude Bernard Lyon, Villeurbanne, France.</em></td>
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<td>4</td>
<td>13.5 Muscular and Cardiorespiratory Adaptations to Treadmill Training with Aging are Blunted in Female Compared to Male Mice. <em>K. Huey, T. Drake, G. Dillon, and C. Lee, Drake Univ., Des Moines, IA.</em></td>
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<td>6</td>
<td>13.7 Contribution of the Nuclear Progesterone Receptor (nPR) to Breathing Stability and Hypercapnic Ventilatory Response in Adult Male Mice. <em>S. Laouafa, F. Marcouiller, and V. Joseph, Univ. of Laval, Quebec, Canada.</em></td>
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<td>8</td>
<td>14.1 The Important Role of Nitric Oxide Synthase in Controlling Mitochondrial Respiration of Large Cerebral Arteries in Female and Male Rats. <em>J. Rutkai, S. Dutta, P. Katakam, and D. Busija, Tulane Univ.</em></td>
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Poster Board

14.2 Sex Differences in the Cerebral Vascular Function and R. Channel Role. M. Papaditi, Univ. of Mississippi Med. Ctr., Jackson.

14.3 Characterizing the Gender Differences of Multidrug-resistance Peptide (MRP) Transporter Expression in Mouse Blood-brain Interfaces. K. Flores, J. L. Renfro, and J. Munautt. Univ. of Connecticut.

14.4 Sex and Genotype Differences to Epinephrine Infusions in Humans. A. Eugene, and M. Joyner. Mayo Clinic, Rochester, MN.

14.5 Sex Differences in the Effect of Hypoglycemia on Baroreflex Sensitivity in Patients with Type 1 Diabetes Mellitus. J. Linberg, S. Dube, M. Mozer, A. Basu, R. Basu, and M. Joyner. Mayo Clinic; Rochester, MN.

14.6 The Effects of Testosterone and Oxidative Stress on Neuroinflammatory Signaling in Ovarian Cancer. S. Holmes, and R. Cunningham. Univ. of North Texas Health Science Center, Forth Worth.


Poster Session II

15.0 PREGNANCY

Thurs., 1:30—2:30 PM, Rhode/Severn Room.


15.2 Vitamin D Supplementation Inhibits Blood Pressure and Uterine Artery Resistance Induced by Autoantibodies to the AT1 Receptor. J. Faulkner, L. Amaral, D. Cornelius, T. Ibrahim, M. Cunningham, Jr., D. Thomas, G. Wallukat, R. Dechend, and B. LaMarca. Univ. of Mississippi Med. Ctr., Jackson, and HELIOS Clinic, Berlin, Germany.


Poster Board

15.7 Agonistic Autoantibodies to the Angiotensin II Type 1 Receptor Enhances ANG II Induced Renal Vascular Sensitivity and Reduces Renal Function During Pregnancy. M. Cunningham, Jr., J. Williams, G. Wallukat, R. Dechend, and B. LaMarca. Univ. of Mississippi Med. Ctr., Jackson, and HELIOS Clinic, Berlin, Germany.


15.10 Up-regulation of VEGFR2 Improves Uterine Artery Myogenic Response and Maternal Hypertension Altered by Uterine Perfusion Pressure Reductions. B. Baler, R. Ramirez, D. Crowder, J. Reho, Y. Yun, and J. Novak. Univ. of Akron, Univ. of Iowa, Iowa City, IA, and Walsh Univ., North Canton, OH.


Poster Session II

16.0 DEVELOPMENTAL PROGRAMMING

Thurs., 1:30—2:30 PM Rhode/Severn Room.


16.3 Sex Differences in High Fat Diet-induced Adipocyte Morphology and Fat Distribution Due to Early Life Stress. M. Murphy, L. Schmuckie, D. Powell, and A. Loria. Univ. of Kentucky, Lexington.

16.4 Sphingosine-1-phosphate Receptor Type 3 Plays a Role in the Etiology of High Blood Pressure Programmed by Maternal Undernutrition in Rats. S. Intapad, Univ. of Mississippi Med. Ctr., Jackson.

16.5 Reduced Sleep Time During Pregnancy-Effects on Renal Morphology and Function of Female Offspring. G. N. Gomes, R. Argeri, and S. Tufik. Univ. of São Paulo, Brazil.
## DAILY SCHEDULE

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<td></td>
<td>16.7 Sex Difference in Sensitization of Angiotensin (ANG) II-elicited Hypertension in Offspring of Hypertensive Pregnant Rats. B. Xue, F. Gao, T. Betz, R. Thumborn, and A. Johnson. Univ. of Iowa, Iowa City, IA.</td>
</tr>
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<td>16.8 Sex Differences in Cardiovascular Responses to Stress in Adult Rats Perinatally Exposed to Desmethasone. T. Hale, D. Carbone, L. Madhavpeddi, M. Thompson, and R. Handa. Univ. of Arizona, Phoenix.</td>
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<td></td>
<td>18.1 Studying Both Sexes: A New Frontier for Discovery. Janine Clayton. NIH, Office of Res. in Women's Hlth., Bethesda, MD.</td>
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<th>Symposia VII</th>
<th>19.0 OBESITY, METABOLIC SYNDROME, GENDER AND SEX</th>
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| 19.3 | The Role of Estrogens and Androgen in Control of Glucose Homeostasis. Franck Mauvais-Jarvis. Tulane Univ. |

| 19.4 | Sex Dimorphism In Plasma Soluble Prorenin Receptor (sPrr) Levels In Obese Patients is Associated With Type 2 Diabetes Mellitus in Women But Not in Men. Carla B. Rosales. Tulane Univ. (6.18). |


### Thank You to the Generous Sponsors of this Conference

**Univ. of Mississippi Med. Ctr., Women’s Hlth. Res. Ctr.**

**American Heart Assn. Council**

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## FRIDAY, NOVEMBER 20, 2015

### Symposia VIII

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<td>PREGNANCY AND PRE-ECLAMPSIA</td>
<td>Christine Marie, NIH, NHLBI</td>
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<td>Spontaneous Superimposed Preeclampsia in Dahl Salt Sensitive Rats</td>
<td>Jennifer Sasser, Univ. of Mississippi Med. Ctr, Jackson</td>
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<td>Vasopressin: A New Beginning for the End of Preeclampsia?</td>
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<td>Brittany Balser, Univ. of Akron</td>
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**NOTES**

Join us at the Closing Banquet and Award Presentation

**Thursday, November 19, 2015**

7:00—9:30 PM

Get your complimentary ticket at the registration desk
# 2015 APS Conference
## Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender

### Abstracts of Invited and Contributed Presentations

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### Author Index

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Lupus is an autoimmune disease characterized by the development of anti-nuclear autoantibodies and immune complex-mediated nephritis. Approximately 90% of lupus patients are women, and this sex bias is thought to be driven largely by estrogens. Previously, we showed that estrogens promote lupus via estrogen receptor α (ERα). The SLE1 lupus susceptibility allele promotes the development of anti-nuclear autoantibodies and immune cell activation. The phenotype associated with SLE1 is more robust in females than males, suggesting that estrogens, acting via ERα, may enhance the effect of SLE1. To test this hypothesis, we examined the impact of a targeted disruption of ERα on the development of anti-nuclear autoantibodies and immune cell activation in female B6.Sle1 congenic mice. ERα deficiency attenuated the development of autoantibodies in B6.Sle1 congenic females but not males. ERα deficiency decreased SLE1-induced immune cell activation in females, and to a lesser extent, in males. Altogether, these data demonstrate that the sex bias in SLE1-induced loss of tolerance to nuclear antigens and immune cell activation is ERα-dependent. Support: NIH R01 AI075167 References: Youachim S.D., Hussell T., Bynoe T.K., K. Goka K.A., Estrogen receptor alpha signaling promotes SLE1-induced loss of tolerance and immune cell activation and is responsible for sex bias in B6.Sle1 congenic mice. Clin Immunol. 2015, 158(2):153-66.

Hypertension is now considered a state of low-grade inflammation. While T cells have broadly been implicated in blood pressure control, the most is known regarding the role of Th17 cells and regulatory cells (Tregs). Th17 cells mediate pro-inflammatory responses through the secretion of the pro-inflammatory cytokine, IL-17, and a role for Th17 cells in hypertension has been indirectly surmised based on studies manipulating IL-17 levels. In contrast, Tregs are crucial in maintaining immunologic self-tolerance and protection from auto-immune disease as well as regulating immune responses to pathogens by impacting effector T cell function. Adoptive transfer studies have conclusively linked Tregs with decreases in blood pressure and improved cardiovascular outcomes. Despite an ever expanding literature base supporting a causal role of T cells to hypertension and related end-organ damage in both the basic sciences and clinically, the majority of this literature has been performed exclusively in males despite the fact that both men and women develop hypertension. Recent studies by our group and others, have highlighted important sex differences in the immune profile and blood pressure responses to T cells. These results highlight the need to better understand the influence of sex on the immune system and delineate the potential complexity of immune system regulation of blood pressure and cardiovascular function. More work is needed to define the physiological impact of sex differences in immune system components, but also how each of these components may impact overall cardiovascular health. References: McMaster, W.G., Kinabo A., Madhar M. S., Harrison, D. G., Inflammation, immunity, and hypertensive end-organ damage. Circ. Res. 2015 Mar 13;116(6):1022-33; Tipton AJ and Sullivan JC. Sex and gender differences in T cells in hypertension. Clinical Therapeutics, 36(12):1882-1900, 2014.

Estrogen is a major regulator of adipogenesis and lipid synthesis in the liver and other tissues. Estrogen receptors are required for suppression of the genes that are important for the bone-marrow derived pluripotent stem cell to differentiate into the adipocyte lineage. This is also true for preventing adipocyte hypertrophy and proliferation. In contrast, lipid synthesis by the mature adipocyte is inhibited by estrogen only through engaging the membrane ERα. Experimental animal models may be useful to understand the complex role that estrogens have in this disease.
3.3 GPER AND VASCULAR FUNCTION

Sarah Lindsey¹

¹Pharmacology, Tulane Univ., 1430 Tulane Ave., Mailbox 8683, New Orleans, LA, 70112.


4.0 CARDIOVASCULAR DISEASE

4.1 MATRIX METALLOPROTEINASE-9 IS CRITICAL FOR 2-METHOXYESTRADIOL MEDIATED ANGIOTENSI N TYPE 1 RECEPTOR DOWN-REGULATION

Benard Otedola¹, Yonge Zang¹, and Thomas Thiedikram¹

¹Dept. of Biomedical Sci., Texas Tech. Univ. Hlth. Sci. Ctr. Sch. of Pharmacy, 1300 S. Coulter, Amarillo, TX, 79106.

Recently, studies have demonstrated that one of the final end products of estrogen metabolism, 2-methoxyestradiol (2ME2) has the therapeutic potential in a number of cardiovascular disorders, including hypertension. However, the exact mechanism(s) remains unknown. Inhibiting angiotensin type 1 receptor (AT1R) has been shown to be critical for controlling hypertension and associated disorders. Ongoing studies in our laboratory show that epithelial and smooth muscle cells exposed to 2ME2 down-regulates AT1R protein and mRNA in a concentration and time dependent manner. In this study, continuously passed epithelial cells expressing native AT1R were exposed to 2ME2, and angiotensin II radio ligand binding and signaling pathways were assessed. In the presence of 2ME2, cells exhibited significant phosphorylation and nuclear translocation of ERK1/2 and down-regulation of AT1R. Using GM6001, a broad-raised matrix metalloproteinasises (MMPs) inhibitor, and AG1478, an epidermal growth factor receptor (EGFR) selective inhibitor, we determined that 2ME2 mediated phosphorylation of ERK1/2 is dependent on activation of MMPs and transactivation of EGFR receptors. Furthermore, immunohistostaining, a matrix metalloproteinase-9 (MMP9) specific inhibitor attenuated 2ME2 induced phosphorylation of EGFR and ERK1/2 and reversed AT1R down-regulation. Under similar conditions, stimulation of G-protein coupled estrogen receptor (GPER) with the selective agonist 16-ethyl estradiol stimulated the signaling pathway and down-regulated the AT1R expression. Moreover, immunoprecipitation studies show that 2ME2 and G1 phosphorylate EGFR at tyrosine 1173, which is a critical residue on EGFR to interact with Src homology domain-containing tyrosine phosphatase 1 (SHP1), which controls the level of EGFR phosphorylation. Collectively, our study demonstrates for the first time that 2ME2 mediated activation of MMP9 results in EGFR phosphorylation at tyrosine 1173 leading to ERK1/2 activation; a signaling pathway essential for AT1R down-regulation. Furthermore, our study results suggest a potential mechanism for the observed effects of estrogen against cardiovascular disorders in premenopausal women.

4.2 UNDERREPRESENTATION OF SEX IN REPORTING TRADITIONAL AND EMERGING BIOMARKERS FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE: A SYSTEMATIC REVIEW

Aisha Gohar¹, Renate Schrappe¹, Martin Hughes¹, Tanja Zeller¹, Stefan Blankenburg², Gerard Pasternak², and Hester den Ruijter²


In the Athero-Express biobank study, we dissected atherosclerotic plaques and measured the level of sex-specific biomarkers in blood from 308 men and 157 women. We found that the level of atherosclerotic plaque in male and female patients was not significantly different. To determine whether there is sex-specific atherosclerotic plaque phenotypes, we tested LOY for association with measures of cardiovascular disease (CVD) phenotype, atherosclerotic plaque area, and inflammation. We found that LOY was associated with CVD phenotype and inflammation. In a cohort of 368 men, we found that LOY was associated with CVD phenotype, and inflammation. In our study, we found that LOY was associated with CVD phenotype and inflammation. In conclusion, our study suggests that LOY is associated with CVD phenotype and inflammation. In a cohort of 368 men, we found that LOY was associated with CVD phenotype and inflammation. In our study, we found that LOY was associated with CVD phenotype and inflammation. In conclusion, our study suggests that LOY is associated with CVD phenotype and inflammation. In a cohort of 368 men, we found that LOY was associated with CVD phenotype and inflammation. In our study, we found that LOY was associated with CVD phenotype and inflammation. In conclusion, our study suggests that LOY is associated with CVD phenotype and inflammation.
Our data support that LOY is associated with an increased risk for the occurrence of secondary cardiovascular events. However, we did not observe an association with inflammatory plaque characteristics that could explain this result, suggesting that LOY affects secondary outcome by alternate mechanisms. **Funding:** Saskia Hafitjema is supported by the FP7 EU project CVgenes@target (HEALTH-F2-2013-601456).

### 4.4 CIRCULATING GDF-15 LEVELS ARE EXPLICITLY VALUABLE FOR THE PREDICTION FOR FUTURE CARDIOVASCULAR COMPLICATIONS IN WOMEN

Aisha Gohar1, Joyce Vrijenhoek1, Gerrard Pasterkamp1, Hester den Ruiter1, and Saskia de Jager1.


**Background:** Cardiovascular disease (CVD) remains a major contributor to global morbidity and mortality. The underlying mechanisms for CVD and clinical presentations of diseases have been found to differ between men and women. Growth differentiation factor (GDF) 15 is a member of the transforming growth factor (TGF-β) family, which operates in acute phase responses. Elevated GDF-15 serum levels are established risk factors for several cardiovascular diseases ranging from early chest pain to acute coronary syndromes and heart failure. In this study we aimed to evaluate the predictive value of GDF-15 as a biomarker for secondary cardiovascular events in men and women undergoing carotid endarterectomy.

**Methods:** Circulating GDF-15 levels were determined using ELISA in a subset of 200 patients from the Express Biobank. Multiple linear regression models were used to investigate the associations between GDF-15 and clinical risk factors. Multivariable Cox regression models were performed to analyze secondary events.

**Results:** The Median GDF-15 level was 104206 ng/L (51803, 182296) for the entire cohort, which is higher than previously observed levels in CVD. We did not discern a difference in baseline GDF-15 levels between men and women (Men: 106375 [51182, 182596] vs. Women: 94042 [5204, 17372]), p value for difference 0.241. However, GDF-15 levels were associated with increasing age, reducing renal function, and a history of diabetes. In women, only increasing age was found to be associated with GDF-15 levels. Interestingly, we show that a high level of circulating GDF-15 is a strong predictor for secondary cardiovascular events specifically in women (composite events: Quantile 4: HR 2.69 95% CI 1.25-5.81 p=0.01 in women vs. HR 0.96 95% CI 0.66-1.40 p=0.82 in men) and more precisely for peripheral events (Quantile 4: HR 3.41 95% CI 1.10-10.79, p=0.03 in women vs. HR 0.68 95% CI 0.40-1.17 p=0.17 in men).

**Conclusions:** High circulating GDF-15 is predictive of secondary outcome in women but not men, suggesting a potential role for GDF-15 as a biomarker for secondary prevention in women. In addition, this again illustrates the differences in atherosclerotic disease mechanisms in women, where the role of GDF-15 clearly deserves further interest. **Funding:** AG is supported by EUTRAIN. This project has received funding under the Marie Curie grant agreement No 289903.

### 4.5 A STUDY OF THE POTENTIAL RISK FACTORS OF CARDIOVASCULAR DISEASES IN YOUNG SAUDI FEMALES

Lubna Al-Assom1

1Physiology, Univ. of Dammam, King Saud, Dammam, Saudi Arabia.

**Background:** Multiple risk factors have been blamed to precipitate wide range of cardiovascular diseases such as hypertension, ischemic heart diseases, stroke, and heart failure. These risk factors might differ between selected age, sex and ethnic groups. **Aim and objectives:** In the current study, we aim to find out indicators of cardiovascular risk in young Saudi females by studying the correlation of three main risk factors i.e. body adiposity, physical fitness, and plasma level of 25-OH-vitamin D and haemodynamic parameters.

**Subject and methods:** Convenient sample of 88 young Saudi females was recruited from University of Dammam, Dammam, Saudi Arabia in the period from November 2014-April 2015. All participants were healthy with no history of pregnancy or lactation in the last two years, no current or past smoking, no medical history of hypertension or diabetes, no chronic disease, no medication use, no exercise for stress test, no endocrine diseases and no vitamin D supplementation in the last two years. Normal subjects were divided into two groups based on age, men and women. Independent upregulation of ACE2 and AT2 receptor expression was found in female as compared to male SHR. This study shows that the SHR model is a valuable tool to understand gender-specific age-dependent changes of the cardiovascular system. As gender related differences are overt, the model may be well suited to improve our understanding of causal mechanisms. This project was financed by the Else Kröner-Fresenius Foundation.

### 4.7 INDICES OF CARDIOVASCULAR FUNCTION DERIVED FROM PERIPHERAL PULSE WAVE ANALYSIS USING RADIAL APPLANATION TONOMETRY IN HIV POSITIVE PATIENTS FROM MTHATHA DISTRICT OF SOUTH AFRICA

Kofo Awotedu1, Raj Erasmus2, Abolade Awotedu3, and Ambrose Namugowa1

1Physiology, Walter Sisulu Univ., Fac. of Hlth. Sci., Nelson Mandela Dr., Mthatha, 5100, South Africa, Chemical Pathology, Univ. of Stellenbosch, Eys. van Riebeeck Dr., Cape Town, 5100, South Africa, 2Internal Med., Walter Sisulu Univ., Nelson Mandela Dr., Mthatha, 5110, South Africa.

**Background:** The objective of the study was to see if there is increased arterial stiffness or cardiac dysfunction in HIV patients by using applanation tonometry. **Methods:** A cross sectional study. 169 participants took part in the study between December 2012 and June 2013. There were 63 HIV positive participants, 52 HIV negative participants, and 54 HIV treatment naive participants. Augmentation index (Aix (75), Kg/m2, mean VO2max= 33.7±11.0 ml/kg/min, mean plasma 25-OH-vitamin D= 15.10±0.73 ng/mL. Multivariable linear regression model revealed significant positive linear relationship between body weight and resting diastolic (y3), and resting systolic blood pressure(y4) with p and R2 values (0.041, 0.006) (0.121, 0.107) respectively, and linear equation y4=0.244x+65.3, y3=0.70x+127.1 respectively. Negative linear regression was demonstrated between VO2max, and maximum-diastolic blood pressure (y3), resting pulse(y4) and maximum pulse rate(y5) with p and R2 values (0.017, 0.018, 0.001) (0.153, 0.113,0.185) and linear equations y3=-0.398x+130.128, y5= -0.805x+214.94. Vitamin D level showed no significant correlation with any of the haemodynamic parameters. **Conclusion:** The present study demonstrated that body adiposity and reduced physical fitness appeared to be the most important risk factors toward developing future cardiovascular abnormalities in young Saudi females. Body weight and reduced physical fitness can directly and independently predict the increment in arterial blood pressure and pulse rate in this studied group.
Ejection duration index (ED %) and subendocardial variability ratio (SEVR) and other parameters of interest were measured using arterial wave reflection in these participants. **Results:** SEVR was highest in the HIV negative participants and lowest in HAART naïve HIV participants (p<0.001). In both groups, the HIV positive participants had significant arterial stiffness compared to HIV negative participants (p<0.025). The HIV positive participants also had higher ejection duration index (ED %) and endocardial variability ratio being observed. In both groups, the HIV positive participants had a higher endocardial variability ratio (p<0.001). SEVR had negative correlation with HR using Pearson’s correlation and Stepwise Linear regression p<0.001. **Conclusion:** HIV patients are prone to having systolic dysfunction which may lead to myocardial ischemia. **Keywords:** HIV, subendocardial variability ratio, ejection duration index, arterial stiffness, cardiac function.

## 4.8 Functional and Structural Changes in Intra-Pelvic Arteries Underlying Erectile Dysfunction Induced by Androgen Deprivation

**Rheo Lopez,1 Karla Neves,1 Mariaconce Barboza,1 Vanja Obilic,1 Silvia Rasinski,2 Jose Antunes,2 Leandro Ramalho,1 Fernando Carneiro,3 and Rita Troest1**

1Pharmacology, Univ. of São Paulo, Av. Bandeirantes 3900, Med. Sch. of Ribeirão Preto, Ribeirão Preto, 14049-900, Brazil, 2Physiology, Univ. of São Paulo, Av. Bandeirantes 3900, Med. Sch. of Ribeirão Preto, Ribeirão Preto, 14049-900, Brazil, 3Pathology & Legal Med., Univ. of São Paulo, Av. Bandeirantes 3900, Med. Sch. of Ribeirão Preto, Ribeirão Preto, 14049-900, Brazil.

Androgen deficiency is strongly associated with erectile dysfunction (ED). Inadequate penile arterial blood flow is one of the major causes of ED. The blood flow to the corpus cavernosum is mainly derived from the internal pudendal arteries (IPAs); however, no study has evaluated the effects of androgen deprivation on IPAs functions. We hypothesized that castration impairs IPAs reactivity and structure, contributing to ED. Wistar male rats, 8 weeks-old, were castrated and studied 30 days after orchidectomy. Functional and structural properties of rat IPAs were determined using wire and pressure myograph systems, respectively. Protein expression was determined by western blot and immunohistochemistry. Plasma testosterone levels were determined using the IMMULITE 1000 Immunoassay System. Castrated rats exhibited impaired erectile function, represented by decreased intracavernosal pressure/mean arterial pressure ratio. IPAs from castrated rats exhibited decreased phenylephrine- and electrical field stimulation (EFS)-induced contraction and decreased acetylcholine- and EFS-induced vasodilatation. IPAs from castrated rats exhibited increased internal diameter, external diameter, thickness of the arterial wall and cross-sectional area. Castration decreased nNOS and alpha actin expression and increased collagen expression, p38 (Fh180/γ182) phosphorylation, as well as caspase 3 cleavage. In conclusion, androgen deficiency is associated with impairment of IPA reactivity and structure and increased apoptosis signaling markers. Our findings suggest that androgen deficiency-induced vascular dysfunction is an event involving hypotrophic vascular remodeling of IPAs. Financial support: CRID, FAPESP, Brazil. Key words: Androgen, castration and internal pudendal artery.

## 4.9 Effects of Aerobic Exercise Training on Renin-Angiotensin System Components in Hypertensive Women

**Aline Jarret1, Rodrigo Esposti2, Maycon Fereira2, Carlos Sponhor1, Chadi Angrutti2, Tiago Fernandes2, Fernanda Fernandes3, Eldimar Oliveira2, Dulce Casarin2, and Angelina Zanesco1**


The renin-angiotensin system (RAS) plays a major role in the pathogenesis of hypertension mainly through the classic axis, composed by angiotensin-converting enzyme (ACE), angiotensin II (Ang II) and AT1 receptor. Evidence has shown that RAS is influenced by age and sex hormones. Experimental studies have shown an inhibitory role of estrogen on ACE/Ang II/AT-1 receptor axis with lower concentration of Ang II in female rats compared with male. However, the protective effect of estrogen in women, especially in climacteric phase, is not fully understood. Indeed, it has demonstrated that menopausal hormone therapy increases cardiovascular risk. Thus alternative strategies, like physical exercise, with well-controlled studies should be performed in an attempt to improve the health of this population. Therefore, the objectives of this study were a) to examine angiotensin peptides Ang I, Ang II and Ang (1-7) and ACE activity in hypertensive (HT) women comparing with non-menopausal (NT) at baseline; b) whether aerobic exercise training (AET) exerts beneficial effects on RAS components as well as on blood pressure (BP) in both groups. This study was approved by Ethics Committee. Twenty-eight HT (55±1 yrs) and sixty-six NT (52±4 yrs) women were evaluated at baseline. Blood samples were collected after 12 hours of overnight fast. The components of RAS were quantified by High Performance Liquid Chromatography (HPLC). ACE activity was determined using fluorometric substrates. BP was measured by auscultation with aneroid sphygmomanometer after 15 minutes of rest. A subgroup of women participated in AET, at moderate intensity, for 30-40 min, 3 times/week, for 24 sessions. At baseline, HT women showed higher concentrations of Ang I (240%), Ang II (90%) and Ang (1-7), (140%) compared with NT. No differences were found in ACE activity. In HT (n=16) women, AET was effective in lowering BP (about 5%) that was accompanied by decrease in Ang I and Ang II levels, without changes in ACE activity. In NT (n=34) women, we found a reduction in systolic BP accompanied by a decrease in Ang II and ACE activity (approximately 2%). Our findings show that AET promoted a reduction in BP that was associated with decrease in RAS components in HT women, without affecting ACE activity. The striking of our study is that the beneficial effects of AET on RAS components might be the link between physical exercise and sympathetic activity in human population. Financial support Fapesp, Capes.

## 5.0 CARDIAC

### 5.1 Soluble Guanylyl Cyclase Exerts Opposite Effects in the Myocardium of Male and Female Endotoxemic Mice

**Ion Hobai1,2, Kanwal Aziz1, Deborah Sivick1, and Wilson Colucci1**


Sepsis induced cardiomyopathy (SIC) develops as the result of a decrease in myocardio myocyte contractile function. A central role is thought to be played by nitric oxide (NO) synthesized by inducible NO synthase (NOS2). NO acts by activating cGMP production by the enzyme soluble guanylyl cyclase (sGC), and also by causing oxidative modifications of calcium (Ca²⁺) transporters. Despite a wealth of in vitro data that indicated a pathological role for cGMP, we found that in male (M) mice, cGMP plays a protective role by antagonizing the redox-mediated decrease in cellular
Carotid transients (ΔCa). No data is available about the effect of cGMP in septic mice (F). We studied mice treated with 10 mg/kg of LPS-pretreated mice (WT, n = 5) vs. male WT (n = 4 mice). In contrast, female sGCα2−/− mice had lower mortality (25% after a dose of 20 mg/kg LPS, n = 8) than female WT mice (100%, n = 4 mice). We measured serum corticosterone (SS) and ΔCa in isolated, extensively perfused cardiomyocytes (5 Hz), at 37°C, 14 h after challenge with 25 µg LPS. WT M mice had decreased SS and ΔCa at 60 ± 7 and 78 ± 4% of baseline (BL), respectively (n > 60 cells from 8 mice for all groups, 60/8). In sGCα2−/− mice, the decrease in SS and ΔCa was more pronounced than in WT (to 26 ± 3 and 53 ± 3% of BL, respectively, n = 60). In WT, LPS induced a decrease in SS (to 41 ± 6% of BL, n = 20), but not in sGCα2−/− (suggesting a myocardial dysfunction). SS decrease was less in sGCα2−/− mice (61 ± 10%, n = 20) than in WT F. In conclusion, sGCα2−/− cGMP plays opposite roles in the pathophysiology of LPS-induced cardiomyopathy in M and F mice. In M, cGMP is protective, and mitigates ΔCa decrease. In contrast, in F, cGMP contributes to the development of myocardial dysfunction. Different therapeutic approaches may thus be required in septic M and F patients. Funded by K08GM096062 (NIH, to IAH).

5.2 HAEMOSTATIC AND RHEOLOGIC FACTORIALS AS DETERMINANTS OF ACUTE MYOCARDIAL INFARCTIONS IN NIGERIANS

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Background: Myocardial infarction (MI) is defined as necrosis of a portion of the cardiac muscle caused by obstruction in coronary artery through either atheroembolism, a thrombus or spasm. The causative factors have been well documented and its risk has been reduced to the lowest in advanced countries of the world while in developing countries such as Nigeria, the advent of MI as a major cardiovascular problem is moderately recent. Therefore, researches into the responses of rheological and fibrinolytic parameters are modestly new and ongoing. Objectives: We aimed to highlight basic information on pattern of presentation of haemorheologic and fibrinolytic parameters with a view to indicate their possible use as management indices in MI. Methods: We investigated longitudinally, 10 acute myocardial infarction (AMI) patients (5 males and 5 females) together with 20 age and sex-matched apparently healthy subjects as controls. Blood samples were taken at the point of admission (Day 0), on the 4th and 7th day respectively after treatment has commenced. Rheologic and fibrinolytic indices such as hematocrit (HCT), Erythrocyte sedimentation rate (ESR), Plasma Fibrinogen concentration (PFC), D-dimer concentration (DDC), Eitioglobin hysis time test (ELT) and Plasma viscosity (PV) were measured using standard laboratory methods. Results: We recorded a significantly reduced values of Haematocrit and fibrinolytic activity coupled with significantly increased D-dimer levels, PFC, ESR and PV in AMI patients on admission compared with controls (P < 0.05, respectively). However, PFC, DDC and PV became significantly lowered from the 4th day of admission while all the parameters became significantly reduced from the 7th day of admission and treatment (P < 0.05, respectively). There were no significant sex variations in all the parameters except haematocrit and whole blood viscosity which were lower in females than in males (P < 0.05, respectively). 5) Decreased D-dimer activity coupled with significantly increased fibrinolytic activity and high plasma viscosities could be likely associated risk factors of thrombosis in Nigerians with AMI and their reduction during treatment are positive indicators and as possible factorials in its pathogenesis.

5.3 INCREASED PREVALENCE OF ATRIAL FIBRILLATION IN MALE MICE IS ASSOCIATED WITH LOWER EXPRESSION OF CONNEXIN 40 AND 43

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The risk of developing atrial fibrillation (AF) is more prevalent in men than women, with a 2:1 male preponderance. The electrical remodelling of the atria is one of the critical processes involved in the development of AF and is characterized by a decrease in conduction velocity and shortening of the atrial action potential duration. Even though AF is the most common sustained cardiac arrhythmia, the basis of the sex difference has not been explored. Therefore, the objective of this study is to identify the sex differences in electrophysiological AF substrates responsible for the increased male susceptibility to AF. Accordingly, we used electrical programmed stimulations (EPS) to compare the inducibility of AF in adult male and female CD1 mice. Results obtained reveal that, similarly to humans, the probability of inducing AF in males was significantly higher compared to females (Males: 11 mice out of 21 (52%); Females: 6 mice out of 24 (25%)). Since the left atrium is particularly vulnerable to the development of AF we then used voltage-clamp technique to compare the ionic currents in left atrial myocytes isolated from mice of both sexes. The density of Na+ current (INa) (at -35 mV, males: -20.3 ± 2.1 pA/pF, n = 11; females: -19.1 ± 2.2 pA/pF, n = 13) and K+ current (IK) (at +30 mV, males: 20 ± 5.2 pA/pF, n = 13; females: 16 ± 1.0 pA/pF, n = 13) were significantly lower in males, respectively. However, Na+ current (INa) and K+ current (IK) were significantly lower in males than females. In contrast, females had a significantly higher mortality (25% after a dose of 20 mg/kg LPS, n = 8) than male WT mice (100%, n = 4 mice). We measured serum corticosterone (SS) and ΔCa in isolated, extensively perfused cardiomyocytes (5 Hz), at 37°C, 14 h after challenge with 25 µg LPS. WT M mice had decreased SS and ΔCa at 60 ± 7 and 78 ± 4% of baseline (BL), respectively (n > 60 cells from 8 mice for all groups, 60/8). In sGCα2−/− mice, the decrease in SS and ΔCa was more pronounced than in WT (to 26 ± 3 and 53 ± 3% of BL, respectively, n = 60). In WT, LPS induced a decrease in SS (to 41 ± 6% of BL, n = 20), but not in sGCα2−/− (suggesting a myocardial dysfunction). SS decrease was less in sGCα2−/− mice (61 ± 10%, n = 20) than in WT F. In conclusion, sGCα2−/− cGMP plays opposite roles in the pathophysiology of LPS-induced cardiomyopathy in M and F mice. In M, cGMP is protective, and mitigates ΔCa decrease. In contrast, in F, cGMP contributes to the development of myocardial dysfunction. Different therapeutic approaches may thus be required in septic M and F patients. Funded by K08GM096062 (NIH, to IAH).

5.4 INDICES OF CARDIAC SYMPATHETIC ACTIVITY DURING LOWER BODY NEGATIVE PRESSURE IN MEN AND WOMEN THROUGHOUT THE MENSTRUAL CYCLE

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Women experience orthostatic intolerance to a greater degree than men and recent studies have begun to investigate the role of sex and the menstrual cycle on muscle sympathetic nerve activity (MSNA) during orthostatic stress (Stickford et al. 2015; Yang et al. 2012; Fu et al. 2009). However, MSNA does not necessarily equate to cardiac sympathetic activity. Eleven women (5 not taking oral contraceptives (OC), 2 taking cyclic OC, and 4 taking non-cyclic OC) and eleven men were recruited and a standard electrocardiogram was recorded throughout a lower body negative pressure (LBNP) protocol. This protocol consisted of 5 minutes at -10, -20, -30 and -40mmHg. Women were investigated during the low-hormone phase (LH phase, day 8-11) and high-hormone phase (HH phase, day 18-24). At baseline and -40mmHg, heart-rate variability (HRV; time and frequency domains) and T-wave amplitude were determined. T-wave amplitude was investigated as Haunert et al. (2011) suggested that it may provide a tool to assess sympathetic outflow to the heart during orthostatic stress. Indeed, the percent change in T-wave amplitude due to LBNP was found to be significantly correlated with the percent change in low-frequency power (LF) (p=0.0003) and the percent change in the ratio of low frequency to high frequency power (LF/HF; p=0.0005) in these participants. LBNP resulted in: 1) decreased T-wave amplitude in all groups (Men: -18.9±3.3%, LH phase: -17.3±5.6%, HH phase: -15.6±4.1%); 2) increased LF in all groups (Men: +7.4±17.7%, HH phase: +8.7±13.2%, LH phase: +4.3±3.9%); 3) increased LF/HF in all groups (Men: +35.7±13.2%, LH phase: +61.7±37.6%, HH phase: +196±87%); and 4) decreased SDNN in men and women in the LH phase (Men: -17.7±6.7%, HH phase: -1.1±7.9%, LH phase: -19.6±5.2%). When comparing men to the HH phase, there were no significant differences in the responses of T-wave amplitude (p=0.815), LF (p=0.743), LF/HF (p=0.793) or SDNN (p=0.624) to LBNP. When comparing the two phases of the menstrual cycle, there were no significant differences in the responses of T-wave amplitude (p=0.807), LF (p=0.278) or LF/HF to LBNP (p=0.365); however, women in the LH phase had a greater decrease in SDNN (p=0.018). These results indicate that men and women have similar cardiac sympathetic responses to LBNP.
of people in Latin America, with over 40,000 new cases per year and approximately 14,000 cases of congenital transmission. In the USA and Europe alone, it is estimated that 1 million immigrants suffer from CD. Though many infected individuals will remain asymptomatic indefinitely, 20-30% of CD patients will progress to the symptomatic, chronic phase of disease within a period of 10-30 years after infection. This symptomatic phase, known as Chronic Chagas Cardiomyopathy (CCC), is the most frequent and severe manifestation of CD. Several risk factors for CCC include myocardial inflammation, myocytolysis, fibrosis, and cardiomyopathy. Studies have shown that these negative effects may also manifest into cardiac rhythm disturbances, as identified in humans and various animal models of T. cruzi infection. However, it remains unknown whether chronic T. cruzi H1 infection: 1) impairs cardiac performance and reproduces human CCC or 2) has greater susceptibility based on gender. Objective: Determine the effects of T. cruzi H1 strain on cardiac function in mice. Methods and Results: To evaluate CCC, male and female ICR mice (Tacoxin, Biosciences, Inc.) were infected intraperitoneally with a low dose of 500 T. cruzi H1 (Yucatan, Mexico) blood trypomastigotes (bpt) for a period of 180 days post infection (DPI) and monitored by electrocardiography (ECG) and echocardiography. By 50 DPI, infected male mice showed high mortality rates (84%) and low survival curves, whereas, 70% of female mice survived beyond the acute phase (50 DPI) and entered into the chronic phase of disease. By 70 DPI, ECG analysis revealed a significant delay in the conduction of electrical impulses from the sinoatrial (SA) node to the atrioventricular (AV) node, indicated by prolonged P-R intervals (1st-degree AV block) in 20% of mice. In addition, 2nd-degree AV block was evident in 20% of mice. As surviving mice progressed to chronic infection (180 DPI), ~30% of mice displayed severe 2nd and 3rd-degree AV blocks, while another 30% began to display 1st-degree AV block or AV dissociation, indicating that prolonged PR intervals precede severe AV block and heart failure in marine CCC. Conclusion: Our results suggest that T. cruzi H1 infection in ICR mice serves as a model to study the pathology and mechanisms of human CCC.

5.6 ANGIOTENSIN II MODULATES SEX STEROID METABOLIZING ENZYME AND RECEPTOR EXPRESSION IN CARDIAC FIBROBLASTS FROM MALE AND FEMALE RATS

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Pathological cardiac remodeling involving fibrosis is a major underlying feature of progressive heart disease leading to heart failure. Gonadal sex steroids have been shown to attenuate angiotensin II (AngII)-induced cardiac fibrosis and fibroblast activation. Given that AngII has been shown to influence androgen and estrogen receptor expression in non-cardiac tissues, in the present study we investigated the impact of AngII on sex steroid receptor and enzyme expression in primary rat cardiac fibroblasts. Cardiac fibroblasts were isolated from adult male and female rats and treated at passage 1 in 2% charcoal-stripped FBS for 24 hours with AngII or vehicle (Veh). Gene expression of aromatase, 5α-reductase, androgen receptor (AR), and estrogen receptor (ER) was determined by qRT-PCR. Cardiac fibroblasts from male rats expressed more ERα, ERβ, and AR, as well as the metabolizing enzymes 5α-reductase and aromatase; however, levels of expression were not influenced by sex. AngII significantly and equivalently reduced mRNA expression levels of ERβ, ERα, and 5α-reductase in both male and female cardiac fibroblasts. Aromatase was expressed at low levels in male and female fibroblasts and was not altered by AngII. In separate studies the impact of testosterone, a potential substrate for local 17β-estradiol production via aromatase, was assessed to indirectly determine if AngII alters local aromatase activity. Fibroblasts isolated from male rats were treated with testosterone for the final 6 hours of AngII incubation. However, the addition of testosterone did not alter AngII effects on sex steroid receptor or enzyme gene expression, nor levels of 17β-estradiol in the culture media. These findings demonstrate that AngII downregulates the local sex steroid receptor expression and at least one enzyme involved in gonadal sex steroid metabolism. Given the previously-described protective effects of testosterone and 17β-estradiol, the downregulation of androgen and estrogen receptors in cardiac fibroblasts may contribute to the cardiac fibrosis induced by AngII in both male and females. Funding: AHA 13BGA14720053.

5.7 CARDIAC REMODELING IN FEMALE HEARTS BY KVB1 SUBUNIT

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Cardiovascular disease remains the leading cause of death for women in the US. The etiology of the disease largely remains unknown in addition symptoms can remain silent for many years. The hallmarks for the disease demonstrate cardiac functional alterations including higher heart rates, longer QTc duration and a greater propensity for arrhythmias. These symptoms can be caused by cardiac remodeling leading to re-polarization defects. Potassium channels play a major role in maintaining the repolarization reserve and the Kv11.1 subunits are uniquely positioned to modulate Kv (Kv4 and Kv1) channels. The present study investigates the physiological function and roles of Kv11.1 in male and female mouse heart line (Kv11.1 KO) and noted enlarged hearts compared with WT female controls (C57BL/6NJ). The physical and morphometric data showed increased heart weight, surface area, and left ventricular internal dimensions (LVID, SD) by echocardiography. KO females further demonstrated greater mean pressure and velocity in the ascending aorta (1.5±0.164mmHg vs. 0.88±0.17mmHg and 617±32mmvs. 456±42mm, KO females demonstrated significant prolongation in both monophasic action potentials (AP)50:1.7±1.7ms vs. 492±2.5ms) and QTc duration (51±2ms vs. 45±2ms). Taken together, Kv11.1 KO females demonstrated cardiac remodeling, electrical dysfunction, and defects. This report clearly demonstrates that the Kv11.1 subunit is involved in cardiac growth and electrical remodeling. Funding source: NIH 1R01HL102171-01A1.

5.8 IMPAIRED DIASTOLIC FUNCTION FOLLOWING ACUTE STARVATION IN MEN BUT NOT PREMENOPAUSAL WOMEN

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Alterations in cardiac fatty acid uptake and metabolism have been implicated in the development of myocardial diastolic dysfunction. The majority of this work however remains limited to transgenic mice or rodent models of dietary obesity. We therefore sought to translate these preclinical findings into human subjects. To augment fatty acid uptake and metabolism, we performed an acute (48 hours) starvation intervention in ten healthy volunteers (6 men/4 women, age: 29±4 yrs). Myocardial triglyceride content and left ventricular diastolic function were measured by magnetic resonance spectroscopy and imaging, respectively; at baseline (BL), immediately after the 48 hour fast, and 48-72 hours following re-feeding with the subjects normal diet. As expected, acute starvation caused a significant, but transient, mean elevation in circulating free fatty acids (ABL: 162±11%, P<0.002, ketone bodies (ABL: 2387±168%, P<0.001), and myocardial triglyceride content (ABL: 396±139%, P<0.001), returning to baseline upon follow-up. Remarkably, left ventricular relaxation rate was reduced in each of the men following the 48 hour fast (ABL: -19±3%, P<0.05), but remained unchanged in the female subjects (ABL: +2±2%, P=0.1976). Sex specific analysis also revealed significantly greater elevations in ketone bodies in females than males (ABL: 4235±651% vs. 1877±399%, respectively), despite a similar increase in circulating free fatty acids (ABL: 147±15% vs. 213±29%, female vs. male, respectively). Because ketone bodies are known to be anti-inflammatory, we speculate that premenopausal women may be protected against metabolic fatty acid-induced inflammation through this specific pathway. Further work in a larger sample size including post-menopausal women is warranted to further understand the role of estrogen on sex differences in metabolism and cardiac health and disease.

5.9 ATTENUATION OF CARDIAC AGING AND LEPTIN-DEPENDENT CARDIOPROTECTION IN LONG-LIVED AMUPA MICE


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Susceptibility of the heart to ischemia increases with age in man and rodents. AMUPA transgenic mice and mice treated for caloric restriction (CR) are two longevity models. AMUPA spontaneously consume less food compared with their wild type (WT) ancestors, and show endogenously increased levels of leptin, a satiety hormone known to decline under CR. To understand mechanisms linked to cardiac aging and protection, female AMUPA and WT mice were subjected to myocardial infarction (MI) in vivo at several ages and to ischemia/reperfusion ex vivo. Compared to WT mice, AMUPA showed functional and hormonal advantages under all experimental conditions. By 24 months, none of the WT mice survived the first ischemic day while AMUPA mice demonstrated 50% survival after 7 ischemic days. At baseline and post MI, leptin levels almost doubled in the AMUPA sera. Pretreatment with leptin neutralizing antibodies, or with inhibitors of leptin signaling (AG-490 and Wortmannin),
The myocardial contractility in heart failure is impaired in adult males but preserved in adult females. This is associated with the protective effect of sex hormones. In immunopositivity, the protection is limited. We characterized auxotonic twitch of isolated right ventricular (RV) cardiomyocytes from young male/female healthy and RV failing rats. The experiments have been conducted on 2-month Wistar rats in conformance with the Declaration of Helsinki and the APA’s Guiding Principles in the care and use of animals. RV cardiomyocytes were obtained from non-failing males/females (NF-m/f) and CR-induced cardiomyopathy (CR-m/f; MCT-m/f) from each group. Auxotonic twitches (~20 cell/gp) were measured at 25°C and 1 Hz pacing rate under different preloads using carbon fiber technique. Data presented as mean±SE, difference is significant at P<0.05. At low preloads (<10% of slack length, Ls), end-systolic tension was two-fold larger in males vs. females in NF or MCT and was significantly larger in MCT-m/T-m vs. NF-m/NF-f (by 42.6±1.4/70.0±1.7%, respectively). The normalized rate of tension development did not differ in NF-m vs. NF-f (12.5±0.3 vs. 12.3±0.2 1s) but was significantly lower in MCT-m vs. NF-m (12.8±0.1 vs. 13.7±0.2 1s). The time-to-peak tension and twitch duration were sex-independent in NF or MCT but both parameters were significantly lower in MCT-m vs. NF-m (by 7.7±0.7% and 7.5±0.3%, respectively) and in MCT-f vs. NF-f (by 17.4±0.1% and 16.5±0.7%). These proportions in general remain under increased preloads (115±130%). End-systolic tension was higher in MCT-m vs. NF-m (by 75.1±2.8%, significant) and in MCT-m vs. NF-f (by 17.6±6.3%). The normalized rate of tension development was significantly lower in NF-m vs. NF-f (10.6±0.3 vs. 11.2±0.2 1s) and in MCT-m vs. MCT-f (11.8±0.2 vs. 12.8±0.1 1s). This parameter was substantially higher in MCT vs. same-sex NF. Time-to-peak tension and twitch duration were significantly shortened in MCT vs. same-sex NF. In conclusion, the characteristics of auxotonic twitch of RV cardiomyocytes of immature male and female rats with monocrotaline-induced RV heart failure display similar changes from those observed in the same-sex healthy animals. The minor gender-specific differences were found both at low and physiological preloads. In contrast to adults, the protective effect of sex hormones in female myocardium is not in action yet in young rats. The study is supported by RFBR 13-04-00367.

5.11 LOWER LEVELS OF INTERLEUKIN-6 IN FEMALE MICE AT DAYS 1 AND 3 POST-MYOCARDIAL INFARCTION ATTENUATE NEUTROPHIL INFILTRATION, RUPTURE, AND LEFT VENTRICULAR DILATION

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Survival after myocardial infarction (MI) is improved in female compared to male mice of the same age, yet the mechanisms to explain this phenotype remain undefined. We hypothesized that female mice have lower acute systemic pro-inflammatory cytokine production leading to improved survival and cardiac function post-MI. We used C57BL/6 male and female mice (3-month old, n=93) for this study. Females had better day (D) 7 survival (73%, 26 out of 34) compared to males (40%; 29 out of 59; P<0.05). In addition, rupture rate (rupture/total deaths) was reduced in females (1.9%; 11% compared to males (16/35; 46%; P<0.05). Out of 52 analyses measured at D1, D3, D5 or D7 days post-MI (n=10-12/sex/day), 5 were identified as possible regulators of sex-related differences post-MI: neurotrophic factor B (NGF), interleukin-6 (IL-6), macrophage inflammatory protein (MIP) 1-g, plasminogen activator inhibitor-1 (PAI-1), and tissue inhibitor of metalloproteinase (TIMP)-1. Regression analysis showed only IL-6 levels positively correlated with end diastolic dimension (EDD) in both males (R²=0.47, p<0.05) and females (R²= 0.32 p<0.05). By time course analysis, IL-6 increased early post-MI in males, peaking at D3, and quickly decreased to baseline levels by D7. Females, on the other hand, had a subtle yet significant increase early post-MI that remained steady until D7 such that IL-6 was elevated in females at D7 compared to males (p<0.05). Interestingly, despite higher IL-6 at D7 post-MI in female mice, EDD was decreased in females (5.4± 0.10 mm) compared to males (5.9± 0.24 mm; p<0.05; n=10-12/sex/day) highlighting the importance of early post-MI events. Since IL-6 is known to regulate neutrophil infiltration early post-MI, we evaluated neutrophil numbers and found females had a 2-fold reduction compared to males at D1 and 3 post-MI (p<0.05 for both days n=6-10/day). In conclusion, females had reduced circulating IL-6 at D1 and D3 post-MI, which led to decreased neutrophil infiltration and attenuated cardiac rupture and LV dilation.

5.12 THE CHARACTERIZATION OF AUXOTONIC TWITCH OF RIGHT VENTRICULAR CARDIOMYOCYTES FROM NON-FAILING AND FAILING HEARTS OF IMPUBERAL MALE AND FEMALE RATS

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The myocardial contractility in heart failure is impaired in adult males but preserved in adult females. This is associated with the protective effect of sex hormones. In immunopositivity, the protection is limited. We characterized auxotonic twitch of isolated right ventricular (RV) cardiomyocytes from young male/female healthy and RV failing rats. The experiments have been conducted on 2-month Wistar rats in conformance with the Declaration of Helsinki and the APA’s Guiding Principles in the care and use of animals. RV cardiomyocytes were obtained from non-failing males/females (NF-m/f) and CR-induced cardiomyopathy (CR-m/f; MCT-m/f, MCT-f) from each group. Auxotonic twitches (~20 cell/gp) were measured at 25°C and 1 Hz pacing rate under different preloads using carbon fiber technique. Data presented as mean±SE, difference is significant at P<0.05. At low preloads (<10% of slack length, Ls), end-systolic tension was two-fold larger in males vs. females in NF or MCT and was significantly larger in MCT-m/T-m vs. NF-m/NF-f (by 42.6±1.4/70.0±1.7%, respectively). The normalized rate of tension development did not differ in NF-m vs. NF-f (12.5±0.3 vs. 12.3±0.2 1s) but was significantly lower in MCT-m vs. NF-m (12.8±0.1 vs. 13.7±0.2 1s). The time-to-peak tension and twitch duration were sex-independent in NF or MCT but both parameters were significantly lower in MCT-m vs. NF-m (by 7.7±0.7% and 7.5±0.3%, respectively) and in MCT-f vs. NF-f (by 17.4±0.1% and 16.5±0.7%). These proportions in general remain under increased preloads (115±130%). End-systolic tension was higher in MCT-m vs. NF-m (by 75.1±2.8%, significant) and in MCT-m vs. NF-f (by 17.6±6.3%). The normalized rate of tension development was significantly lower in NF-m vs. NF-f (10.6±0.3 vs. 11.2±0.2 1s) and in MCT-m vs. MCT-f (11.8±0.2 vs. 12.8±0.1 1s). This parameter was substantially higher in MCT vs. same-sex NF. Time-to-peak tension and twitch duration were significantly shortened in MCT vs. same-sex NF. In conclusion, the characteristics of auxotonic twitch of RV cardiomyocytes of immature male and female rats with monocrotaline-induced RV heart failure display similar changes from those observed in the same-sex healthy animals. The minor gender-specific differences were found both at low and physiological preloads. In contrast to adults, the protective effect of sex hormones in female myocardium is not in action yet in young rats. The study is supported by RFBR 13-04-00367.

**Introduction:** Serum C-reactive protein (CRP) is a marker for inflammation produced by the liver in response to factors released by adipocytes and macrophages. Its level in circulation is linked with benign prostate hyperplasia (BPH), the primary cause of bladder outlet obstruction (BOO) in adult males. It is also directly related to the severity of lower urinary tract symptoms (LUTS). Diet has been strongly associated with inflammation and some diets have been related to chronic inflammation. We evaluated the effects of diets of varying macronutrient composition on inflammation in the unobstructed bladder and BOO, by assessing its influences on Serum CRP levels. **Materials and Methods:** Appropriate institutional ethical approval for use of animals in laboratory research was obtained from the Ethical Committee of the College of Medicine, University of Ibadan and all protocols were carried out in accordance with the Guide for the Care and Use of Laboratory Animals. Partial BOO was surgically induced in male wistar rats. Animals were fed on various diets which were continued for 4 weeks after surgery. Rats were divided into sham-operated and BOO groups each with the following: control (normal rats’ feeds), high-carbohydrate (HCD), high-fat (HF), high-protein (HP) dietary groups. After the experimental feeding period, blood was collected and Serum CRP level was assessed using Enzyme-linked immunosorbent assay (ELISA). **Results:** In the unobstructed bladder, serum CRP was elevated only in animals fed on the HFD (P < 0.05). In the obstructed groups also, only the animals fed on the HFD showed an increase in CRP, an increase that was higher (P < 0.05) than that in the HFD without obstruction. **Conclusion:** A high fat diet results in an increase in serum- CRP in both the unobstructed and obstructed rat bladder. As obesity and BOO are independently associated with the severity of LUTS in both sexes, these findings indicate that the worsening of LUTS seen with BOO and in obese patients may be due in part to increased inflammation.

### INCREASED OREXIGENIC INNERVATION OF DOPAMINE NEURONS REDUCES PROLACTIN SECRETION IN OBESE FEMALE RATS

Natalia Toporikova1, Melina Krabe2, Veronica Porhebra1, Tyra Barrett1, Patrick Orzer1, and Sarah Blythe1


**Introduction:** Obesity adversely affects reproductive health in women causing menstrual irregularity, anovulation, miscarriages, and decreased conception. This suggests that an individual’s metabolic state is pivotal for reproductive success. Neural circuits underlying feeding behavior and reproductive cycling are both found in the hypothalamus, specifically within the arcuate nucleus (ARC). Dopaminergic (DA) neurons within the ARC send inhibitory projections to lactotrophs in the pituitary which release prolactin (PRL), a hormone critical for lactation and maintenance of pregnancy. Dopamine release is inhibited by kisspeptin (KISS), a neuropeptide of the HPG axis, and prolactin (PRL), a hormone critical for lactation and maintenance of pregnancy. Do-

**Materials and Methods:** At 23 days old, Sprague-Dawley rats were split into two groups: control chow and high fat, high sugar (HFHS) diet. The HFHS diet consisted of a 32% sucrose solution and food containing 60% calories from fat. After three weeks of diet consumption, HFHS animals weighed significantly more than control- fed rats and continued to weigh more for the remainder of the experiment. Additionally, insulin sensitivity was assessed with fasting blood samples and the HOMA-IR calculation. When the rats reached sexual maturity at ten weeks of age, daily vaginal smears were taken over the course of five weeks in order to assess the effect of diet and weight gain on estrous cycling. While over 50% of the cycles occurring in control rats lasted for the normal four-day duration, only about 40% of HFHS rats exhibited the normal four-day pattern. Furthermore, HFHS rats experienced an increased number of days spent in consecutive estrus compared to their control counterparts. It was noted that these days spent in consecutive estrus occurred in the obese subjects after weight gain had occurred, therefore suggesting that obesity induces estrous cycle irregularity in previously normally cycling animals. Rats were ovarioctomized, and ovaries were assessed for follicle development. In conclusion, our findings suggest that diet-induced obesity leads to a disruption in the regularity of estrous cycling, which may result in reduced fertility.

### 6.6 INFLUENCES OF DIET ON SERUM C-REACTIVE PROTEIN IN UNOBSTRUCTED AND OBSTRUCTED BLADDERS OF MALE WISTAR RATS

Terrance Adekola1, Adeosun Fasammade1, and Eriolabola Olapade-Olaopa2


**Introduction:** Serum C-reactive protein (CRP) is a marker for inflammation produced by the liver in response to factors released by adipocytes and macrophages. Its level in circulation is linked with benign prostate hyperplasia (BPH), the primary cause of bladder outlet obstruction (BOO) in adult males. It is also directly related to the severity of lower urinary tract symptoms (LUTS). Diet has been strongly associated with inflammation and some diets have been related to chronic inflammation. We evaluated the effects of diets of varying macronutrient composition on inflammation in the unobstructed bladder and BOO, by assessing its influences on Serum CRP levels. **Materials and Methods:** Appropriate institutional ethical approval for use of animals in laboratory research was obtained from the Ethical Committee of the College of Medicine, University of Ibadan and all protocols were carried out in accordance with the Guide for the Care and Use of Laboratory Animals. Partial BOO was surgically induced in male wistar rats. Animals were fed on various diets which were continued for 4 weeks after surgery. Rats were divided into sham-operated and BOO groups each with the following: control (normal rats’ feeds), high-carbohydrate (HCD), high-fat (HF), high-protein (HP) dietary groups. After the experimental feeding period, blood was collected and Serum CRP level was assessed using Enzyme-linked immunosorbent assay (ELISA). **Results:** In the unobstructed bladder, serum CRP was elevated only in animals fed on the HFD (P < 0.05). In the obstructed groups also, only the animals fed on the HFD showed an increase in CRP, an increase that was higher (P < 0.05) than that in the HFD without obstruction. **Conclusion:** A high fat diet results in an increase in serum-CRP in both the unobstructed and obstructed rat bladder. As obesity and BOO are independently associated with the severity of LUTS in both sexes, these findings indicate that the worsening of LUTS seen with BOO and in obese patients may be due in part to increased inflammation.

### 6.5 DIET-INDUCED OBESITY IMPAIRS ESTROUS CYCLE REGULARITY IN FEMALE RATS

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**Introduction:** While over 50% of women in the United States are overweight or obese, this condition can lead to high rates of menstrual irregularity and infertility. Therefore, the objective of this study is to determine the relationship between obesity and reproduction using female rats as a model. At 23 days old, Sprague-Dawley rats were split into two groups: control chow and high fat, high sugar (HFHS) diet. The HFHS diet consisted of a 32% sucrose solution and food containing 60% calories from fat. After three weeks of diet consumption, HFHS animals weighed significantly more than control- fed rats and continued to weigh more for the remainder of the experiment. Additionally, insulin sensitivity was assessed with fasting blood samples and the HOMA-IR calculation. When the rats reached sexual maturity at ten weeks of age, daily vaginal smears were taken over the course of five weeks in order to assess the effect of diet and weight gain on estrous cycling. While over 50% of the cycles occurring in control rats lasted for the normal four-day duration, only about 40% of HFHS rats exhibited the normal four-day pattern. Furthermore, HFHS rats experienced an increased number of days spent in consecutive estrus compared to their control counterparts. It was noted that these days spent in consecutive estrus occurred in the obese subjects after weight gain had occurred, therefore suggesting that obesity induces estrous cycle irregularity in previously normally cycling animals. Rats were ovarioctomized, and ovaries were assessed for follicle development. In conclusion, our findings suggest that diet-induced obesity leads to a disruption in the regularity of estrous cycling, which may result in reduced fertility.

### 6.3 WITHDRAWN
6.7 A HIGH-FAT DIET IMPACTS GLUCOSE AND BLOOD PRESSURE IN FEMALE AND MALE DAHL SALT-SENSITIVE RATS

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²There are numerous reported sex differences in metabolic parameters and blood pressure (BP), although many fewer studies have examined the molecular mechanisms driving high-fat (HF)–induced increases in BP and metabolic disorders in males vs. females. Obesity and a HF diet are risk factors for hypertension, and male Dahl salt-sensitive rats (DSS) exhibit an increase in free fatty acids and BP in response to a HF diet; nothing is known in females. The current study was designed to determine the impact of a HF diet on blood glucose levels, metabolic parameters, and BP in male and female MA pre-contracted with phenylephrine (PE) or U446619. In addition, EDV to ACh and tubulin-1 (ET-1) were also measured. Systolic BP was significantly elevated in both male and female rats (125±1 vs. 132±2 mmHg; p=0.008) and were smaller than males (220±9 vs. 324±9 g; p=0.01), although females have greater percent body fat (10±0.7 vs. 7±0.4%; p=0.005). DSS were implanted with a PhysioTel HD-XG glucose telemetry for the continuous measurement of blood glucose. A glucose tolerance test was performed and revealed that females have a better glucose tolerance at baseline than males (AUC: 2034±206 vs. 2381±916 g; p=0.05). If females were then placed on a HF diet (36% fat; Bio-Serv). After 1 week on the HF diet, both female and male rats gained weight (247±3 vs. 385±12 g, respectively), although blood glucose levels were comparable between female and male rats (105±2.2 vs. 103±3 mg/dl; p=0.45). The HF diet also significantly increased BP in both female (145±4) and male rats (154±3; p=0.001 for both sexes vs. baseline BP), however, the increase in BP was comparable between the sexes (14% increase for both). To date, our studies indicate that female and male DSS rats exhibit similar alterations in metabolic and cardiovascular parameters. Rats will continue to be followed for an additional 3 weeks on the HF-diet to determine if sex impacts the trajectory of fat-induced increases in glucose handling or BP. We would like to offer a special thanks to DSI for the glucose implants and technical support.

6.8 HIGH FRUCTOSE INTAKE EXACERBATES THE IMPAIRMENT OF MESENTERIC ARTERIAL FUNCTION COMPARED TO GLUCOSE IN FEMALE RATS: POSSIBLE INVOLVEMENT OF EDHF CONTRIBUTION IN MODULATING VASCULAR REACTIVITY

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Intake of high fructose in diet has shown to contribute to variety of metabolic disorders such as obesity and diabetes. Limited data is available on the relative effects of different dietary sugar intake on vascular reactivity. The aim of current study was to investigate and compare the effects of high glucose (HG) and high fructose (HF) consumption on mesenteric arterial (MA) functions in female rats. Sprague-Dawley female rats were supplemented with 20% w/v glucose or fructose in drinking water for 30 days. Female rats were placed on a HG diet (60% carbohydrate and control diets. Our initial study looked at the effects of TrpM5 deletion (TrpM5<sup>-/-</sup>) in mice compared to wild-type mice (TrpM5<sup>+/+</sup>) while on a high-fat diet (60% fat diet for 46 days). KO male mice took in significantly less calories than their WT counterparts and subsequently gained significantly less body weight while on the 60% high fat diet. Similar, though less dramatic, effects were seen in mice lacking the IP3 receptor (IP3R3<sup>-/-</sup>) or the fatty acid transport protein, CD36, which are implicated in the fatty acid pathway. Since both pre- and post-ingestively, lead to specific changes in the intake of dietary fat in male mice and female rats respectively elucidated. This transduction pathway for polyunsaturated fatty acids (PUFAs) involves PUFA binding to CD36 and/or fatty acid activated GPCRs, and downstream activation of PLC. While on the 60% high fat diet, male mice gained significantly less body weight while on the 60% high fat diet. The effects of TrpM5 deletion were gender specific – female mice lacking TrpM5 were more susceptible to atherosclerosis. Key words: HIV infection, Highly Active Antiretroviral Therapy (HAART), Adiponectin, Lipid profile, Resting Energy Expenditure (REE).
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Transsexual women (female to male - FT-M) experience significant changes in adipose fat distribution after sex reassignment surgery, suffer from increased metabolic risk and premature mortality. The exact mechanisms by which sex reassignment surgery and/or female hormone treatment leads to metabolic impairment remains incompletely understood. To begin to address this question, we recruited 12 transsexual women who had undergone bi-lateral orchectomy (n = 4) or had not (n = 8).

Both groups were using female hormones. Glucose tolerance was assessed using a standard 75g oral glucose tolerance test (OGTT). Hepatic steatosis was assessed by 1H magnetic resonance spectroscopy. The major novel findings were three-fold: First, the hormone only group were insulin resistant, as evidenced by a marked increase in plasma insulin during the OGTT compared to the orchietomy group (AUC glucose: 20,380 ± 1263 vs. 17,923 ± 859; AUC insulin: 14,235 ± 4694 vs. 5,941 ± 1538, respectively). Second, hepatic steatosis was markedly elevated in the hormone only group compared to the orchietomy group (90±2.4 vs. 1.5±0.3 %fat/water, respectively). Third, hepatic steatosis was associated with insulin resistance (n=12, R²= 0.4482). These pilot data provide novel mechanistic insight, and suggest hepatic steatosis and insulin resistance are prevalent in trans-sexual women treated with cross-sex hormones, and that orchietomy may be “protective.” Future studies will focus on increasing sample size and investigating the hormonal milieu and impact on metabolic dysfunction.

6.13 DO WOMEN NEED TO LOSE MORE WEIGHT THAN MEN TO INCREASE CIRCULATING ADIPONECTIN?

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Adiponectin is an anti-inflammatory protein and plays a protective role in the development of atherosclerosis. Obese individuals have lower circulating concentrations than their lean counterparts. However, previous studies do not consistently show increased adiponectin concentrations with weight loss induced by dietary restriction and/or exercise. The purpose of this review is to determine whether sex is a factor in the explanation of different study results. Methods: Previous studies that involve caloric restriction and/or exercise-induced weight loss, and have reported adiponectin concentrations before and after weight loss are examined. Percentage of weight lost, method of weight loss (caloric restriction only, exercise only, or combined), number and proportion of participants of each sex, and circulating adiponectin concentration changes are summarized. Results: In studies involving mostly men, approximately 10% of weight loss is associated with an increase in adiponectin concentration. In studies involving only women or women as the majority of the study participants, adiponectin does not significantly increase with up to 15% of weight loss; adiponectin increases with greater than 15% of weight loss. With the addition of exercise, less than 10% of weight loss significantly increases adiponectin. Conclusion: It appears greater weight loss is needed for women than men to show an increase in adiponectin concentration. This may be related to the greater body fat percentage in women than men. Exercise may help reduce the amount of weight loss needed to induce an increase in adiponectin. This work is partially supported by NIH AG031297.

6.14 SEX, LEPTIN STATUS, AND OBESITY MODULATE BUPRENORPHINE-INDUCED RESPIRATORY DEPRESSION IN MICE

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Opiates cause sex-specific differences in modulation of pain (Pain 155:388, 2014; Biol Psych 76:213, 2014) and respiratory depression (Br J Anaesthesiol 100:747, 2008). The mechanisms contributing to the foregoing differences are not understood, yet are clinically relevant for efforts to elucidate sex-specific differences in response to opioid therapy (Pain Res Manag 20:23, 2015). Previous studies using mice showed that leptin levels are sexually dimorphic (Obesity Res 12:1481, 2004) and contribute to the regulation of both breathing (Respir Physiol 119:173, 2000) and nociception (Neuroscience 275:531, 2014). This ongoing study is testing the hypothesis that buprenorphine (bup) causes dose-dependent alterations in breathing as a function of sex, leptin status, and obesity. Subjects include three groups of male and female mice from the Jackson Laboratory (1) lack leptin and are obese (Lept−); (2) lack leptin receptors, are obese, and are diabetic (Lept−); and (3) have normal leptin levels and normal body weight (B6). Bupe (0.1, 0.3, 0.5, 1, and 10 mg/kg) or saline were administered intraperitoneally and breathing was measured for 1 h using whole body plethysmography. All data are reported as percent change. Bupe caused dose-dependent changes in breathing for all three genotypes. An antinociceptive dose (0.3 mg/kg) decreased rate of breathing in the Lept− (10% decrease) and the Lept− (11%) mice relative to the mice. The largest dose (10 mg/kg) decreased rate of breathing relative to rates after saline injection (B6 = 0.8%, Lept− = 22.3%, Lept− = 0.5%). Tidal volume (Vt, ml/g body weight) was increased by the 0.3 mg/kg dose (B6 = 31.5%, Lept− = 48.5%, Lept− = 148%). Minute ventilation (Vt, ml/min/body weight) also varied by genotype after 0.3 mg/kg bupe (B6 = 24.7%, Lept− = 37.3%, Lept− = 11%).

Male (M) versus Female (F) differences in Vt (saline vs 0.3 mg/kg bupe) were (B6 = 47%, B6 = 61%; Lept− =69.5%, Lept− =52.6%; Lept− =11%, Lept− =54.2%). These results encourage efforts to determine the extent to which leptin modulates increases in opiate-induced adverse events associated with female sex and obesity (Anesthesiology 122: 659, 2015). Support: 5-R01-HL06272-12 and University of Tennessee.

6.15 INCREASING LEPTIN SENSITIVITY WITH PROTEIN TYROSINE PHOSPHATASE 1B DELETION LEADS TO MORE SEVERE CARDIAC ALTERATIONS IN FEMALE THAN MALE MICE

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High circulating levels of the adipocyte-derived hormone leptin, contributes to the development of cardiac dysfunction in males. Despite the fact that females secrete 3-4 times more leptin than males and that left ventricular dysfunction correlates to fat content and BMI in women only, the interaction between leptin and cardiac dysfunction has not been studied in women. Here we hypothesized that female mice are more prone to leptin-mediated cardiac alterations than males. To test this hypothesis, we characterized the cardiac phenotype of lean male and female mice receiving hyper-sensitve to leptin via the deletion of the molecular brake on the leptin signaling, the protein tyrosine phosphatase 1B. Leptin sensitization in lean animals similarly increased blood pressure in male and female KO (124±4 vs 126±4 respectively; WT: 102±15 mmHg) but induced a higher increase in fibrosis (Masson’s trichrome) in the ventricle of female (WT: 2.7%, KO: 7.3%) compared to male mice (WT: 3.8%, KO: 4.2%). Red oil staining revealed deposition of fat droplets in the myocardium, which was significantly higher in KO females (14±6%) compared to male mice (3±3%), mostly in the intra-ventricular septum. Quantification of gene expression via quantitative real-time RT-PCR, showed an increase in hypertrophic and cardiac stress markers: β-myosin and ANP in the ventricle of KO female only. Furthermore, fibrotic (CTGF) and inflammatory markers (COX2) were highly up-regulated in KO female only. Metabolic factors involved in cardiac energy metabolism were differentially regulated in leptin-sensitized mice. In particular, VLD was decreased when GLUT4 was increased in KO females only, revealing a shift in energy metabolism. Together these data showed that leptin sensitization induced a more severe increase in cardiac fibrosis, fat deposition and metabolic changes, in females than males, for the same level of hypertension. These data could explain the rise of cardiovascular diseases in young obese women. This work was supported by a Scientist Development Grant from the American Heart Association (11SDG5060006 to EJ.BdC) and Start-up funds from Georgia Regents University.

6.16 SEX DIFFERENCES IN RENAL SODIUM HANDLING IN MICE ON HIGH-FRUCTOSE AND HIGH-SALT DIET

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Many studies suggest a protective element associated with female sex under various conditions that increase blood pressure. Metabolic syndrome and hypertension are linked to high fructose and high salt consumption, and studies indicate sex differences in the physiological effects of these diets. Maintaining sodium balance is of major concern. The goal of this study was to investigate sex differences in mice consuming high levels of both fructose and salt (F+S). Female and male 5-week-old CD-1 intact mice (n=6/group) were placed in metabolic cages and consumed a normal (0.4% salt) diet and water for 4 days followed by 30 days on the F+S diet consisting of a 20% fructose and 1% salt solution and a powdered 4% salt chow. Measurements included blood pressure via the tail-cuff method and urinary sodium excretion. Separate mice kept in plastic bins and maintained on the same dietary protocol were used for molecular analysis of the renal sodium transporters via real-time PCR using custom-made PCR arrays (QIAGEN). Results demonstrated that mean blood pressure (MBP),
6.17 SEXUALLY DIMORPHIC MYELOID INFLAMMATORY AND METABOLIC RESPONSES TO DIET-INDUCED OBESITY

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Background: It is well known in clinical and animal studies that women and men have different disease risk as well as different disease physiology. Women of reproductive age are protected from metabolic and cardiovascular disease compared to post-menopausal women and men. Most murine studies are skewed towards the use of male mice to study obesity-induced metabolic dysfunction because of similar pro-inflammatory responses in male and female mice with higher increase occurring in females. We propose the estrogen-induced stimulation on the renal handling of sodium plays a key role in the increased blood pressure in female mice under the F+5 diet and studies are underway to test this proposal. This study was funded by NIH-sponsored Oklahoma INBRE summer research program (PA-12-313).

Objective: To understand if sex differences in obesity-induced inflammation contribute to differences in metabolic disease risk. Design/Methods: Male and female C57Bl/6j mice were fed a 60% high fat diet (HFD). Assessments for glucose metabolism were performed as well as evaluations of inflammatory responses in leukocyte activation in bone marrow, blood, and adipose tissue as well as pre-adipocyte populations. BM was cultured from male and female animals and stimulated with LPS to investigate sex differences in inflammatory responses. TLR4+ animals were also challenged to understand the dependence of the inflammatory changes to the presence of TLR4. Monocyte transfer and reciprocal bone marrow transplant experiments were performed to further assess sex differences in bone marrow myeloid responses to obesity independent of host-sex. Results: Males and females both gained adiposity after high fat diet but females had higher energy expenditure rates and dampened inflammatory activation are due to cell intrinsic differences in hematopoietic responses of obesity- induced independent of host-sex. Results: Males and females both gained adiposity after high fat diet but females had higher energy expenditure rates and dampened inflammatory responses with reduced CD11c+ adipose tissue macrophage populations and inflammatory cytokines. Ex vivo female marrow produced reduced cytokines after LPS stimulation. TLR4+ males had attenuated but persistent macrophage accumulation while females remained protected. Male BM cells continued to remain primed for a pro-inflammatory response after monocyte transfer to bone marrow transplantation. Conclusion: Sex differences in high fat diet induced inflammatory activation are due to cell intrinsic differences in hematopoietic responses to obesity independent of host-sex. This work was supported, in whole or in part, by American Heart Association Scientist Development Grant 14SDG17980004 and Department of Pediatrics Janette Ferrantino Investigator Award.

6.18 SEX DIMORPHISM IN PLASMA SOLUBLE PROREIN RECEPTOR (SPRR) LEVELS IN OBESE PATIENTS IS ASSOCIATED WITH TYPE 2 DIABETES MELLITUS IN WOMEN BUT NOT IN MEN

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Obesity markedly increases the occurrence of Type 2 diabetes mellitus (T2D). Adipose tissue expresses all components of the renin-angiotensin system (RAS), which may contribute to inappropriate RAS activation and increased risk of end-stage organ damage (ESOD) in T2D. Increased circulating levels of soluble prorein receptor (SPR) and other cardiovascular biomarkers suggest that plasma SPR might be a potential biomarker of RAS activation. While women with T2D exhibit disproportionately greater burdens of ESOD than men, sex differences in the RAS during T2D are poorly understood. To test the hypothesis that plasma sPRR levels are associated with T2D in obese patients and differ between men and women, we examined plasma samples from 201 patients (mean age; 41 ± 13 years; 39% men), including 107 controls (Ctrl; BMI<30), 66 obese (Ob; BMI=30) and 28 obese with T2D (Ob+T2D) patients. The waist-to-hip ratio (WHR) was used as a measurement of abdominal adiposity. Plasma sPRR levels, measured by ELISA, were significantly higher in Ob+T2D patients (21.5 ± 1.6ng/mL) compared to Ctrl (16.5 ± 0.4ng/mL) and Ob (16.6 ± 0.5ng/mL; P < 0.0001). Urine Albumin/Creat ratio showed a similar trend (Ob: 31.0 ± 4; Ob+T2D: 53.1 ± 8 vs. Ctrl: 24.9±2 mg/g uc; P < 0.0001). Plasma sPRR levels negatively correlated with WHR in the Ob+T2D (r=−0.62, p=0.0395) but not with Ctrl or Ob patients. Control lean men patients exhibited significantly higher plasma sPRR levels compared to women (18.1 ± 0.8 vs. 15.4 ± 0.4 ng/mL; P<0.001). Interestingly, the plasma sPRR, differences among groups of same sex were greater in Ob+T2D patients compared to Ctrl (20.9 ± 1.7 ng/mL vs. 15.4 ± 0.4 ng/mL; P<0.0001) and Ob (15.8 ± 0.6 ng/mL; P<0.0001) patients, but did not differ among men groups. The interaction between sex and group was significant (p=0.036) suggesting that the increase in plasma sPRR levels in T2D patients is greater in women than men. Multiple regression analysis, adjusted by age, WHR, and groups indicated a significant association between plasma sPRR levels and T2D status in women (P<0.0001) but not men. Our data indicate that plasma sPRR levels are associated with T2D in women but not in men, and that this effect is independent of obesity. The results indicate that plasma sPRR may serve as a biomarker of RAS activation allowing for a better understanding of the association between obesity, T2D, and its complications. Supported in part by 1 U54 GM104940 from the General Medical Sciences of the National Institutes of Health, which funds the Louisiana Clinical and Translational Science Center (LA CiTS).
We recently discovered that female rats display lower proximal tubule (PT) Na reabsorption compared to males, i.e. Na/H exchanger isoform 3 relocalized to the base of the microvilli, less Na-Pi cotransporter isoform 2, increased renal clearance of lithium and more rapid excretion of a saline challenge. In the distal tubule we detected higher levels of Na-CI- cotransporter (NCC), its activation by phosphorylation (NCC-P) and evidence for epithelial Na channel (ENaC) activation in females vs. males. These findings suggest that lower PT Na reabsorption drives a volume load dependent activation of NCC and ENaC. ENaC activation drives potassium (K) secretion in principal cells. Dietary K rapidly reduces NCC-P, shifting Na downstream for reabsorption by ENaC which drives K secretion. Based on these findings, this study aimed to test the hypothesis that females have a lower plasma K set point than males. Female and male Sprague Dawley rats (n=6) were fasted overnight (16 hr) with free access to water, and then fed a 3 hr meal containing either 0%K or 2%K. Overnight urine volumes (urinary metabolic cages), Na and aldosterone production were determined. Food consumed during the 3 hr meal was similar in all four groups. After the 0%K meal, supporting our hypothesis, plasma K, Na and osmolality were all significantly lower in females vs. males: [K]: 3.9±0.2 vs. 4.5±0.1 mM, [Na]: 133±1 vs. 135±1 mM, Osm: 296±3 vs. 302±2 mOsm. Differences appeared independent of the estrous cycle (vaginal smear). Upon the 2%K meal, plasma K increased in both sexes: to 4.6±0.1 mM in females and to 5.6±0.4 mM in males, associated with 7 fold increases in urinary K (mmol/3 hr): from 0.12±0.3 to 0.99±0.1 in females, and from 0.10±0.3 to 0.7±0.2 in males. Plasma Na (mM) was unchanged in both sexes after meals, but urinary Na (mmol/3hr) increased in females from 0.3±0.1 to 0.5±0.1, evidence for lower NCC activation. In response to the K rich meal, NCC total protein decreased 20% in females, not males, and NCC-P decreased 50% in both females and males (p=0.05). In summary, lower baseline plasma K set point is unmasked in females after an overnight fast. Despite lower plasma K, the kaliuretic response to a K rich meal are indistinguishable between sexes. Females actively adapt to maintain their plasma K set point at a lower level than males, suggesting that they could be protected from hyperkalemia. NIH DK 083785.

7.2 LONG-TERM ESTROGEN TREATMENT INCREASES RENAL TUBULAR CASTS AND TGFβ IN AGED OVARIECTOMIZED LONG EVANS RATS

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Our lab previously reported that long-term (80 days) estradiol (E2) treatment initiated immediately after midlife ovariectomy (OVX) in Long Evans rats increases proteinuria and renal hypertension compared to short-term (40 days) E2 treatment. Therefore, the beneficial effects of E2 on renal health may be dependent on treatment duration. The goal of the current study was to determine why long-term but not short-term E2 was detrimental to the kidney. We hypothesized that long-term E2 had a negative impact on glomerular filtration, glomerulosclerosis, renal fibrosis, and TGFβ expression. Urine, serum, and formalin-fixed renal sections were obtained from ovariectomized Long Evans retired breeders that received an implant of E2 or vehicle (veh) for 40 days followed by a new treatment for an additional 40 days (groups: veh+veh, E2+ E2, E2+veh). Estimated glomerular filtration rate (eGFR) was measured by creatinine clearance and renal pathology was assessed through histological staining. Neither short-term nor long-term E2 impacted eGFR as compared to vehicle controls (veh+veh: 0.36 ± 0.04 ml/min/kg weight, E2+veh: 0.39 ± 0.05, E2+ E2: 0.36 ± 0.04; p=0.87). There was no difference in the glomerulosclerosis index (GSI) as assessed by Periodic acid-Schiff staining (veh+veh: 1.76 ± 0.12, E2+veh: 1.79 ± 0.13; E2+ E2: 1.83 ± 0.15; p=0.04). Renal interstitial collagen formation assessed by Gomori’s trichrome staining also revealed no changes (veh+veh: 9.20 ± 0.34%, E2+veh: 8.60 ± 0.47%, E2+E2: 9.50 ± 0.85%, p=0.50). Interestingly, the percentage of tubular casts was significantly decreased by short-term E2 and increased in the long-term E2 group (veh+veh: 3.73 ± 0.93%, E2+veh: 1.29 ± 0.23%, E2+E2: 1.76 ± 0.06%, p=0.01). Additional immunohistochemistry studies revealed up-regulation of renal cortical transforming growth factor β (TGFβ) by long-term E2 treatment (veh+veh: 10.20 ± 0.58%, E2+veh: 10.49 ± 1.09%, E2+E2: 14.26 ± 0.32%). These results indicate that long-term E2 treatment may promote an increase in TGFβ and associated renal injury in the aging ovariectomized Long Evans rat. Our findings highlight the importance of understanding how E2 treatment duration influences post-menopausal renal health. Research supported by NIH grant 4R00HL103974 awarded to S.J.L.

7.3 ALTERATIONS IN 20-HETE PRODUCTION CONTRIBUTE TO END ORGAN DAMAGE IN DAHL’S RATS

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We previously reported that treatment of Dahl’s rats with either angiotensin II (AngII) or the angiotensin receptor blocker (ARB) losartan partially prevented the development of renal injury. The aim of this study was to further characterize the role of the vasoconstrictor 20-hydroxyeicosanoid, 20-HETE, in mediating kidney injury. Dahl’s rats were treated with AngII, losartan or saline and renal expression of 20-HETE and its metabolism was analyzed by LC-MS/MS. Statistical analysis was performed using R software. 20-HETE expression and proteinuria were significantly higher in Dahl’s rats compared to healthy Sprague Dawley rats. Administration of losartan resulted in a marked reduction of 20-HETE expression and proteinuria. These data support a role for 20-HETE in mediating AngII-induced renal injury.
FEMALE MICE

WITHDRAWN

SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

REPERFUSION INJURY IN MALE AND FEMALE

APOPTOTIC CELL DEATH IN RENAL ISCHEMIA-

7.4

APOPTOTIC CELL DEATH IN RENAL ISCHEMIA-

REFUSION INJURY IN MALE AND FEMALE

SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

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Males develop a greater extent of ischemia-reperfusion (IR) induced injury than females. Recent studies have shown that renal IR injury is primarily mediated by necrosis in male mice, and pilot studies in our lab indicate a sex difference in renal cell death in SHR with females having more apoptotic cell death than males under control conditions. Based on the potential protective role of apoptosis vs. necrosis, the goal of this study was to test the hypothesis that female SHR exhibit greater apoptotic cell death following renal IR compared to male. 13 week old male and female SHR were studied: control and 45 minute warm bilateral renal ischemia followed by reperfusion. Apoptotic cells were detected by TUNEL assay and renal injury was measured by histological analysis (H&E) and kidney function (UNaV).

7.5

WITHDRAWN

7.6

KIDNEY EPITHELIAL-SPECIFIC KNOCKOUT OF SHP-1 ENHANCES URINARY CONCENTRATION IN FEMALE MICE

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Urinary concentration by the kidney medulla is a primary mechanism to maintain body fluid balance. The transcription factor NFAT5 is essential for urinary concentration, because it activates expression of osmoprotective genes like betaine/glycine transporter and aldose reductase, which are necessary for the kidney medulla to survive and function under hypertonicity, and because it contributes to expression of aquaporin-2, possible aquaporin-1, and urea transporter. Despite the importance of NFAT5 in urinary concentration, how NFAT5 is regulated in the kidney medulla remains largely unknown. Through screening a genome-wide siRNA library against phosphatases in HEK293 cells, we previously identified the protein tyrosine phosphatase SHP-1 as a negative regulator of NFAT5. The viable mice with spontaneous mutation of SHP-1 (m6ev) express ~30% of SHP-1 protein in the kidney inner medulla as compared with wild type. As the first step to test whether SHP-1 also regulates NFAT5 activity in the kidney inner medulla, we measured urinary osmolality of the mutant and wild type mice under ad lib water and food intake and found that urinary osmolality of mutants is 29% higher than that of wild type (p<0.05, n=4, males and females are roughly equal). We then generated mice with the kidney epithelium-specific deletion of SHP-1, and found that females have significantly higher (p<0.05) urinary osmolality compared to the male knockouts (69% higher than that of the control mice, which express Cre recombinase alone (p<0.05, 3 males and 3 females in each group). To determine whether the knockouts have increased urinary concentration and whether gender influences the concentration ability, we controlled water and food intake with gel diets under both water replete and water-restricted (reduced by 80%) conditions. There is no significant difference in urinary osmolality under the water replete condition among the groups. However, the female knockout elevates urinary osmolality more than the female controls in the kidney function depressed mice (147% vs 74%, p<0.05, n=6), whereas it has no significant difference in the male counterparts. We conclude that the kidney epithelium-specific knockout of SHP-1 increases urinary concentration only in female mice.

7.7

PROGESTERONE SYNERGIZES ESTRADIOL-INDUCED NATRIUREESIS IN RESPONSE TO INCREASED DIETARY SODIUM INTAKE.

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Hypertension and renal diseases are more prevalent in postmenopausal women compared to premenopause, suggesting a central role for ovarian hormones in cardiovascular and renal protection. The renal endothelin (ET) system, which plays a critical role in Na regulation and blood pressure control, appears to function differently between the sexes. Recent preliminary data from our laboratory showed that estradiol (E2) increases ET-1 gene expression in inner-medullary collecting duct cells. However, the role of ovarian hormones in regulating renal ET control of Na balance is not known. Therefore, we determined the effects of supplementation with E2 and/or progesterone (P) on renal Na handling and urinary ET levels in O VX Sprague-Dawley rats on normal NaCl (NS) and high NaCl (HS) diets. Females were ovariectomized (OVX) and implanted with 21-day controlled release pellets containing 0.35 mg E2 (OVX+E2), 25 mg P (OVX+P), both (OVX+E2+P) or placebo (OVX). On NS (0.4% NaCl) diet, OVX+E2 and OVX+E2+P showed significant increases in urinary Na excretion (UNaV) compared to OVX rats (3.5±0.3 and 4.0±0.2 vs 2.1±0.2 μmol/min/kg, respectively, p<0.05), whereas P supplementation of OVX rats did not affect UNaV. Interestingly, urinary ET-1 excretion was significantly enhanced by 3 fold in OVX+E2+P rats compared to OVX rats, but was not affected by E2 or P alone in OVX rats fed NS. After 24 hrs of HS diet, UNaV was enhanced by 3.5 fold in OVX and OVX+E2+P, 6 fold in OVX+E2, and 9 fold in OVX+E2+P rats. Urine flow followed the same pattern as UNaV. No significant changes were detected in urinary ET-1 with HS except in OVX+E2 rats where it was doubled. These data indicate that P synergizes the effect of E2 to facilitate the natriuretic and diuretic response to HS. The renal ET-1 system and possibly other natriuretic pathways appear to be playing a role in the synergistic effects of P on renal Na handling. These studies were funded by NIH grants P01 HL69999 and P01 HL95499.

7.8

WITHDRAWN

7.9

HIGH SALT ALTERS CELLULAR TRANSCRIPTIONAL AL MICIEU AND HUMAN ANGIOTENSINOGEN EXPRESSION IN A GENDER-DEPENDENT MANNER: AN EFFECT EXACERBATED BY A RISK HAPLOTYPE

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Angiotensinogen is the substrate for the entire RAS cascade and polymorphisms leading to its overexpression are linked to hypertension. Studies have shown that SNPs in the promoter of the hAGT gene are associated with hypertension. Important-ly, these SNPs can further modulate the gene of interest in various physiologi-cal/environmental settings like gender or high-sodium diet. In this regard, the human angiotensinogen gene (hAGT) gene has polymorphisms in its 2.5Kb promoter that form two haplotypes (Hap block) -6A/G (-6A/G) in 5'-flanking region elevates angiotensinogen expression, whereas Hap -6G/-217G (-6G/-217G) reduces cardiovascular risk. Therefore, the goal of this study was to determine whether gender impacts the association of these SNPs in the angiotensinogen gene and how this association is influenced by high-sodium diet. Among white females, male individuals harbor more copies of the angiotensinogen gene -6G/-217G haplotype than females (p<0.01). However, in white males, the distribution of the angiotensinogen gene -6G/-217G haplotype does not differ between genders (p=0.33). Thus, the gender susceptibility to hypertension may be mediated through the angiotensinogen gene -6G/-217G haplotype, and the effects of high-sodium diet on angiotensinogen expression may be gender-dependent. These findings may have implications for understanding how sex differences in angiotensinogen expression could impact disease risk. The study was funded by the American Heart Association grant 10PRE4230011N.
Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects women during their reproductive age, and is associated with hyperandrogenemia, increased blood pressure (BP) and increased cardiovascular risk. Several studies have shown that elevated androgens increase cytochrome P450 (CYP) 4A expression and 20-hydroxytestosterone, a cytochrome P450 1B1-derived metabolite of testosterone (20-HETE) syntheses in rats. In particular, evidence from our laboratory, indicates that CYP4A2 expression is elevated in the renal vascular bed of hyperandrogenemic female Sprague-Dawley rats. Dahl Salt Sensitive (DS) rats have a deficiency in CYP4A α-hydroxylation/20-HETE system in the kidneys compared with either Dahl Salt Resistant (DR) or SS,5BNhαα5th-4th1st strain. Thus if an increase in 20-HETE, mediated via CYP4A, is necessary for the increase in BP in HAF rats, then DS rats that lack CYP4A may be resistant to hyperandrogenemic increases in BP. In the present study we tested the hypothesis that BP in DS rats maintained on low-salt diet would be unresponsive to hyperandrogenemia. Four weeks old female DR, DS (from HAF rats) and SS,5BNhαα5th-4th1st rats were implanted with dihydrotestosterone (DHT; 7.5mg/90d) or placebo pellets (n=6-8/group). At 14 weeks of age, radiotelemetry transmitters were implanted, and after two weeks recovery, mean arterial pressure (MAP) was measured for 5 days. DHT significantly increased MAP in female SR rats (placebo: 84±8 vs. DHT: 95±1 mmHg, p<0.05) and female SS,5BNhαα5th-4th1st rats (placebo: 104±1 vs. DHT: 130±6 mmHg, p<0.005). In contrast, DHT did not change MAP in female DS rats (placebo: 160±4 vs. DHT: 153±4 mmHg, p=NS). Interestingly, MAP in female SR was lower than in SS,5BNhαα5th-4th1st females, and with DHT there was a more robust increase in MAP in female SS,5BNhαα5th-4th1st than in female SR rats. In addition, placebo female DS rats, despite the low salt diet, had significantly higher MAP than the other groups (p<0.001). These data suggest that an active CYP4A α-hydroxylation/20-HETE system is necessary for hyperandrogenemia to increase BP in our HAF model. The data also suggest alternative treatments, namely 20-HETE synthesis inhibition, to attenuate elevated BP in women with PCOS. Supported by NIH-R01HL60072, P01HL51971 (JFP), 1P40ST840015 (ROM).

7.12 MULTIPLE ESTROGEN RECEPTOR SUBTYPES SELECTIVELY INFLUENCE FLUID INTAKE IN FEMALE RATS
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Estriol (E2) decreases fluid intake in female rats. Although this has been known for decades, the underlying mechanisms are still unknown. Our understanding of these mechanisms is complicated by the existence of five identified estrogen receptor (ER) subtypes including the classically recognized ERα and ERβ proteins and more recently discovered membrane-associated receptors: GPER-1, ERX and GqαmER. In addition to the complex nature of the movement of multiple subtypes, these receptors can act through multiple mechanisms (surface receptors or transcription factors) and can engage a variety of intracellular signaling pathways. In this series of experiments, we first tested the hypothesis that activation of membrane-associated ERs decreases fluid intake in ovariectomized rats. This hypothesis was supported by the observation that ERα, β, and GPER-1 (p<0.05). Furthermore, analysis of drinking microstructure revealed differences in the underlying behavioral differences in the respective effects of ERα and ERβ on water and saline intakes. This analysis found that estrogen-mediated decrease in water intake was a function of a decrease in burst number (p < 0.05), unlike the change in burst size that was underlying the ERβ-mediated change in intake. These findings demonstrate that specific ERs selectively influence water intake and saline intake through specific mechanisms in the female rat.

7.13 6B-HYDROXYTESTOSTERONE, A CYTOCHROME P450 1B1-DERIVED METABOLITE OF TESTOSTERONE, PLAYS AN IMPORTANT ROLE IN RENAL DYSFUNCTION ASSOCIATED WITH ANGIOTENSIN II-MEDIATED HYPERTENSION IN MALE MICE
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Angiotensin II (ANGII) is a critical regulator of body fluid homeostasis. Drinking after injection of ANGII has been an important model of the behavioral regulation of fluid homeostasis, and studying ANGII-induced drinking has led to findings that extend to the regulation of blood pressure. Although acute ANGII potently stimulates drinking, repeated injections of ANGII have bivalent effects; daily injections of ANGII sensitize responses, but more acute repeated injections cause a transient desensitization. This desensitization reduces water intake stimulated by ANGII without reducing the hypertensive effect of the peptide. Moreover, we found sex differences in the desensitizing potency of ANGII; females did not show the desensitization that is reliably observable in male rats. Preliminary studies suggest that this resistance to desensitization is not affected by ovarian hormones, and ongoing studies are testing the importance of testicular hormones. Additional studies found that the bivalent effects of ANGII can counter each other. Specifically, we found that the sensitization of intake initially occurring after daily ANGII administration is not induced if daily injections are given with the timing of a desensitizing treatment, suggesting that desensitization can ameliorate sensitization. Given the highly conserved sex differences in blood pressure, and the role that ANGII-sensitization may play in the development of hypertension, it is tempting to speculate that properly timed increases in ANGII may help thwart sensitization and, therefore, could be used to prevent or treat hypertension. This would be a radical departure from current anti-hypertensive drugs that act by reducing angiotensinergic tone. Funding provided by NIH HL091911.

8.3 ADIPOKINES, OBESITY, AND SEX: IMPLICATIONS FOR CARDIOVASCULAR FUNCTION
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In addition to the storage of lipids, adipose tissue contributes to energy homeostasis by producing multiple adipokines, such as leptin and nesfatin-1, which regulate food intake and energy expenditure. Plasma levels of these adipokines, which inhibit appetite, increase as a function of adipocyte mass, thus decreasing food intake during times of energy excess. In addition to modulating energy intake, these adipokines also impact cardiovascular function, particularly through activation of the sympathetic nervous system. Like leptin, nesfatin-1 interacts with the central melanocortin system to exert its hypertensive effects. Interestingly, melanocortin neurons are heavily influenced by sex hormones, particularly estrogen, which regulates the responsiveness and activity of these neurons. The functional implication of this observation is that females may respond to the hypertensive effects of adipokines, like nesfatin-1, differently than males. We previously reported that male rats exhibit significant, dose-related increases in blood pressure following injection of nesfatin-1 into the lateral cerebroventricle, and that this effect could be blocked by pretreatment with a melanocortin receptor antagonist. In contrast, the hypertensive effect of nesfatin-1 in females appears to be dependent upon sex hormone levels, as the response to nesfatin-1 varied according to stage of the estrous cycle. We propose that this sex-related difference in the hypertensive effect of nesfatin-1 is due to the modulatory activity of estrogen on nesfatin-1-responsive melanocortin neurons, and that loss of estrogen, as observed in menopause, will lead to enhanced nesfatin-1 signaling and hypertension.

8.0 NEURO CONTROL OF CARDIOVASCULAR, RENAL AND METABOLIC DISEASES: IMPACT OF GENDER AND SEX

8.1 AUTONOMIC REGULATION OF BLOOD PRESSURE IN ADULT HUMANS: EFFECTS OF SEX & AGE
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Over the past 10 plus years my colleagues and I have made physiological measurements of the determinants of mean arterial blood pressure (MAP) in normotensive younger and older men and women. These measurements include muscle sympathetic nerve activity (MSNA), cardiac output (CO), and total peripheral resistance (TPR). In younger subjects of both sexes there is no relationship between MSNA and blood pressure. However, the relationships between MSNA, CO and TPR show divergent patterns. In young women there is no relationship between MSNA and TPR (or CO) largely because β-adrenergic vasodilator mechanisms offset α-adrenergic vasoconstriction. In young men there is a direct relationship between MSNA and TPR and no relationship with blood pressure because CO is lower in those with higher MSNA. In older men these relationships are less clear cut due to age related alterations in peripheral vasodilator function. In older women there is a loss of tonic β-adrenergic vasodilation and the relationship between MSNA and TPR seen in men emerges. These observations raise questions about sex specific causes and mechanisms of hypertension in human aging. Supported by HL83947.

8.2 SEX DIFFERENCES IN DESSENSITIZATION OF THE DIPSOGENIC EFFECT OF ANGIOTENSIN II
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11.2 SEX DIFFERENCES IN CARDIOVASCULAR AND METABOLIC RISKS DUE TO EARLY LIFE STRESS

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Clinical studies indicate that adults exposed to adverse childhood experiences or early life stress (ELS) develop several risk factors for cardiovascular and metabolic disease including higher systolic blood pressure, increased BMI, and clustering of metabolic risk biomarkers. Maternal separation is an established model of ELS during the early postnatal life in rodents ("first hit"). This procedure induces heightened reactivity to stressors later in life ("second hit"), altering the normal physiological responses. Despite similar blood pressure and heart rate under baseline conditions, ELS enhances the angiotensin II (AngII)-induced hypertension in male and female rats. However, we found that impaired renal function and imbalanced plasma sex hormones were present in male but not female rats exposed to ELS. Additionally, ex-vivo studies revealed that AngII-mediated responsiveness in vasculature is exaggerated in male rats only. Both male and female rats demonstrate reduced baroreflex sensitivity; however, only male rats display signs of increased sympathetic outflow to the kidney including lower glomerular filtration rate which is normalized following bilateral renal denervation. In order to investigate the ELS-induced metabolic disease risk, we challenged maternally separated rodents with a chronic high fat diet (HFD, 60% kcal from fat). We found that females display a much more exaggerated rise in plasma insulin and leptin levels, impaired glucose tolerance and increased visceral fat mass compared to males. Taken together, these data indicate that ELS induces a sex-specific risk to develop chronic diseases that is dependent on the type of stressor. References: Loria AS, Yamamoto T, Pollock DM, Pollock JS. Early Life Stress induces renal dysfunction in adult male but not female rats. Am J. Physiol Regul Integr Comp Physiol, 15304(2):B121. Murphy MO, Evans L, Mahanes T, Loria AS. Impaired baroreflex response correlates with reduced conduit vessel contractility in female maternally separated rats and reveals α-adrenergic receptor dysfunction. FASEB J, 29, 9681.11.

11.3 MATERNAL UNDERNUTRITION SIGNIFICANTLY IMPACTS OVARIAN FOLLICLE NUMBER AND INCREASES OVARIAN OxIDATIVE STRESS IN ADULT RAT OFFSPRING

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There is now considerable epidemiological and experimental evidence indicating that early life environmental signals, including nutrition, affect development. A relationship exists between the periconceptional, fetal and early infant phases of life and the subsequent development of chronic diseases including obesity and type 2 diabetes. This relationship, the “developmental origins of health and disease” (DOHaD), suggests that the embryo/fetal/neonate makes adaptations in response to early life cues, resulting in adjustments in homeostatic systems that are maladaptive in postnatal life, leading to an increased risk of chronic disease and/or the inheritance of risk factors across generations. Reproductive maturation and function is similarly influenced by early life events. This should not be surprising, since the primordial germ cell pool is established during embryonic life and is thus vulnerable to early life events. In both males and females, early life nutritional adversity accelerates pubertal onset. In males, prenatal events have been shown to modify sperm counts and fertility, and in females modify ovarian function. In females, a multitude of “modifying” cues inducing developmental adaptations have been identified that result in a decline in ovarian follicular reserve, changes in ovulation rates and altered age at onset of puberty. We have shown that fetal growth restriction induced by maternal caloric restriction, results in a premature loss of adult ovarian follicles, underpinned by an increase in apoptosis and increased ovarian oxidative stress levels. Critically, low birth weight offspring show impaired ovarian follicle function already as neonates, and demonstrate a loss of follicles and reproductive cycle impairment early in young adulthood, well before full adult reproductive maturity. Many pathways have been suggested to underpin these associations, where studies have investigated the maternal-fetal-placental relationship as well as events occurring in the early postnatal environment in modulating pubertal onset and ovarian function. But the underlying ovarian mechanisms regulating the relationship between the early life developmental environment and postnatal reproductive dysfunction remain unclear.

12.0 NON-REPRODUCTIVE EFFECTS OF SEX HORMONES AND RECEPTORS-B

12.1 ANDROGEN EFFECTS ON ENDOTHELIAL FUNCTION IN WOMEN IN POLYCYSTIC OVARY SYNDROME

Nina Sanchenfeld1


Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy in young women, affecting 6-10 % of women of reproductive age. Our studies focus on humans, and address the most common PCOS phenotype, androgen excess (AE-PCOS). AE-PCOS is associated with insulin resistance and elevated endothelin-1 (ET-1) levels, indicating poor endothelial function. Endothelin-1 binds two receptor subtypes, endothelin A (ETaR) and endothelin B (ETbR). To control and isolate androgen effects on microvascular circulation in humans, we administer a gonadotropin-releasing hormone antagonist for 7-11 days in obese, otherwise healthy young women and obese, young women with AE-PCOS, adding methyl testosterone on days 8-11. We use cutaneous microdialysis to perfuse ETaR and ETbR blocking agents and use laser Doppler flowmetry to measure cutaneous microcirculatory responsiveness. These combined techniques enable us to examine the interaction of these subtype receptors with androgens on the microcirculation in women with AE-PCOS using mildly invasive methods, that are well tolerated by humans. With this model of microcirculation, we have demonstrated that ETaR mediates vasoconstriction and ETbR mediates vasodilation in women with and without AE-PCOS, but vasodilation is blunted in women. Only ETaR are expressed in the endothelium, so our data suggest peripheral microvascular endothelial dysfunction in AE-PCOS. We have also demonstrated that the androgenic milieu is a key element to this endothelial dysfunction, and that the androgen effects on the endothelium are mediated by the ETaR in AE-PCOS. These findings illustrate an interaction between androgens and the endothelin system on cardiovascular function and identify a potential new target for treatment in women with AE-PCOS.

12.2 MECHANISMS INVOLVED IN CARDIOPROTECTION IN FEMALES MECHANISMS INVOLVED IN CARDIOPROTECTION IN FEMALES: ROLE OF ESTROGEN AND ESTROGEN RECEPTORS (ERS)

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Our goal was to gain insight into the role of estrogen and ERs in reducing ischemia reperfusion (IR) injury and hypertrophy in females. To examine the role of plasma membrane bound ERs, we used a non-nuclear selective ER modulator (estrogen-dendrimer conjugate, EDC). We treated ovarioctomized WT mice with EDC, estradiol or dendrimer control using osmotic minipumps. Using a Langendorff perfused heart model of IR we found that EDC reduced IR injury. We studied cardiac-specific ERα-knockout (ERα-KO) mice, and found that EDC treatment significantly decreased infarct size and improved functional recovery compared to the vehicle-treated ERα-KO mice, suggesting that the protection is not mediated by plasma membrane ERαTs. To induce hypertrophy, male and female mice were treated with angiotensin II or saline via osmotic minipumps. At 3 weeks, females showed significantly less cardiac hypertrophy and better cardiac function than males. We also studied female and male mice with oestR -KO and their WT littermates. The reduction in hypertrophy observed in the WT females was not altered by ablation of ERα. We also evaluated differences in long non coding RNA and miRNA between males and females that might contribute to these sex differences. Our findings show that females exhibit significantly less angiotensin II-induced hypertrophy than males at 3 weeks of treatment and the reduction in hypertrophy in females is retained in hearts lacking ERα, suggesting that ERα is not required for either the reduction in hypertrophy or cardioprotection. Funded by NIH intramural program.

12.3 SEX AND SEX HORMONE EFFECTS IN CARDIOVASCULAR PATHOPHYSIOLOGY

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Increased circulating volume, pressure overload and mineralocorticoid excess contribute differently to cardiovascular pathology in women and men, in male and female rodents. In order to understand sex-specific mechanisms, underlying protection or maladaptation in females and males, we analyse different stressors like exercise, pressure overload and biochemical stressors on heart and lung function in both sexes. We are using animal models and cell culture models of hemodynamic and neurohormonal stress as well as animal models with modified sex hormone receptor expression- ER alpha and ER beta cell specific knock-outs and overexpression. We are using animal models and cell culture models of hemodynamic and neurohormonal stress as well as animal models with modified sex hormone receptor expression- ER alpha and ER beta cell specific knock-outs and overexpression. We studied the interaction of the stressors with sex and sex hormone effects. Exercise led to physiological myocardial hypertrophy. Females develop more pathological myocardial hypertrophy than males with better metabolic adaptation. Pressure overload and/or mineralocorticoid excess lead to pathological myocardial hypertrophy. Fibrosis, a hallmark of pathological myocardial hypertrophy, is more prominent in males than in females. Estrogen is protective in females but may be harmful in males in some conditions. Estrogen receptor alpha and beta activation have different effects on fibrosis and metabolism in females and males. Female animals under stress maintain energy metabolism better than males and have more favourable Calcium signalling. Women with aortic stenosis develop less exsudant myocardial hypertrophy with less fibrosis than men and this is associated with better myocardial survival. Adaptation to cardiovascular stress and end organ damage are sex specific and sex specific approaches to treatment may lead to further benefit.

13.0 RESPIRATORY

13.1 SEX DIFFERENCES IN DIET AND INHALED OZONE (O3) INDUCED METABOLIC IMPAIRMENT

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Diet and environmental stressors, including inhaled pollutants, have been implicated in the development and progression of metabolic diseases. Since metabolic processes of males and females are likely influenced by sex hormones, we hypothesized that high fat versus high fructose diet will produce different metabolic impact in each sex, and that the injury induced by inhaled O3 as an environmental stressor, will be influenced by sex and dietary interventions. Male and female Brown Norway rats were fed either normal, high fructose or high fat diet beginning 1 month of age for 3 months. At 4th months they were exposed to air or O3 acutely (0.8 ppm) for 5 hours. The body fat composition and glucose tolerance (GT) were measured prior to O3 exposure. GT was also examined immediately after air or O3 exposure (n=10). Pulmonary toxicity and systemic metabolic changes were examined immediately after O3 exposure in a separate group of rats (n=10). Compared to males, female BN rats fed a normal diet had relatively greater body fat %, higher levels of serum triglycerides, cholesterol and glucose, and lower leptin and insulin. At baseline, male rats fed high fat diet had increased body fat but not females. GT did not differ between males and females but high fat diet induced a small degree of glucose intolerance in both males and females. High fructose but not high fat diet induced marked increases in circulating triglycerides in both males and females. High fat but not high fructose diet increased circulating leptin in both males and females. O3 exposure increased lung injury as determined by lavage fluid protein and albumin analysis in females fed all diets but only in high fat diet males. Both males and females had >10% of cells as eosinophils in the lung lavage fluid. No specific differences in BALT inflammatory cells were noted between air and O3 exposed rats of either sex on any diet, however, both diets decreased baseline levels of neutrophils in each sex. O3 induced glucose intolerance in both sex regardless of diet. O3 also increased circulating leptin (females=males) regardless of diet. No O3 effects occurred in circulating cholesterol or triglycerides in either sex. These data provide the evidence that although dietary inter-ventions did not have major sex specific effects, female BN rats are more susceptible to O3-induced pulmonary and metabolic effects. (Does not reflect USEPA policy).

13.2 LUNG ANTIOXIDANT LEVELS IN NEONATAL RATS AND RESPONSE TO AIR POLLUTION: INFLUENCE OF SEX AND STRAIN

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Emissions from biomass combustion in rudimentary cookstoves (CS) are causally linked with higher incidence of respiratory infections, especially in women and chil-dren. As with other air pollutants, oxidative insults are believed to play a major role in the etiology of CS-related lung pathologies. We are seeking to develop rodent models of respiratory infection for assessment of health benefits derived from use of more ef-ficient cookstoves. Previous studies indicated that FIS rats exhibited a reduced susceptibility to influenza virus, and showed that acutely, FIS pups developed minimal lung changes. We have also observed altered (O3)-induced effects in adult FIS rats and found that they exhibited the least change compared to Sprague-Dawley (SD) or Wistar (W) rats. This pilot study evaluates lung antioxidant levels in air- and O3-exposed neonatal FIS, SD, and W pups to determine which strain/race was most susceptible to early life oxidative insult. Smaller litters in time-pregnant FIS pups dictated uneven group sizes, FIS were 30-40% smaller than SD or W pups. Subsets of females (F) and male (M) 14- and 21-d-old (pre- and weaning) pups were exposed to air, 0.5, or 1.0 ppm O3 x2h. In controls, body wt increased >60% between 14-21 d. At weaning, no sex differences in body wt or lung antioxidants were apparent within strains. Except for increased uric acid (UA) in 14-d F W rats, no age/stain differences were apparent for lung UA, total protein, or glutatione (GSH) peroxidase/reductase (per gm of wet lung wt). At 14-d, FIS rats had 6-22% more GSH than SD or W rats, respectively. GT changed in all strains at 14-21 d. Lung SOD decreased in all strains from 14-21 d, with FIS rats having 25-35% more than SD or W rats. Post-O3, F 14-d rats of all strains had minor GSH decrements (±20%), while M pups were unchanged. Relatedly, F SD and W rats had decreased GSH peroxidase (30-36%), GSH reductase (15-26%), SOD (13-30%), and UA (22-42%); while levels in F pups were unchanged or increased. M 14-d rats had minimal changes. Conversely, F 21-d pups post-O3 showed minimal change while M pups had increased SOD (25-31%), and SD and W pups had increased GSH peroxidase (18%). In summary, FIS pups appear relatively resistant to lung insult, while neonatal F SD and W rats appear more prone to oxidative effects than M of the same age. We will pursue using non-FIS F pups to evaluate CS emission effects on susceptibility to early life infection. (Abstract does not reflect USEPA policy.).

13.3 ESTRADIOL PREVENTS CARDIO-RESPIRATORY DYSFUNCTIONS INDUCED BY CHRONIC INTERMITTENT HYPOXIA IN FEMALE RATS

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The prevalence of sleep-disordered breathing (SDB) and associated chronic intermittent hypoxia (CIH) increase after menopause in women. Despite evidence showing that hormonal replacement therapy can reduce apnea frequency, the potential pro-ductive roles of sex steroid hormones against the cardio-respiratory dysfunctions in-duced by SDB and CIH are unknown. We tested the hypothesis that estradiol protects female rats against the cardio-respiratory dysfunctions induced by CIH. Sleep-disordered breathing (SDB) and associated chronic intermittent hypoxia (CIH) increase after menopause in women. Despite evidence showing that hormonal replacement therapy can reduce apnea frequency, the potential pro-ductive roles of sex steroid hormones against the cardio-respiratory dysfunctions in-duced by SDB and CIH are unknown. We tested the hypothesis that estradiol protects female rats against the cardio-respiratory dysfunctions induced by CIH. Sleep-disordered breathing (SDB) and associated chronic intermittent hypoxia (CIH) increase after menopause in women. Despite evidence showing that hormonal replacement therapy can reduce apnea frequency, the potential pro-ductive roles of sex steroid hormones against the cardio-respiratory dysfunctions in-duced by SDB and CIH are unknown. We tested the hypothesis that estradiol protects female rats against the cardio-respiratory dysfunctions induced by CIH. Sleep-disordered breathing (SDB) and associated chronic intermittent hypoxia (CIH) increase after menopause in women. Despite evidence showing that hormonal replacement therapy can reduce apnea frequency, the potential pro-ductive roles of sex steroid hormones against the cardio-respiratory dysfunctions in-duced by SDB and CIH are unknown. We tested the hypothesis that estradiol protects female rats against the cardio-respiratory dysfunctions induced by CIH.
capnia were lower. Furthermore, these values were similar when comparing OVX-
E$_2$-CH to sham-RA rats, likely indicating that the estradiol treatment remained in a
physiological range. We conclude that estradiol efficiently prevents the cardio-respi-
datory dysfunctions induced by CHI in female rats. Funded by CIHR (MOP-102715).

13.4
POTENTIAL ROLE OF ESTROGEN IN 15-HYDRO-
XIECOSATETRANOIC ACID PRODUCTION AND
ACTIVITY IN HUMAN PULMONARY ARTERY ENDO-
THELIAL CELLS
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Pulmonary arterial hypertension (PAH) has a consistently higher risk occurrence in
women compared to men. Mechanisms to explain the female predominance are scarce but likely relate to hormonal changes that contribute to the pathogenesis of the
disease. The bioactive lipid anachidonic acid is metabolized to a variety of compounds
that effect pulmonary vascular function. Key enzymes in the biosynthetic pathway of
anachidonic acid are altered by estrogen. Our central hypothesis is that estrogen has a
dual effect to increase 15-lipoxygenase (LO) gene transcription, and phosphorylation
of 5-LO, which together result in increased production of the proliferative compound,
15-hydroxycosatetraenoic acid (HETE). Human pulmonary artery endothelial cells
(HPAEC) from a male donor were incubated with estrogen (17$^1$-estradiol, 1 µM; 18
hrs), 15-LO and 5-LO protein expression increased compared to untreated cells. How-
ever, there was no evidence of 5-HETE production when cells were incubated with
17$^2$-estradiol and analyzed by HPLC. 15-HETE was detected in the HPAECs, based on co-migration and similar retention time of authentic 15-HETE
standard (17.8 min). Others showed that phosphorylation of Ser663 in 5-LO by
ERK1/2 converts the enzyme to an active 15-LO (1). Cell lysates from estrogen-
treated HPAECs were analyzed using the phosphorylated (p)-5-LO (Ser663) antibody.
Expression of p-5-LO increased compared to control cells which supports a role for
this enzyme in 15-HETE production. Functionally, the interaction of estrogen and
the anachidonic acid/LO pathway in endothelial cell proliferation has important
implications in understanding overall mechanisms for the vascular remodeling
changes that occur in PAH. In the H$_2$-thyroidine production assay, both 15-HETE
(1 µM) and estrogen (1 µM) independently increased HEPAC proliferation. More
importantly, when estrogen-treated cells were preincubated with the 15-LO Inhibitor
ERK1/2 inhibitor, FR190244 (1 µM) or the estrogen receptor antagonist, 1
IC$_{50}$2780 (1 µM) proliferation was attenuated. In summary, these studies suggest
a novel mechanism whereby estrogen regulates the anachidonic acid pathway which
may potentially contribute to alterations in vascular function in sex-based diseases like
PAH. Supported by HL093181 and AHA-0151421Z. Reference: Gilbert NC, Ruiz Z,

13.6
EFFECT OF EXERCISE ON RED BLOOD CELLS
VARIABLES IN HIGHLY TRAINED FEMALE
ATHLETES
Dhruva Afdher$^1$

$^1$Physiology, Holy Family Red Crescent Med. Coll., 1, Eskaton Garden Rd., Dhaka,
Bangladesh.
Background: A suboptimal hematological status has often been recorded in athletes
involved in intensive physical activity. A single bout of physical effort and even more
repeated exercise may changes the morphological indices of blood and influence the
erythropoietic process in the bone marrow. Objectives: To assess the basic red blood
cell variables in highly trained female athletes and to compare the results with those
for a control untrained groups. Methods: This was a cross sectional study was con-
dercted in the Department of Physiology, Dhaka Medical College, Dhaka during the
period of July 2005 to June 2006, on sixty apparently healthy female subjects aged 16
to 20 years. Thirty highly trained athletes as experimental group were recruited from
Sultana Kamal Women Complex, whereas thirty non-athletes as control group were
collected from different halls of Dhaka University. Venous blood samples were
drawn from the cubital vein, and the red blood cell count, packed cell volume, hemo-
globin concentration, were measured. The mean corpuscular volume, mean cor-
puscular hemoglobin, mean corpuscular hemoglobin concentration, were determined
by equations. Statistical indices were computed for each group and for each variables.
Statistical analysis was done by unpaired Student’s t test. Results: The experimental
group was found to have lower red blood cell count, packed cell volume, and hemo-
globin (p<0.05) than that the control group. No significant differences were found in
the mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular
hemoglobin concentration. Conclusion: Continuous high intensity sports training over
more than one year decreases basic red blood cell (RBC) variables in female athletes,
this being more pronounced for submaximal sports. Key words: Female athletes, ex-
ercise, RBC, PCV, MCV, MCH, MCHC.

13.7
CONTRIBUTION OF THE NUCLEAR PROGESTER-
ONE RECEPTOR (NPR) TO BREATHING STABILITY
AND HYPERCAPNIC VENTILATORY RESPONSE IN
ADULT MALE MICE
Soften Laouaff$^1$, François Marcouiller$^1$, and Vincent Joseph$^2$

$^1$Pediatric, Univ. Laval/CHU de Quebec, SFA, 10 Rue de l’espiny, Local D0-711,
Quebec, QC, G1L 3L5, Canada.
Progestrone is a potent respiratory stimulant that reduces the frequency of sleep-
disordered breathing and apneas in women. Adult female mice carrying a mutation in
the NPR gene (PRKO mice) have elevated apnea frequency during sleep, showing a
role for NPR in respiratory regulation. So far it remains unknown if NPR has similar
roles in males. Therefore, we tested the hypothesis that NPR contributes to respiratory
regulation and mediates the respiratory effects of progestrone in adult male mice.
Adult PRKO male mice and wild-type controls (WT) were implanted with an osmot-
ic pump delivering vehicle or progestrone (4 mg/kg/day). 7 days after the surgery,
the animals were placed in a whole body plethysmograph to record ventilation, the
frequency of sighs (associated with micro awake) and post-sigh apneas for 4 consec-
tive hours. All parameters were analyzed during sleep (determined by visual exami-
nation of the recordings). Then the animals were exposed to hypercapnia (5% CO$_2$),
hypoxia (12% O$_2$) and hypoxia-hypercapnia (5% CO$_2$ + 12% O$_2$ – 5 min each) to
assess chemoreflex function. PRKO and WT mice treated with vehicle had the same
level of minute ventilation during sleep, but PRKO mice had a slightly higher fre-
quency of sighs than WT mice (29.1 +/- 1.0 vs. 23.9 +/- 0.9 sighs/hour, p<0.0001).
The ventilatory response to hypoxia-hypercapnia was 34% lower in PRKO mice
compared to WT (p<0.016). Progestrone treatment did not change ventilation re-
corded during sleep in WT or in PRKO mice. Progestrone treatment decreased the
frequency of sighs (from 29.1 +/- 1.0 to 24.6 +/- 0.7 sighs/hour, p<0.0006) and in-
creased the frequency of post-sigh apneas (from 8.3 +/- 1.4 to 14.8 +/- 2.3 ap-
neas/hour, p<0.009) in PRKO, but not in WT mice. Contrastingly, progestrone treat-
ment increased the tidal volume response to hypercapnia (+40%, p<0.023) in WT, but
not in PRKO mice. In progestrone treated mice, the ventilatory responses to hyper-
mill pre-tests, young groups ran longer than aged groups (p<0.05). Treadmill test time
was not increased in any SET group. Similar increases in treadmill test time after TM
training occurred in young and aged male mice with respective 1,094+130 and 1,133+138 second increases from pre to post test (p<0.05). In contrast in female mice, increases in treadmill test time with TM training from pre to post were greater in young than aged groups, 1,046+141 and 565+173 seconds, respectively (p<0.05). These findings suggest treadmill exercise training is more effective in attenuating age-
associated reductions in muscle force and cardiorespiratory fitness in male than fe-
nale mice. Funded by NIH R15AR06469.

13.8
CONTRIBUTION TO TREADMILL T RAINING WITH AGING
Sandra Pfister$^1$

$^1$Pharmacology & Toxicology, Med. Coll. of Wisconsin, 8701 Watertown Plank Rd.,
Milwaukee, WI, 53226.
Aging is associated with reductions in muscle strength and cardiovascular fitness that
may be offset with regular exercise training. However, it is unclear if these exercise
adaptations are affected by gender due to factors such as different hormonal and/or
anatomical changes with aging. We tested the hypothesis that aging reduces muscle
function and cardiorespiratory endurance; however, treadmill (TM) training exercise
will halt or reverse these age-associated decreases in muscle mass, strength and fitness in both species. Male and female mice. In vivo plantarflexor maximal force and fatigue (50% of max force after
10 contractions) were measured in young (4 mo. old) and aged (24 mo. old) sedentary
(SED) male and female mice and following 2 wks of TM training (45 min/day, 5
day/wk). Cardiorespiratory adaptations were assessed with pre- and post-maximal
treadmill tests. Maximal muscle force was lower in aged than young SED mice in
both genders (1.5±0.01 g/g body mass for females, respectively, p<0.05). In young groups, TM did
not increase force over SED in either gender. In aged male groups, TM was as-
dressed with 26% higher maximal force than SED mice (p<0.05), but was still lower
than young groups. In contrast in female aged groups, TM was not associated with
significant increases in maximal muscle force over SED (15% increase). Plantar-
flexor fatigue resistance was higher in aged than young SED male mice (50.3 vs.
35.3% of max, respectively, p<0.05) with no age differences in TM groups. In fe-
nale mice there were no differences in fatigue resistance among all groups. In tread-

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capnia and hypoxic-hypercapnia were respectively 44% and 50% higher in WT than in PRKO mice. We conclude that, as previously observed in female mice, npr contributes to the regulation of breathing in males. The effects of progesterone on apnea in PRKO males are probably related to other types of progesterone receptors, or to allopregnalone, the neuroactive metabolite of progesterone. These results highlight the role of npr and endogenous progesterone production on respiratory regulation in males. Funded by CIHR (MOP-102715).

14.0 NEUROCONTROL

14.1 THE IMPORTANT ROLE OF NITRIC OXIDE SYNTHASE IN CONTROLLING MITOCHONDRIAL RESPIRATION OF LARGE CEREBRAL ARTERIES IN FEMALE AND MALE RATS

Bobby Rutka1, Sombrita Dutta2, Prasad Katkadi1, and David Basag1

1Pharmacology, Tulane Univ., 1430 Tulane Ave., SL8683, New Orleans, LA, 70112.

We have found that mitochrondrial oxygen consumption (OCR) is substantially greater in large cerebral arteries in female compared to male rats. However, the underlying mechanisms underlying this sex-based difference have never been fully determined in intact cerebral arteries. Due to higher nitric oxide synthase (NOS) levels in female compared to male cerebral arteries, we tested the hypothesis that differences in NOS signaling mechanisms contribute to sex-based differences in mitochondrial respiration. The Seahorse XF24 analyzer was used to examine the mitochondrial OCR (μM/min/μg protein) in isolated, large cerebral arteries (middle cerebral artery, circle of Willis, and basilar arteries from male and female Sprague-Dawley rats in the absence and presence of the NOS inhibitor L-NAMe. Western blots were used to determine both phosphorylated and total endothelial (eNOS) and neuronal NOS (nNOS). The components of mitochondrial respiration in arteries in the absence of L-NAMe (vehicle) normalized to protein levels (μM/min/μg protein) including basal respiration (0.69 ± 0.152), ATP production (3 ± 0.53), proton leak (63.6 ± 8.5), maximal respiration (147.2 ± 21.6), and spare respiratory capacity (~2.3 fold higher in female MCA compared to males (1µM SNP: Females 21.2 ± 6.6, 62.8 ± 16.4, 26 ± 7.3, respectively). Treatment with 100 μM L-NAMe resulted in an increase over vehicle values in the OCR of all groups which was significant for all components of mitochondrial respiration in the male group: basal respiration (98.7 ± 8.8), ATP production (48.6 ± 8.6), proton leak (43.2 ± 11.7), maximal respiration (117.7 ± 16.7), and spare capacity (85.9 ± 9.7). However, L-NAMe treatment in the female group caused a significant increase only in maximal respiration and spare capacity (22.4 ± 2.8 and 125.6 ± 20.2, respectively) compared with vehicle. The ratios of phosphorylated eNOS and total eNOS and phosphorylated nNOS and total nNOS were significantly higher in the female (2.2 ± 0.6%, 1.2 ± 0.2%, respectively) compared with the male arteries (0.88 ± 0.2%, 0.5 ± 0.2%, respectively). Thus, NOS inhibition enhanced mitochondrial respiration in cerebral arteries from male and female rats but the relative effects of NOS inhibition were much greater in male than female arteries. Our findings support the concept that sex differences in mitochondrial respiration in cerebral arteries are in part due to involvement of NOS signaling pathways.

14.2 SEX DIFFERENCES IN THE CEREBRAL VASCULAR FUNCTION AND K CHANNEL ROLE

Malikajura Pabbidi1

1Pharmacology, UMMC, N. State St., Jackson, MS, 39216.

Cerebrovascular incidence rate is lower in adult females compared to adult males but the role of vascular function and K channel is not clear. Using a combination of vascular and electrophysiological approaches we explored the hypothesis that sex differences in the cerebral vascular function in adult Sprague-Dawley (SD) rats is associated with differential K channel function in the vascular smooth muscle cells (VSMCs). The diameter of female middle cerebral arteries (MCAs) increased with increase in the lumen pressure from 40 to 140 mmHg in 20 mmHg steps, whereas the diameter of males decreased in male MCAs (p = 0.05). Eta males (16 ± 6). Males (25 ± 4, p = 0.05, n = 8). Female MCAs have ~1.76 fold lower diameter at 40 mmHg compared to age matched males in the presence of calcium (Fe males 81 ± 5, Males 143 ± 13 μM, p < 0.05). In contrast, passive dilation was similar (~2 Calcium, 2mM EGTA) (Females 168 ± 12, Males 167 ± 10 μM, n = 6). Percent myogenic tone (%MT) (calculated from active and passive diameters) is ~3.4 fold higher in females compared to male counterparts (%MT at 40 mmHg for females (51 ± 6, males (55 ± 5, n = 8, p = 0.05). Endothelin-independent (Sodium nitro prusside (SNP)) relaxation was ~2.5 fold higher in females compared to males (1μM SNP: females 88 ± 10%, males (90 ± 5 %, n = 3 - 5, p < 0.05). Spontaneous transient outward currents (STOC) that represent BK channel function are ~1.73 fold higher in VSMCs isolated from female SD rats compared to males (pA: females 90 ± 6, males 53 ± 5, n = 5, p = 0.05). In contrast, the mean amplitude of transient spontaneous hyperpolarization (TSHs) that also represent BK channel function in membrane potential were ~0.8 fold lower in the female SD rats compared to males (mV: females (212 ± 3, males (217 ± 3, n = 4). Together these results suggest that female MCAs may have higher myogenic tone but exhibit an attenuated pressure-mediated myogenic response compared to males. Higher BK channel function in VSMCs of adult female rats may contribute to the attenuated myogenic response and participate in the endothelium-independent vasodilatation. These results may have important implications with which women in adult hood are protected from cerebrovascular incidences compared to males due to their greater vasodilator capacity that is associated with higher BK channel function. Supported by AHA SDG (13SDG14000006) to Malikajura R. Pabbidi.
vascular responses to epinephrine infusions are influenced by both sex and β2-adrenergic receptor genotype. These responses may explain why some of the responses to physiological stressors differ by sex and genotype.

Effect of Gender and Genotype on Human Cardiovascular Response

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<td>72±21.7</td>
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<td><strong>Females</strong></td>
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<td><strong>Gly/Gly</strong></td>
<td>15±7.5±5.2</td>
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14.6 THE EFFECTS OF TESTOSTERONE AND OXIDATIVE STRESS ON NEUROINFLAMMATORY SIGNALING IN Dopamine Neurons

Shalanea Holmes1, and Rebecca Cunningham1
1Pharmacology & Neuroscience, Univ. North Texas Hlth. Sci. Ctr. at Fort Worth, 3500 Camp Bowie Blvd., Fort Worth, TX, 76107.

Parkinson’s disease, a progressive neurodegenerative disorder characterized by oxidative stress and neuroinflammation, is distinguished by the loss of dopamine neurons in the nigrostriatal pathway. Interestingly, men have a two-fold prevalence for Parkinson’s disease than women. While the mechanisms underlying this sex difference remain elusive, we propose that the primary male sex hormone, testosterone, is involved. Our previous studies show that under oxidative stress conditions, testosterone increased oxidative stress generation and cell death in dopamine neurons. Oxidative stress can induce neuroinflammation, a prominent mechanism involved in the neurodegeneration of dopamine neurons. Pro-inflammatory mediators, NFκB and COX2, can increase oxidative stress in dopamine neurons and lead to apoptotic cell death. Thus, we hypothesize that under oxidative stress conditions, testosterone will increase COX2-mediated oxidative stress to induce alpha synuclein Lewy bodies and apoptosis in dopamine neurons. To test our hypothesis, we exposed a dopaminergic cell line (N27 cells) to a sublethal concentration of the pro-oxidant, tert-butyl hydroperoxide (tBuOH) and assessed the role of testosterone on oxidative stress, cell viability, pro-inflammatory markers and apoptosis. Our results showed that under oxidative stress conditions, testosterone increased COX2 protein expression, alpha synuclein Lewy bodies, and apoptosis in dopamine neurons. Inhibiting COX2 blocked testosterone’s negative effects on oxidative stress generation and apoptosis. Therefore, our results indicate that testosterone may mediate the sex differences observed in Parkinson’s disease by increasing oxidative stress induced neuroinflammation and apoptosis in dopamine neurons.

14.7 DOXORUBICIN REDUCES PROINFLAMMATORY MEDIATOR EXPRESSION IN BRAIN AND PIAL ARTERIES FROM Ovariectomized Female Rats

Rayna Gonzales1, Puneet Ramam1, Nimnal Vijayiavv1, Colleen Kerrigan1, Jennifer Echeverria1, Jared Dickinson2, Chad Carroll3, Taben Hale1, and Siddhartha Anagati2

Doxorubicin (DOX) is a highly effective chemotherapy agent. Its use is hampered however owing to severe dose-dependent cardiovascular toxicity in cancer survivors. Multiple mechanisms have been implicated in the pathogenesis of DOX cardiotoxicity, one of which involves inflammation mediated by activation of the NF-κB/TLR4/COX-2 pathway in the heart. Knowledge regarding the toxic effects of DOX-induced inflammation in other organ systems such as the brain is sparse. Therefore, we explored the inflammatory potential of DOX by assessing TLR4 and COX2 levels in cortex and pial arteries isolated from ovariectomized (OVX) female Sprague-Dawley rats. We hypothesized that DOX would promote inflammation by increasing COX2 expression along with expression of its upstream innate immune receptor, TLR4, both of which are under the transcriptional regulation of NF-κB. OVX rats were treated with three, bi-weekly, i.p. injections of DOX (4 mg/kg; cumulative dose 12mg/kg) or vehicle (saline) and euthanized 5 days after the last dose. Tissues were isolated, snap frozen, homogenized, and analyzed for COX2 and TLR4, both of which are under the transcriptional regulation of NF-κB. OVX rats were treated with three, bi-weekly, i.p. injections of DOX (4 mg/kg; cumulative dose 12 mg/kg) or vehicle (saline) and euthanized 5 days after the last dose. Tissues were isolated, snap frozen, homogenized, and analyzed for COX2 and TLR4 expression. In conclusion, ovariectomy was followed by DOX treatment, and pial arteries showed a reduction in both the COX2-72 kDa band and 74 kDa band with the greatest reduction observed in the 72 kDa. The 72 kDa band corresponds to the partially glycosylated inactive form of enzyme, while the 74 kDa band has been shown to represent the fully glycosylated active form. Cytosolic levels of NF-κB were significantly lower in brain and pial vessel lysates, however levels were not altered by DOX. Similar to brain and pial arteries, basal expression of COX2 and TLR4 were detected in left ventricle and DOX treatment attenuated expression. In conclusion, although others have suggested the involvement of the NF-κB pathway during the development and progression of DOX-induced cardiomyopathy, our studies demonstrate a possible novel action for the anticancer agent implicating anti-inflammatory mechanisms, particularly in female cohorts with low circulating levels of gonadal hormones.
14.8 CEREBRAL BLOOD FLOW REGULATION IS AFFECTED THROUGHOUT THE MENSTRUAL CYCLE IN YOUNG WOMEN
Michelle Faire1, Levy A. Reyes2, Apollonia Fox3, and Jorge M. Semador2
1Pharmacology, Physiology & Neuroscience, Rutgers Biomedical & Health Sci., 65 Bergen St, Newark, NJ 07107, 2War Related Illness & Injury Study Center and Dept of Veteran Affairs. This study was conducted in compliance with the Declaration of Helsinki. The objective was to determine if cerebral blood flow regulation is affected throughout the menstrual cycle in young, healthy women with naturally cycling hormones (NOC) compared to women on combined oral contraceptives (OC). Nine (4 NOC and 5 OC) healthy, young women (mean age 20.3 years) were tested during menstruation, the late follicular phase, and the mid-luteal phase. Each visit consisted of a cerebrovascular reactivity test, sit-to-stand tests, and squat-to-stand tests. In steady-state flow velocity when standing in women on oral contraceptives was increased (14.8 ± 3.6% vs. 10.1 ± 3.4% in NOC women; p < 0.05). There was also a significant effect of menstrual cycle phase or oral contraceptive use effects cerebral blood flow regulation (R2=0.88 vs. 0.01 in NOC women). These data demonstrate that in women on oral contraceptives reduced stability in cerebral blood flow regulation during the menstrual cycle when compared to women on non-contraceptives. More studies are required to elucidate the role of CSF cytokines/chemokines in contributing to increased seizure susceptibility following placental ischemia. Funding: NIH: P20GM104357, P01HL051971, and AHA 13091T642000.

15.2 VITAMIN D SUPPLEMENTATION INHIBITS BLOOD PRESSURE AND UTERINE ARTERY RESISTANCE INDUCED BY AUTOANTIBODIES TO THE AT1 RECEPTOR
Jessica Faulkner1, Lorenz Arruval1, Denise Corielus3, Tarak Ibrahim, Mark Cunningham, D’Andrea Thomas, Gerd Walldörfl, Ralf Dechend, and Babbette LaMer4
1Pharmacology, Univ. of Mississippi Med. Ctr., 2500 N. State St, Jackson, MS, 32016, 2Campus-Buch & Max-Delbrück Ctr, HELIOS Clinic, Charite, Luisenstraße 56, Berlin, 10117, Germany. Studies in our lab have previously shown that Vitamin D supplementation in the RUPP rat model of preeclampsia lowers blood pressure and reduces autoantibodies to the AT1 receptor (AT1-AA). Therefore, we sought to determine the efficacy of Vitamin D supplementation to inhibit AT1-AA-induced endothelial dysfunction and hypertension during pregnancy. We hypothesized that Vitamin D supplementation to AT1-AA-induced hypertensive pregnant rats would reduce anti-angiogenic factor soluble FMS-like tyrosine kinase-1 (sFlt-1) and uterine artery resistance index (UARI) while improving blood pressure (MAP). Purified rat AT1-AA was infused (1:40) into Sprague-Dawley rats via miniosmotic pump from gestational day 12 (GD) to 19 (GD19). On GD14-18 we administered Vitamin D2 or D3 (VD2 or VD3) to AT1-AA rats (50 μg/ml) by oral gavage. On GD18 indocarboxyl catheters were inserted and UARI assessed by Doppler sonography and MAP was measured on GD19. Consistent with previous studies, MAP was increased in AT1-AA-infused pregnant rats (123.3±7.4 mmHg, n=3) compared to normal pregnant (NP) rats (101.2±1.2 mmHg, n=9, p=0.005). MAP was reduced with VD2 treatment in AT1-AA-infused rats (105.0±2.3 mmHg, n=4, p=0.004) and AT1-AA+VD3 rats (110.4±1.5 mmHg, p=0.06). Our data indicated that UARI was increased in AT1-AA rats (0.05±0.02, n=4) compared to NP (0.04, n=1) and was unchanged with VD2 treatment (0.57, n=2) but reduced with VD3 (0.46±0.02, n=3, p=0.03). Plasma sFlt-1 levels were measured with ELISA and were greatly increased with AT1-AA infusion (>1050 pg/ml, n=3) compared to NP rats (74.9±10.71 pg/ml, n=4). sFlt-1 levels were reduced in AT1-AA+VD2 (42.3 pg/ml, n=2) and AT1-AA+VD3 rats (24.0±18.7 pg/ml, n=3). Our preliminary data demonstrate that Vitamin D supplementation improves uterine artery vascular resistance and sFlt-1 which are possible mechanisms for improved hypertension induced by AT1-AA during pregnancy. This study was funded by NIH grants RO1HD067541 and T32HL105324.

15.0 PREGNANCY

15.1 PLACENTAL ISCHEMIA INCREASES SENSITIVITY TO PENTYLENETETRAZOL-INDUCED SEIZURES AND CEREBROSPINAL FLUID INFLAMMATION
Junie Warrington1
1Physiology & Biophysics, Univ. of Mississippi Med. Ctr., 2500 N. State St., Jackson, MS, 30126.
Eclampsia is diagnosed in preeclamptic patients who develop convulsions and/or unexplained coma during pregnancy or postpartum and accounts for ~13% of maternal deaths worldwide. The mechanisms contributing to the pathophysiology of eclampsia are not known, partly due to the lack of suitable animal models. The aim of this study was to test the hypothesis that placental ischemia, induced by reducing uteroplacental perfusion pressure, increases susceptibility to seizures, cerebral edema, cerebrospinal fluid (CSF) cytokines/chemokines, and plasma neurokinin B (NKB). Pentylenetetrazol (PTZ), a pro-convulsive drug, was injected into pregnant and placental ischemic rats at the sub-convulsive dose of 40 mg/kg, i.p. on gestational day 19 followed by video monitoring for seizure activity for 30 minutes. Seizure scoring was blindly conducted. Placental ischemic rats (n=8) had reduced latency to the first seizure (264.5±57.8% compared to 83.7±24.6% in normal pregnant rats (n=7), p=0.005) and increased brain water content (78.8±4.1% vs. 78.4±0.1% in normal pregnant rats; p=0.05). PTZ treatment increased brain water content in both pregnant (78.8±4.1% vs. 78.4±0.1%; p=0.05) and placental ischemic rats (78.9±4.1% vs. 0.01). Associated with reduced seizure latency, placental ischemia led to a significant increase in 4 out of 27 CSF cytokines/chemokines tested: IL-2, -17, IL-18, and eotaxin (CCL11). Placental ischemia had no effect on plasma NKB concentrations (p=0.05); however, PTZ increased plasma NKB in both pregnant and placental ischemic rats (p=0.05). NKB was strongly correlated with seizure susceptibility only in normal pregnant rats (R2=0.88 vs. 0.02 in placental ischemic rats). These data demonstrate that placental ischemia increases seizure susceptibility potentially through increases in CSF cytokine levels and edema formation; thus, the rat model of placental ischemia is an excellent model for studying mechanisms contributing to eclampsia-like symptoms. Further
deficiency decreases uterine artery blood flow by increasing myogenic tone at least partly through prolonged Gia activation. Thus, mutations that decrease vascular RGS2 expression may be a predisposition to decreased uterine blood flow. Targeting Gia signaling therefore might improve uteroplacental underperfusion during pregnancy.

15.6 IMPACT OF OBESITY ON NITRIC OXIDE SYNTHASE (NOS)-MEDIATED REGULATION OF BLOOD PRESSURE DURING PREGNANCY IN RATS

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Although obesity is a major risk factor for preeclampsia, defined as new-onset hypertension during pregnancy, the mechanisms have yet to be elucidated. It is known that the dependency of blood pressure regulation on NOS is increases during normal pregnancy in lean rats. Whereas the role of NOS to control of blood pressure during obese pregnancies is less clear as human studies have shown both reductions and increases in NO bioavailability. Therefore, we examined the impact of obesity on NOS-mediated regulation of blood pressure during pregnancy. MC4R-deficient obese rats (MC4R+/--) and wild-type Wistar Hannover controls (MC4R+/++) were maintained on NHBD standard chow; mated at 11 weeks old; and supplemented ad libitum in drinking water with the non-selective NOS inhibitor L-N^2-tertiary amine salt (L-NAME, 100 μmol/L) starting at gestational day (GD) 14 until assessment of mean arterial blood pressure (MAP) and pregnancy weights at GD 19. Maternal body weight was greater in MC4R+/++ (untreated: 366±10, N=12 vs. L-NAME: 359±9 g, N=10) than MC4R+/-- (untreated: 337±10 g; N=16 vs. L-NAME: 332±8 g, N=12) regardless of treatment (P=0.05). The same true was true for visceral adipose tissue mass with MC4R+/++ (untreated: 70.0±1.1 vs. L-NAME: 52±0.5 g) being greater than MC4R+/-- (untreated: 3.4±0.1 vs. L-NAME: 3.5±0.4g) (P=0.05). Fetal weight was reduced by L-NAME only in MC4R+/-- (1.9±0.3 vs. 1.82±0.06g, P<0.05) not MC4R+/++ (1.92±0.3 vs. 1.95±0.06g) while placental weights were similar among untreated and L-NAME-treated groups alike, respectively, (MC4R+/++: 0.50±0.01 vs. 0.50±0.03 g) and (MC4R+/--: 0.56±0.02 vs. 0.55±0.02 g). MAP was greater in untreated MC4R+/-- vs. MC4R+/++ rats (P=0.005). The effect of NOS inhibition to raise MAP was statistically higher in --/A (MC4R+/++) than /A (MC4R+/--) (P=0.001) compared to MC4R+/--. The name=OLE_LINK2 data-listid>G</SUP>-Nitroarginine methyl ester  (L-NAME, 100 μmol/L) significantly decreased (P<0.05) by L-NAME similarly in MC4R+/-- (1.1±0.1 vs. 1.0±0.1ml/min/100g) and MC4R+/++ (1.5±0.2 vs. 1.3±0.1 ml/min/100g). Circulating leptin (MC4R+/--: untreated: 5.9±0.6 vs. L-NAME: 5.8±0.0ng/ml; MC4R+/++: untreated: 3.8±0.3 vs. L-NAME: 3.4±0.8ng/ml) and total cholesterol levels (MC4R+/--: untreated: 123±5 vs. L-NAME: 137±23mg/dL; MC4R+/++: untreated: 93±5 vs. L-NAME: 113±11mg/dL) were greater in obese pregnant rats but unaltered by L-NAME. In conclusion, these data indicate that NOS-dependent regulation of MAP is reduced in obese pregnancies and may contribute to higher preeclampsia rates found in obese pregnant women.

15.7 AGONISTIC AUTOANTIBODIES TO THE ANGIOTENSIN II TYPE 1 RECEPTOR ENHANCES ANG II-INDUCED RENAL VASCULAR SENSITIVITY AND REDUCES RENAL FUNCTION DURING PREGNANCY

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Preeclamptic women produce agonistic autoantibodies to the Angiotensin II type 1 receptor (AT1-AA) and exhibit increased blood pressure (BP) and vascular sensitivity to angiotensin II (ANG II). Although, together AT1-AAs and ANGII increase the dependency of blood pressure regulation on NOS is increases during normal pregnancy in lean rats. Whereas the role of NOS to control of blood pressure during obese pregnancies is less clear as human studies have shown both reductions and increases in NO bioavailability. Therefore, we examined the impact of obesity on NOS-mediated regulation of blood pressure during pregnancy. MC4R-deficient obese rats (MC4R+/--) and wild-type Wistar Hannover controls (MC4R+/++) were maintained on NHBD standard chow; mated at 11 weeks old; and supplemented ad libitum in drinking water with the non-selective NOS inhibitor L-N^2-tertiary amine salt (L-NAME, 100 μmol/L) starting at gestational day (GD) 14 until assessment of mean arterial blood pressure (MAP) and pregnancy weights at GD 19. Maternal body weight was greater in MC4R+/++ (untreated: 366±10, N=12 vs. L-NAME: 359±9 g, N=10) than MC4R+/-- (untreated: 337±10 g; N=16 vs. L-NAME: 332±8 g, N=12) regardless of treatment (P=0.05). The same true was true for visceral adipose tissue mass with MC4R+/++ (untreated: 70.0±1.1 vs. L-NAME: 52±0.5 g) being greater than MC4R+/-- (untreated: 3.4±0.1 vs. L-NAME: 3.5±0.4g) (P=0.05). Fetal weight was reduced by L-NAME only in MC4R+/-- (1.9±0.3 vs. 1.82±0.06g, P<0.05) not MC4R+/++ (1.92±0.3 vs. 1.95±0.06g) while placental weights were similar among untreated and L-NAME-treated groups alike, respectively, (MC4R+/++: 0.50±0.01 vs. 0.50±0.03 g) and (MC4R+/--: 0.56±0.02 vs. 0.55±0.02 g). MAP was greater in untreated MC4R+/-- vs. MC4R+/++ rats (P=0.005). The effect of NOS inhibition to raise MAP was statistically higher in --/A (MC4R+/++) than /A (MC4R+/--) (P=0.001) compared to MC4R+/--. The name=OLE_LINK2 data-listid>G</SUP>-Nitroarginine methyl ester  (L-NAME, 100 μmol/L) significantly decreased (P<0.05) by L-NAME similarly in MC4R+/-- (1.1±0.1 vs. 1.0±0.1ml/min/100g) and MC4R+/++ (1.5±0.2 vs. 1.3±0.1 ml/min/100g). Circulating leptin (MC4R+/--: untreated: 5.9±0.6 vs. L-NAME: 5.8±0.0ng/ml; MC4R+/++: untreated: 3.8±0.3 vs. L-NAME: 3.4±0.8ng/ml) and total cholesterol levels (MC4R+/--: untreated: 123±5 vs. L-NAME: 137±23mg/dL; MC4R+/++: untreated: 93±5 vs. L-NAME: 113±11mg/dL) were greater in obese pregnant rats but unaltered by L-NAME. In conclusion, these data indicate that NOS-dependent regulation of MAP is reduced in obese pregnancies and may contribute to higher preeclampsia rates found in obese pregnant women.
isometric handgrip exercise in normotensive women with a history of HTNP and women with a history of HTNP who are currently being treated for hypertension. **Methods**: Beat-to beat BP (finger plethysmography) was recorded at rest and during first third phase, second third phase and final phase of isometric handgrip (HG) exercise (30% of maximal voluntary contraction) to fatigue in postmenopausal women (58 ± 1 years) with a history of HTNP. Isometric handgrip exercise was followed by 90 seconds of post-exercise isometric HG. BP was analyzed in three phases of 30 seconds each during cuff occlusion. **Results**: Women with a history HTNP women currently using anti-hypertensive medications (n=14) had a significantly higher rise in diastolic blood pressure (DBP) during the 1st and 2nd third of isometric HG (8 ± 1 and 12 ± 2 %) as compared to non-medicated (n=15) HTNP women (4 ± 1 and 8 ± 2 %; p=0.015 and p=0.036). Additionally, medicated women had a significantly higher rise in DBP during 1st cycle of cuff occlusion (12 ± 2 %) as compared to non-medicated HTNP women (6 ± 2 %; p=0.026). Changes in systolic or mean arterial BP were not different between groups (p=0.05). **Conclusions**: These results identify differences in BP responses to physical stressors in women with a history of HTNP that are currently hypertensive versus normotensive. These data suggest the presence of two distinct phenotypes in women with a history of HTNP, which may be identified by the presence or absence of an altered muscle chemoreflex response along with an increased peripheral vascular resistance. Further investigation is needed to evaluate if these changes can be primarily attributed to a history of HTN pregnancy and how this affects overall cardiovascular risk. Funding: NIA 1P50AG044170-01, CTSA UL1TR000135, HL 118154, HL83947.

15.10 **UP-REGULATION OF VEGFR2 IMPROVES UTERINE ARTERY MYOCYanic RESPONSE AND MATERNAL HYPTERTENSION ALTERED BY UTERINE PERFUSION PRESSURE REDUCTIONS**

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1Innovative Biosciences Program, Univ. of Akron, 302 Buechel Mall, Akron, OH, 44325, 2Biology, Univ. of Akron, 302 Buechel Mall, Akron, OH, 44325, 3Biomedical Engineering, University of Akron, 302 Buechel Mall, Akron, OH, 44325, 4Molecular Physiology & Biophysics, Univ. of Iowa, 51 Newton Rd., Iowa City, IA, 52242, 5Mathematics & Sci., Walsh Univ., 2020 E. Maple St., N. Canton, OH, 44720. Treatment options for the hypertensive disorder of pregnancy, preeclampsia (PE), remain limited. An imbalance in angiogenic factors (via the VEGF pathway) favoring a vasocostrictory phenotype and inadequate vascular remodeling contribute to the maternal hypertension. Previous studies of VEGF signaling pathway have focused on either the soluble form of the VEGF receptor, or modifying VEGF release and/or production. The current study is unique in that it focuses on the VEGF receptor 2 in the uterine vasculature. We hypothesize that increased uterine vasculature VEGFR2 receptor will improve uterine vascularity behavior, maternal hypertension, and growth restriction in pregnant rats with PE pathology induced by surgical reductions in utero-placental perfusion (RUPP). VEGF receptor 2 receptors are upregulated by a novel non-viral gene delivery system using L-lysine polyphosphate (LTP) nanoparticles (NP) seeded with DNA plasmid for VEGF2. For the RUPP model, on day 14 of gestation, silver clips are placed on the abdominal aorta (0.2mm i.d.) and the utero-ovarian arteries (0.1mm i.d.) in pregnant Sprague-Dawley rats. SHAM rats undergo surgery without clip placement. On the same day as RUPP surgery, LTP nanoparticles (0.023673mg pDNA:2.5mg NP) are injected into the uterine wall. On day 21 of gestation an anesthetized blood pressure is measured via carotid catheter then resistance vessels (~< 300um) are harvested for study in an isotopic arteriograph. Uterine arteries from RUPP dams (n=8) display increased constriction to intraluminal pressure increases compared to SHAM pregnant rats (n=7; p<0.05). VEGF2 LTP nanoparticle injection normalized the myogenic response in RUPP uterine arteries (p<0.05) so that the responses are similar to responses in arteries from SHAM rats. Maternal mean arterial pressure (MAP) is also normalized by VEGF2 LTP injection. MAP is reduced from 99.0 ±6.4 mm Hg to 81.8 ±6.5 mm Hg injected RUPP dams (n=8; p<0.05). Finally, injection of VEGF2 LTP nanoparticles significantly increased fetal weights in RUPP to 4.8 ±0.72g vs. 2.85 ± 0.5g; p<0.05. In conclusion, uterine injection of LTP nanoparticles with DNA plasmid encoding for VEGFR2 improved the uterine arterial myogenic responsiveness, maternal blood pressure and fetal weights in RUPP animals. These data suggest a novel gene therapy to treat preeclamptics mothers and emphasize the importance of VEGFR2 receptor.

15.11 **EFFECTS OF HIGH-SUCROSE DIET ON BLOOD PRESSURE REGULATION DURING PREGNANCY IN RATS**

Frank Spindelay, Ada Palei, and Joey Granger
While obesity increases the risk for developing preeclampsia, which is new-onset hypertension during pregnancy, the mechanisms are unclear. Although adverse diets such as high sucrose are thought to contribute to hypertension, human and animal studies have failed to demonstrate that high sucrose affects blood pressure during pregnancy. This could be due to the lack of high sucrose to produce frank obesity. However, it is unknown whether body weight, for example segregation of lower vs. higher body weights even within the normal weight range, is important. To consider when examining blood pressure during high sucrose feeding in pregnancy. Therefore, we tested the hypothesis that higher vs. lower body weight status during a high-sucrose diet is accompanied by high blood pressure in pregnancy. Female Wistar hannover rats were started on a high-sucrose diet (20% sucrose) in a controlled normal and colonic diet (NSD, 5% sucrose for 2 weeks old; time timed-pregnant rats generated at 17 weeks old; followed by examination of mean arterial blood pressure (MAP) and pregnancy weights at gestational day (GD)19 while being maintained on respective diets. Maternal body weights at GD19 were segregated as lower (L) or higher (H) than the median for respective NSD (370g) and HS4 (346g) groups. This resulted in 4 experimental groups: NSD-L (N=5), NSD-H (N=3), HS4-L (N=4) and HS4-H (N=5). Maternal body weights were greater (P=0.002) in NSD-H and HS4-H (376±3 vs. 355±4g, respectively) over the NSD-L and HS4-L groups (345±7 vs. 325±12g, respectively). Body weight was greater in NSD-H than HS4-H (P=0.05). Visceral adipose tissue mass was greater (P=0.002) in the NSD-H and HS4-H groups (8.2±0.4 vs. 6.6±0.7g, respectively) than NSD-L and HS4-L groups (5.9±0.2 vs. 4.7±0.8g, respectively). Most interestingly, MAP was greatest (P=0.05) in HS4-H (120±2mmHg) over HS4-L (108±1mmHg) and NSD-H (113±1mmHg), which was similar to NSD-L at 111±2mmHg. Fetal weights (g; NS-L: 1.90±0.05; NS-H: 1.94±0.04; HS4-L: 2.04±0.07; HS4-H: 1.92±0.01) and placental weights (g; NS-L: 4.6±0.04; NS-H: 4.54±0.02; HS4-L: 5.3±0.05; HS4-H: 5.7±0.03) were similar between all groups. These data suggest that the hypertensive response to HS4 during pregnancy maybe dependent on the presence of increased body weight and visceral adiposity. In conclusion, pregnant women with higher body weight and visceral adiposity combined with an adverse diet may predict those most likely to develop hypertension during pregnancy.

15.12 MECHANISMS OF RENAL AND COLONIC POTASSIUM RETENTION DURING LATE PREGNANCY

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The fetus requires a large amount of potassium (K+) for normal development. To accommodate this need the normal pregnant rat accumulates considerable K+ over the course of gestation, most of which is retained during late pregnancy. This gestational K+ retention is essential for fetal development but the mechanism is unknown. The purpose of this study was to examine how renal and colonic K+ handling changes during pregnancy in the setting of high circulating aldosterone and enhanced sodium re-absorption. We measured dietary K+ intake and urinary K+ excretion. K+ intake increased in MP and LP vs. V (4.6±0.1, 5.2±0.1 vs. 3.3±1.0 meq/24h, P<0.05) while renal K+ excretion also rose (4.8±1.0, 4.6±1.0 vs. 3.0±0.2 meq/24h, P<0.05). We also measured the mRNA expression of BK, ROMK, H+/K+ -ATPase type 2 (HKA2), and H+-ATPase in the renal cortex, outer medulla, and colon of IUGR and control pregnant rats at GD 14, and late pregnancy (8-10 weeks). We found that increased mRNA expression of BK and ROMK were present in the renal cortex of pregnant rats relative to controls. In the colon, we found increased mRNA expression of HKA2 in pregnant rats relative to controls. These data suggest that the hypertensive response to HS4 during pregnancy maybe dependent on the presence of increased body weight and visceral adiposity. In conclusion, pregnant women with higher body weight and visceral adiposity combined with an adverse diet may predict those most likely to develop hypertension during pregnancy.

16.0 DEVELOPMENTAL PROGRAMMING

16.1 VENDOR-SPECIFIC EFFECTS ON SEX DIFFERENCES IN THE DEVELOPMENTAL PROGRAMMING OF BLOOD PRESSURE IN THE SPRAGUE DAWLEY RAT

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Our laboratory uses a well-established model of intruterine growth restriction (IUGR) induced by placental insufficiency that programs a sex difference in blood pressure (BP) in the Sprague Dawley (SD) rat. IUGR is induced by reduced uterine perfusion (RUP) initiated at day 14 of gestation in timed pregnant rats purchased from Harlan. Previously we reported that male IUGR rats exhibit hypertension at 16 weeks of age associated with a two-fold increase in testosterone relative to male control from sham operated dams whereas female IUGR rats remain normotensive. Hypertension is abolished by castration suggesting that IUGR programs a testosterone-dependent increase in BP in male IUGR. However, BP is significantly increased following ovariectomy (OVX) in female IUGR implicating estrogen is protective. Thus, these studies indicate that sex hormones play a vital role in BP control in Harlan SD IUGR rats. The aim of this study was to determine if the commercial vendor impacts the developmental programming of BP. Timed pregnant SD rats from Charles River underwent either RUP or sham surgery at day 14 of gestation. Birth weight was significantly reduced in male IUGR relative to same-sex controls (P<0.05). At 10 weeks of age animals underwent measure of body composition before and 6 weeks after gonadectomy or sham surgery. Prior to gonadectomy total fat mass did not differ between IUGR and control (Males: 26±1.3% and Females: 19±1.3% IUGR vs. 17±3%; IUGR vs. control, respectively). However, OVX resulted in a significant increase in total fat mass in IUGR and control relative to intact (OVX: 45±6 vs. 37±5g and intact: 20±0 vs. 22±2g; P<0.05; IUGR vs. control, respectively) while CTX had no effect on fat mass in male (data not shown). Baseline BP measured in conscious, chronically instrumented rats at 16 weeks of age did not differ in intact male control relative to intact male IUGR (137±3 vs. 137±3mmHg) or intact female control relative to intact female IUGR (119±5 vs. 123±4mmHg). Testosterone levels were not elevated in male IUGR versus male control; gonadectomy did not alter BP in IUGR rats relative to same-sex intact control (data not shown). Thus, these results suggest...
that vendor-specific differences in the SD rat abolish the developmental programming of sex differences in BP and eliminate the effect of testosterone and estrogen on BP control in the IUGR rat. Dasinger: AHA 15PRE24700010; Alexander: HL074927, AHA GRNT1990004, P01-HL51971, GM104357.

16.2 IS THERE A SEX DIFFERENCE BETWEEN HYPERTE- RISON RISK AND LOW BIRTH WEIGHT IN HEALTHY YOUNG JAPANESE ADULTS?

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Low birth weight (LBW) was confirmed as a risk of high blood pressure (BP) in later stages of life. Low-grade inflammation and deterioration of autonomic regulation play an important role in hypertension. However, the association between birth weight and hypertension are poorly understood. We examined this association in healthy young Japanese adults, and investigated whether the relationship between LBW and hypertension risk factors differs between men and women. We measured the BP and heart rate variability at rest and during postural change from a supine to a sitting position in 26 healthy Japanese volunteers aged 18-23 years. Blood cell counts and levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, triglyceride (TG), and high sensitivity C-reactive protein were measured. Men were taller (p < 0.01), weighed more (p < 0.01), had a higher resting BP (p < 0.01), and had higher DBP levels (p < 0.05) and lower HDL-C levels (p < 0.05) compared to women. In men, the HDL-C levels were lower in the LBW group compared to the normal birth weight (NBW) group (p < 0.05). In contrast, there were no significant differences in women considering any of the hypertension risk factors between the LBW and NBW groups. After the postural change, systolic blood pressure (SBP), diastolic blood pressure, and heart rate showed no significant increases in the LBW, whereas the NBW group had normal responses (p < 0.01). Women displayed an increase in SBP immediately after sitting (p < 0.05) and a decrease in SBP and hypertension risks in healthy young Japanese adults. This work was supported, in part, by a Grant-in-aid for Scientific Research (B) (25305018) from the Japan Society for the Promotion of Science.

16.3 SEX DIFFERENCES IN HIGH FAT DIET-INDUCED ADIPOCYTE MORPHOLOGY AND FAT DISTRIBUTION DUE TO EARLY LIFE STRESS

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Epidemiological studies indicate that adults exposed to early life stress (ELS) are at an increased risk of developing cardiometabolic disease. Previously, we have reported that females exposed to maternal separation (MSep) is an established behavioral stress and a measure of BP. Male IUGR offspring had a significantly higher BP compared to male control via carotid catheter in the conscious state (control: 112.1 ± 2.1, IUGR: 125.0 ± 3.7 mmHg; N=7, P<0.05). MAP did not differ between female control and female IUGR offspring (control: 113.8 ± 2.8, IUGR: 117.8 ± 2.8 mmHg; N=5). Kidney weight body weight was not different between control versus IUGR same-sex counterparts. Renal S1PR3 gene expression levels were increased (2.5 fold vs. control, N=4, P<0.05) whereas S1PR3 protein levels were decreased (0.75 fold vs. control, N=4, P<0.05) in male IUGR. Renal gene and protein S1PR3 expression levels were not different between female control and female IUGR. Together our data suggest that UGR programs a sex-specific alteration in renal S1PR3 expression which may contribute to an increase in BP programmed only in male IUGR but not in female IUGR mice Thus, S1PR3 signaling is a potential putative mechanism underlying the sex-specific hypertension of IUGR mouse offspring. Dr. Intupad is supported by funding from NIH P20GM104357.

16.5 REDUCED SLEEP TIME DURING PREGNANCY EFFECTS ON RENAL MORPHOLOGY AND FUNCTION OF FEMALE OFFSPRING

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The shortening of sleeping time has become common in modern society. This alteration has been associated to several changes such as reduced glucose tolerance, increased blood pressure, and changes in hormonal pathways. Considering that changes in maternal environment may result in changes in the offspring, as shown in male offspring from different models of fetal programming, the aim of this study was to evaluate renal morphology and function of female offspring from rats sleep restricted during the last week of pregnancy. Methods: After confirmation of pregnancy, Wistar rats were divided into two groups: control and sleep restricted. Sleep restriction was performed between 14th and 20th day of pregnancy (20 hours/day). After birth, offspring was designated as C (control) and S (sleep restricted). At two months, half of the offspring were subjected to ovarianization and the others to sham surgery. The groups were then designated Sham (CS and SRS) or ovarioectomized (CO and SRO) and studied at 8 months of age. The parameters analyzed were: systolic blood pressure (BP), creatinine clearance (Ccr), sodium excretion (ENa+), glomerular area (GA), number of glomeruli per field (NG), kidney cross-section area (KA) and kidney mass (KM). The results are shown as means: SEM and number of measurements between parenthesis. Anova, p <0.05. The SR groups presented increased BP (CS: 125±17.7; CO: 130±18.5).
16.6 DELAYED EFFECTS OF PERINATAL HYPOXIA ON ADULT RATS PULMONARY VESSELS STRUCTURE AND REACTIVITY

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Perinatal hypoxia (PH) induces irreversible changes of lung circulation (2). Pulmonary arteries of adults that had been exposed to PH (1 wk before and 1 wk after birth, 12% O2) and then lived in normoxia are more compliant and their vasoconstrictor response to acute hypoxia is increased. Adult females, but not males, with the perinatal experience of hypoxia have right ventricle hypertrophy. However, pulmonary arterial pressure of either male or female rats did not differ from that of controls. We also did not detect low molecular weight extracts in the cytoplasm of prealveolar pulmonary vessels typical for hypoxic pulmonary hypertension (3). The presence of right ventricle hypertrophy only in females led us to question the role of sexual hormones. Rats exposed to PH were therefore gonadectomized as newborns (1). Pulmonary arterial pressure was elevated in adult perinatally hypoxic, neonatally gonadectomized females (24.4 ± 1.7 torr) but not males (17.2 ± 0.6 torr). In perinatally hypoxic, neonatally gonadectomized males the muscularization of peripheral pulmonary vessels (a valuable structural marker of pulmonary hypertension) in adulthood was greater than in intact, perinatally normoxic male controls. In gonadectomized females born in hypoxia the muscularization of prealveolar arteries was increased even more (5 times). Gonadectomy performed in adulthood did affect neither pulmonary vascular structure nor lung hemodynamics. Female pulmonary circulation is therefore more sensitive to the late effects of perinatal hypoxia, and these effects are blunted by the presence of ovaries during maturation. Because pulmonary vascular reactivity depends on transmembranous K+ current, we tested the response of pulmonary vasculature of male and female rats exposed to PH to K+ as to controls. In intact rats, PH increased basal perivascular pressure and reactivity to K+ than control females. The different effects of PH in male and female rats may result from different expression and/or activity of K+ channels. Supported by GACR 13-01710S and IGA NT/13358. References: 1. Humpel V et al. Am J Physiol Lung Cell Mol Physiol 285: L386-392, 2003. 2. Vizek M et al. Life Sci 62: 1 - 12, 1998.

16.7 SEX DIFFERENCE IN SENSITIZATION OF ANGIOTENSIN (ANG) II-ELICITED HYPERTENSION IN OFFSPRING OF HYPERTENSIVE PREGNANT RATS

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Recent studies demonstrate that there is association between maternal health status during pregnancy and cardiovascular disease of adult offspring. The present study test whether maternal hypertension produced by angiotensin (ANG II) infusion (250 ng/kg/min, i.c.v) during pregnancy sensitizes offspring to blood pressure (BP) in adult offspring, and whether there are sex differences. Aortic BP and heart rate (HR) were measured in dams and their offspring by telemetry. When tested beginning at 10 weeks of age, male offspring of hypertensive dams showed an enhanced hypertensive response to ANG II (120 ng/kg/min, Δ41.6±26.8 mmHg) compared to male offspring of normotensive dams (Δ17.1±1.3 mmHg). In females, ANG II treatment produced only a slight, but significant increase in BP in offspring of either hypertensive (Δ5.7±2.5 mmHg) or normotensive dams (Δ11.6±2.5 mmHg). RT-PCR analysis of the lamina terminals and the paraventricular nucleus tissues indicated upregulation of mRNA expression of renin-angiotensin-aldosterone system (RAAS) components and proinflammatory cytokines, including renin, angiotensinogen, mineralocorticoid receptor, interleukin (IL)-6 and IL-1β in male, but not female, offspring from hypertensive dams. The results suggest that maternal hypertension during pregnancy enhances pressor responses to ANG II through upregulation of the brain RAS and inflammatory cytokines in male offspring, and that female offspring are protected from these effects.

16.8 SEX DIFFERENCES IN CARDIOVASCULAR RESPONSES TO STRESS IN ADULT RATS PRENATALLY EXPOSED TO DEXAMETHASONE

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1Basic Med. Sci., Univ. of Arizona, 425 N. 5th St., Phoenix, AZ, 85004. It is well known that even transient prenatal insults can impact cardiovascular function in adulthood. We have hypothesized that adult cardiovascular disease may have its origins in utero as a result of exposure to elevated levels of glucocorticoids. In support of this, we have shown that when pregnant rat dams are treated with the glucocorticoid, dexamethasone (DEX), for the last 4 days of gestation, female-specific changes in metabolism, core body temperature, autonomic function, depression, and anxiety-like behaviors are detected in their adult offspring. The present study investigated the impact of prenatal DEX on arterial pressure and cardiovascular responses to stress in adult pregnant and female offspring. Pregnant dams were administered DEX (0.4mg/kg per day, s.c.) or vehicle on gestation days 18-21. This resulted in a significant reduction in birthweight in DEX-exposed males and females. At 2-3 months of age, arterial pressure was assessed via radiotelemetry. Baseline pressures were collected for 3 days in males and for 7 days in females to evaluate blood pressure throughout the estrous cycle (determined by vaginal lavage). In order to assess whether prenatal DEX alters stress-induced hypertensive and tachycardic responses, rats were placed in a restraint tube for 20 minutes, followed by a 2-hour recovery period. Restraint-stress testing was performed on diestrus in females. In male rats, prenatal DEX had no impact on arterial pressure under basal conditions or in the elevations that occurred in response to restraint stress. In contrast, the systolic blood pressure in DEX-exposed females was ~10% below that of vehicle-exposed offspring throughout the estrous cycle. No treatment differences were observed in basal diastolic pressure or heart rate. However, prenatal DEX exposure resulted in an exaggerated hypertensive and tachycardic response to restraint stress in female offspring (HR: Veh 18% vs. DEX 35%, p<0.05; DBP: Veh 20% vs. DEX 50%, p<0.05; HR: Veh 20% vs. DEX 56%, p<0.05). Moreover, the time to return to baseline pressures and heart rate was longer in female rats prenatally exposed to DEX. Taken together, these findings reveal sex-specific differences in the prenatal programming of stress-induced hypertension and further support a role for elevated glucocorticoids in development as an origin for cardiovascular disease states in females. Funding: NIH R55 HD082679 and AZ Biomedical Research Commission AH1314-082990.

17.0 AGING AND MENOPAUSE

17.1 PREHYPERTENSION AND ENDOTHELIAL FIBRINOLYTIC FUNCTION IN MIDDLE-AGED WOMEN

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Prehypertension (systolic blood pressure: 120-139 mmHg and/or diastolic blood pressure: 80-89 mmHg) is prevalent in ~30% of US adults and is associated with increased atherothrombotic vascular disease risk. We recently demonstrated that the capacity of the endothelium to release tissue-type plasminogen activator (t-PA) is markedly blunted in middle-aged men with prehypertension. Endothelial t-PA release is the primary endogenous defense mechanism against thrombus formation. Interestingly, the capacity of the endothelium to release t-PA has been shown to be significantly higher in middle-aged women compared with men, conferring greater cardiovascular protection. It is currently unknown whether prehypertension is associated with diminished endothelial t-PA release in women. Accordingly, we tested the hypothesis that, similar to men, blood pressure in the prehypertensive range is associated with increased fibrinolytic vascular function in middle-aged women. Thirty-four sedentary, non-obese, post-menopausal, middle-aged women were studied: 17 normotensive (age: 57±1 yr; BMI: 26.1±0.8 kg/m²; BP: 105/66±2/2 mmHg) and 17 prehypertensive (age: 56±1 yr; BMI: 26.4±1.0 kg/m²; BP: 130/79±1/2 mmHg). All women were at least one year post menopause, not taking hormone replacement, and free of other cardiovascular disease. Net endothelial release of t-PA was determined, in vivo, in response to intrabronchial infusions of bradykinin (BKC: 125-500 ng/min) and sodium nitroprusside (SNP: 2-8 μg/min). Basal and stimulated endothelial t-PA release was not significantly different between the groups. t-PA release increased simi-
early in the normotensive (from 0.6±0.7 to 56.3±7.6 ng/100 mL tissue/min) and prehypertensive (from 0.6±1.1 to 54.9±8.5 ng/100 mL tissue/min) groups to incremental doses of BK. In fact, total t-PA release (area under the BK curve) was almost identical between the normotensive (284±46 ng/100 mL tissue) and prehypertensive (273±46 ng/100 mL tissue) groups. There was no effect of SNP on t-PA release in either group.

In summary, contrary to our hypothesis, prehypertension does not adversely influence endothelial function in middle-aged women. The selective, adrenergic-receptor agonist terbutaline are blunted with aging and menopause in healthy women. Funded by AHA 14PRE18040000, NIH HL83947 and HL118154, and NCATS ULI TR000135 (CTSA).

17.4 ET, RECEPTOR ANTAGONISM PREVENTS ANG II-INDUCED HYPERTENSION IN VCD-TREATED POSTMENOPAUSAL FEMALE MICE

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The VCD model of menopause +α1-adrenergic agonist (VCD) preserves the “perimenopause” transitional period and the androgen secreting capacity of the residual ovarian tissue. Using this model of menopause, we recently demonstrated that perimenopausal mice are resistant to Ang II-induced hypertension and displayed minimal changes in blood pressure and cardiac remodeling. In contrast, postmenopausal mice develop a significant Ang II-induced hypertension (significant increase in SBP and MAP), along with renal hypertrophy and cardiac fibrosis. Endothelin (ET)-1, signaling through ETA (ET A), receptors, has been shown to promote renal damage and Ang II hypertension in male rodents, while perimenopausal females were protected. To determine whether ET A, receptor signaling contributes to the increased sensitivity to Ang II hypertension in VCD-treated postmenopausal female mice (Meno), Ang II (800ng/kg/min, 14d) was infused with or without daily injections of the ET A receptor antagonist ABT-627 (5nm/kg, ip) (ET A). Postmenopausal females received saline oil vehicle with and without Ang C (C/Ang II). Ang II infusion induced a significant increase in systemic blood pressure in VCD-treated postmenopausal mice compared to Ang II infusion in perimenopausal mice (Con A2 vs 2 mmHg, Ang II A15 vs 3 mmHg, Meno/Ang II A17 vs 6 mmHg, *P<0.05 vs Con, **P<0.05 vs C/Ang II). ETA, receptor antagonist prevented this increase in blood pressure in perimenopausal females (ET A14 vs 3 mmHg, *P<0.05 vs Meno/Ang II). Quantitative real-time PCR demonstrated that whole kidney mRNA expression of collagen type IV was significantly reduced with ET A receptor antagonism (Meno vs Ang II 1.0±0.7 vs 0.76±0.5 in ETA treated, P<0.05). Together, these data suggest that ET A signaling, via ET A, receptor activation, promotes Ang II induced hypertension and renal damage in postmenopausal females. Targeting this system may be an effective strategy to treat postmenopausal hypertension.

17.5 MYOGENIC TONE IS INCREASED IN RESISTANCE-SIZED ARTERIES ISOLATED FROM RAT MODELS OF POST-MENOPAUSAL PHYSIOLOGY

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Women are at increased risk of heart attack and stroke after menopause. Estrogen replacement therapy is the remedy for the symptoms of menopause (hot flashes, etc.); however, the mechanism for the cardio-protection is not clear. The myogenic behavior of resistance sized arteries is an index of the balance between vasodilatory and vasoconstrictory pathways. The increased risk of heart attack and stroke in postmenopausal women suggests an increase in vasoconstrictor pathways or a decrease in vasoconstrictory mediators. In order to evaluate this we chose to examine the myogenic tone of resistance-sized arteries isolated from different rodent models of post-menopausal physiology. The rodent models include the aged female SHR and the ovariectomized pair-fed Long-Evans rat (OVX). Over a range of pressures (20-100mmHg), the myogenic tone was greater in the cephalic arteries isolated from aged SHR rat compared to young SHR control (i.e. 12.2±3.2% vs 7.5±2.1% at 60mmHg). Greater myogenic tone was also displayed in the posterior arterial branches isolated from the aged SHR. In the OVX model, myogenic behavior was increased in coronary, cerebral, and mesenteric resistance sized arteries. For example, the suprarenal arteries isolated at 80mmHg was 17.7±4.1% in the ovx compared to 7.4±2.5% in the sham controls. In these arteries, we examined the role for vasoconstrictor pathways involving nitric oxide and endothelin B receptor (ET B). Nitric oxide production is further increased in perimenopausal women (2.1±0.6 vs 1.7±0.9 μmol/min/mL tissue/hr, respectively; *P<0.05) and rose significantly within each group at the highest terbutaline dose (10.7±2.1 vs 7.1±1.9 μmol/min/mL tissue/hr, respectively; P<0.05); however, there were no FBF differences between the groups. Baseline forearm vascular conductance (FVC/FBF/MAP100) was not different between groups (2.4±0.4 vs.
example, the coronary arteries percent tone was increased to 28.9±13.7% tone at 60mmHg. In conclusion, myogenic tone is increased in resistance-sized coronary and cerebral arteries isolated from both models of post-menopausal physiology. Furthermore, in the OVX model, vasodilatory pathways involving ETB and nitric oxide remain intact. This work is supported by NIH R15 HL09734.

17.6 CIRCULATING STEROID HORMONES HAVE NO INFLUENCE ON THE CARDIOVASCULAR BENEFICIAL EFFECT IN TRAINED HYPERTENSIVE POSTMENOPAUSAL WOMEN

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Introduction: It has been demonstrated that the prevalence of arterial hypertension increases in women after menopause that has been associated with estrogen deficiency. On the other hand, estrogen administration did not protect women from cardiovascular diseases (CVD). In addition, evidence has shown that high testosterone levels are associated with an adverse cardiovascular risk factor after menopause. However, most of these data are from experimental model of menopause. It is well known that cortisol plays an important role in CVD. Nonetheless, the effects of this steroid hormone are not fully understood in the development of CVD in women. Aim: Therefore, the goals of the study were: (1) to examine testosterone and cortisol concentrations in hypertensive (HT) postmenopausal women comparing with normotensive (NT) group, at baseline; (2) to examine the effects aerobic exercise training (AET) on BP and steroid hormones in both groups. Methods: In order to test the hypothesis, serum testosterone (fasting) and cortisol concentrations (fasting and postprandial state) were measured in 28 HT (57±1 yrs) and 33 NT (56±1 yrs) women at baseline and after AET. Supervised AET was performed in a treadmill, moderate intensity, 30-40 min, three times/week, 24 sessions. This study has been approved by UNESP Ethics Committee (4395/2010). Results: At baseline, no differences were found in both testosterone (NT: 0.8±0.1 and HT: 0.76±0.1 nmol/L) and cortisol (NT: 464.9±28.7 and HT: 453.6±24.6 nmol/L) between the two groups, in fasting state. Cortisol concentrations were also similar between the two groups (NT: 142±4±14.0 and HT: 137±3±16.6 nmol/L) measured at postprandial. After AET, there were no significant changes on steroid levels in both groups in fasting state. However, in postprandial we found a similar decrease in cortisol concentration from trained NT (-41%) and HT (-35%) postmenopausal women. AET was also effective in lowering diastolic BP (-5%) in HT group, but not in NT. Conclusions: Our data show that both steroids hormone have no influence on BP regulation in postmenopausal women. Moreover, both groups respond equally to AET in lowering cortisol concentrations, but differently to BP reduction. Thus, our findings suggest that another signaling pathway is involved in the cardiovascular beneficial effect in trained postmenopausal women. Financial Support: Fapemig.

17.7 RENAL FUNCTION IN AGING HYPERANDROGENIC FEMALE RATS

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Polycystic ovary syndrome (PCOS) is the most common reproductive disorder in premenopausal women. It is characterized by hyperandrogenemia, metabolic syndrome and inflammation. Whether PMW who have had PCOS when young develop early cardiovascular disease (CVD) is controversial despite the fact that androgen levels remain elevated even after menopause. We have characterized a model of hyperandrogenemia in female rats and have aged them to 22 months to mimic hyperandrogenemia in PCOS. In the present study we tested the hypothesis that chronic exposure to hyperandrogenemia with aging in female rats has a deleterious effect on renal function. Female rats, implanted with dihydrotestosterone (DHT 7.5mg/kg) or placebo pellets (n=6/group) beginning at 6 wks of age (pellets were changed every 85 d), were aged to 22-25 months. Renal function was measured by clearance studies in euclidean, anesthetized rats (Inactin 110 mg/kg IP). Catheters were placed into femoral artery (continuous measurement of blood pressure (mean arterial pressure (MAP)), femoral vein (for infusion of 50% glycine/50% BSA in Ringer’s at 10 ml/kg BW/hr for 45 min and then 1.25 ml/kg BW/hr throughout the study), jugular vein (for infusion of 3H-inulin 3 μCi/ml in saline at 1ml/hr). Tracheostomy was performed and a catheter was placed into the left ureter for urine collection. Two 30 min urine collections were performed with midpoint plasma samples taken. At the end of the study, a 23 g needle connected to PE10 tubing was inserted into the left renal vein to measure extraction of 3H-inulin across the kidney to calculate renal plasma flow (RPF). Aging DHT-treated females had significantly higher body weight (420±18 vs. 309±8 g, p=0.001), MAP (130±5 vs 110±4 mm Hg, p=0.05), left kidney weight (1.69±0.11 vs. 0.84±0.02 g, p=0.001) than placebo controls. Placebo treated females had normal GFR whereas DHT-treated females had a 40% reduction in GFR (0.42±0.07 vs 1.00±0.07 ml/min/1.73 m2. p<0.01) and 40% reduction in RPF (2.31±.01 vs 4.08±.01 mL/min/kg, p<0.05). Thus chronic hyperandrogenemia in aging females significantly reduces renal function, and likely contributes to hypertension. Studies must be done in PMW with PCOS that have elevated androgens after menopause to determine if their renal function is compromised. Our data would suggest that women who have had PCOS when younger do in fact have more CVD with age than non-PCOS women. Supported by NIH RO1HL66072 and PO1HL51971.

17.8 EFFECT OF ESTRADIOL REPLACEMENT IN HYPERTENSION IN THE AGING FEMALE DAH D SALT SENSITIVE RAT

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Menopause is associated with a higher prevalence of hypertension, obesity, and insulin resistance in women. The mechanisms underlying menopause-associated cardiovascular metabolic comorbidities remain to be elucidated. Lack of estrogens had been proposed to be one of the main mechanisms. In vivo and in vitro studies suggest that estrogens decrease blood pressure (BP) acting as a vasodilator. However, randomized clinical trials have shown no effect of estradiol replacement on BP in postmenopausal women, suggesting that the time that estradiol replacement begins is a critical factor in the response to estradiol. Aging female Dahl Salt Sensitive (DS) rats develop spontaneous hypertension by 12 mos of age and are no longer estrus cycling. In the present study, we aimed to determine the impact of estradiol replacement on hypertension in the aging female DS rats, and hypothesized that chronic estradiol replacement would normalize BP in aging female DS rats. Female DS rats, aged 12 mos, were implanted subcutaneously with 17β-estradiol pellets of two increasing concentrations (1x and 5x) consecutively. Animals were maintained in standard rodent diet (0.3% NaCl) with free access to water. BP was measured by radiotelemetry throughout the study period. At the end of the experimental period, plasma estradiol, insulin, leptin and aldosterone were determined by radioimmunoassay and visceral fat weight. The low estradiol dose (1x) increased plasma estradiol levels by about 3-fold compared to placebo (13.5±2.29 vs. 4.28±1.2 pg/ml, p=0.01). This dose of estradiol caused a transient 10 mm Hg reduction in BP that lasted only 4 days (164±2 vs. 154±5 mm Hg, p<0.05) and then BP returned to baseline values (164±3 vs. 165±3 mm Hg). Subsequently, the higher dose (5x) of 17β-estradiol increased plasma estradiol by almost 40-fold compared to placebo (84.28±9.67 vs. 2.30±0.45 pg/ml, p<0.001), but caused only a transient decrease in BP without reaching statistical significance. In contrast, high dose estradiol-treated rats had lower levels of plasma aldosterone (19.50± 1.66 vs. 44.62±8.36 ng/dl, p<0.05), leptin (4.32±10.62 vs. 8.20±1.45 ng/ml, p<0.05) and visceral fat (23.5± vs. 11.3± mg body weight) at the end of the treatment. In summary, estradiol treatment caused a tachyphylactic effect on BP in aging female DS rats despite the sustained reduction in plasma aldosterone, leptin and visceral fat.

Our study suggests that the tachyphylactic effect of estradiol on BP with aging may contribute to the lack of cardio-protective effects of estradiol supplementation seen in postmenopausal women.

17.9 ROLE OF THE RENAL NERVES AND ANGIOTENSIN II IN A MODEL OF POSTMENOPAUSAL HYPERTENSION

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Hypertension in postmenopausal women is not as well controlled in men regardless of ethnicity of the cohort. In our model of postmenopausal hypertension, the aging female spontaneously hypertensive rats (PMR), we found that blood pressure remains 110 mm Hg despite concomitant treatment antagonists of angiotensin AT1 receptors, only ETA ET receptors and 20-HETE synthesis inhibitors. We have also shown that the sympathetic nervous system and the renal nerves contribute to the hypertensin in PMR. In the present study, we determined whether renal denervation in combination with AT1 receptor antagonists would reduce BP below that found with triple therapy. PMR (aged 18 mos, n=5-6/group) underwent uninephrectomy, and two weeks...
later, unilateral renal denervation (RD) or sham (S) surgery and telemetry transmitter implantation. After two weeks recovery, mean arterial pressure (MAP) and heart rate (HR) were recorded for 5 days. Then PMR were treated with losartan for 5 days, and kidneys were removed for measurement of noninvasive NE (content). In contrast, while both sexes had an impaired ability to vasodilate to CO2, we have previously reported. Examination of their response to reduced end tidal CO2 has previously found that there was no difference in the reduction of cerebral flow velocity or vasoconstrictor response (Males: 3.7±3.7, Females: 3.5±4.0 %/mmHg CO2, p=0.01). However, it failed to normalize the BP. These results suggest that while renal denervation and AT1 receptor antagonist attenuation the hypertension in PMR, other mechanisms, likely endothelin and 20-HETE also contribute to their hypertension. These data also suggest that multiple interventions including pharmacotherapy may be required to control BP in postmenopausal women. Supported by NIH R01HL60672, P01HL097971 and AHA IHP070340015.

17.10 ELDERLY WOMEN MAINTAIN BETTER CEREBRAL BLOOD FLOW REGULATION TO BOTH PRESSURE AND CARBON DIOXIDE THAN ELDERLY MEN

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Background: We have previously found that both male and female elderly individuals have intact cerebral autoregulation but impaired cerebrovascular reactivity, with women performing better on both. The goal of this work was to examine if there were differences in the cerebrovascular ability to dilate vs constrict with changing end-tidal CO2 levels and if there were sex differences in this response. Previous data in the peripheral vasculature has demonstrated that populations with impaired endothelial function show a lack of dilation with intact constriction. Methods: We used transcranial Doppler to evaluate cerebrovascular reactivity in 419 (186 males) subjects over the age of 70 recruited as part of the MOBILIZE Boston study (MBS). The MBS is a prospective cohort study of a unique set of risk factors for falls in seniors in the Boston area. We assessed CO2 vasoreactivity in cerebral vessels during both hypocapnia (8% inspired CO2 and hypocapnia (100 mL/min ventilation) as well as cerebral autoregulation (sit to stand maneuver). All procedures were approved by the local institutional review board. Results: Male subjects had significantly lower CO2 vasoreactivity (Males: 2.8±1.7, Females: 3.1±0.8 %/mmHg CO2, p=0.001) as we have previously reported. Examination of their response to reduced end tidal CO2 (hypocapnia) found that there was no difference in the reduction of cerebral flow velocity or vasoconstrictor response (Males: 3.7±3.7, Females: 3.5±4.0 %/mmHg CO2, p=0.06). In contrast, while both sexes had an impaired ability to vasodilate to CO2, males demonstrated an even greater impairment than females (Males: 0±1.3, Females: 0.5±2.1 %/mmHg CO2, p=0.006). Interestingly, there was no correlation between the vasodilator or vasoconstrictor response and measures of cerebral auto-regulation. In addition, controlling for diabetes, hypertension or hypertension did not change the results. Conclusion: These data suggest that an impaired response to a dilatory cerebrovascular stimulus (hypocapnia) may indicate that cerebral endothelial dysfunction is present in aged. In contrast smooth muscle regulation of this vasculature remains intact since cerebral vessels were able to constrict during hypocapnia and dilate during a hypertensive stimulus while standing. Thus, improving endothelial function may result in improved dilation of vessels during stimuli that activate the endothelial pathways such as hypcapnia.

17.11 ESTROGENIC PHYTOCHEMICALS REDUCE BONE ADIPOSITY AND IMPROVES BONE QUALITY FOLLOWING OVARIECTOMY

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Dietary phytochemicals have previously been shown to reduce bone adiposity in postmenopausal women. Older menopausal women are taking botanical and dietary supplements to manage adverse body composition changes. Adipocytes and osteoblasts share a common progenitor cell, the mesenchymal stem cell, and thus botanical supplements may improve both adipose tissue and bone together. The efficacy of such supplements are often in question, which may be related to the “one molecule, one target” approach. Thus, the goal of the current research was to combine multiple natural products with synergistic actions resulting in a result of actions on multiple molecular targets that impact the life cycle of adipocytes and bone precursor cells. Aged, ovariecetomized (OVX) Fisher 344 rats from the National Institute of Aging colony were fed either a control diet or one containing various doses of phytochemicals (diet 1: 1000 mg/kg genistein, (G); diet 2: 500 mg/kg G, 200 mg/kg resveratrol (R), and 1000 mg/kg quercetin (Q); diet 3: 1000 mg/kg G, 400 mg/kg R, and 2000 mg/kg Q). Following 16 weeks, a dose-response in the number of adipocytes was found within femoral trabecular bone; diet 3 in particular caused a significant reduction compared to OVX controls (p<0.01). Bone adiposity was also found to be significantly correlated with the retroperitoneal fat depot, which was additionally reduced with dietary phytochemicals (p=0.05). Bone quality was determined using micro CT measures of the femoral bone. To be expected, OVX reduced bone quality compared to sham rats. Phytochemical supplementation improved trabecular bone quality compared to OVX; however it did not completely restore it to levels of sham rats. Serum IGF-1, a bone-promoting hormone, was similarly reduced following OVX. Dietary phytochemicals (diets 1 and 3) improved IGF-1 levels compared to OVX-control rats. While we were unable to completely reverse the damage caused by surgical menopause, the phytochemicals used in our study improved trabecular bone quality and adiposity compared to OVX. Thus we conclude that synergistic, plant-derived compounds with estrogenic properties may be helpful as part of a combined effort to prevent maladaptive bone changes including adipocyte infiltration and structural loss. Further, we provide mounting evidence that dietary phytochemicals may reduce adiposity as a result of menopause. This abstract does not reflect US EPA policy.

17.12 EFFECTS OF MENOPAUSE AND ACUTE EXERCISE ON BRACHIAL ARTERY FLOW MEDIATED DILATION AND PLASMA ENDOTHELIAL MICROPARTICLES

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Menopause is associated with an increase in risk factors for cardiovascular disease. Some evidence suggests a decrease in endothelial function from the peri- to post-menopausal stages. As women move into later menopausal stages, they may not exhibit responses to exercise that are typical in most populations. Objective: To evaluate differences in markers of endothelial function in response to an acute bout of exercise in peri- and post-menopausal women. Methods: Perimenopausal (PERI: 47 ± 2.6 yr) and postmenopausal (POST: 59 ± 2.0 yr) women, free of diabetes and cardiovascular disease, completed an acute bout of exercise at 60-64% of VO2 peak for 30 min. Prior to, and 30 min following exercise, flow-mediated dilation (FMD) was measured and collected to assess CD362E and CD31/C42d endothelial microparticle (EMP) concentrations. FMD (PERI: n=8; POST: n=6) was assessed via imaging of the brachial artery at baseline and after reactive hyperemia. FMD (%) was calculated as: (Diametermax − Diameterrest)/Diameterrest ×100. EMPs (PERI: n=3; POST: n=6) were quantified from plasma using fluorescence-activated cell sorting. Results: Values were presented at each time point ± SEM. Before exercise, PERI women had higher FMD (PERI: 8.4 ± 3.9 % vs. POST: 5.3 ± 0.9 %), lower CD362E EMP concentration (PERI: 344 ± 19 EMPs/μl plasma vs. POST: 402 ± 88 EMPs/μl plasma), and higher CD31/C42d EMP concentration (PERI: 4533 ± 532 vs. POST: 3446 ± 901) compared to POST women. After exercise, PERI women had an improvement in FMD (1.00 ± 3.2%), a slight decrease in CD362E EMP concentration (305 ± 35 EMPs/μl plasma), and a decrease in CD31/C42d EMP concentration (3870 ± 1223 EMPs/μl plasma). In POST women following exercise, FMD changed minimally (5.5 ± 1.0%), CD362E EMP concentration increased (470 ± 99 EMPs/μl plasma), and CD31/C42d EMP concentration decreased (2986 ± 772 EMPs/μl plasma). Statistical significance was not achieved for any markers. Conclusion: These preliminary data indicate impaired endothelial function and enhanced endothelial activation in post- compared to peri-menopausal women at rest. However, perimenopausal women displayed more endothelial apoptosis. The low exercise response may be a result of increases in CD362E EMP concentration in response to exercise may indicate women in later menopausal stages are resistant to the beneficial vascular effects of acute exercise. Funding Source: Research Trust Fund (Witkowski), Start-up (Jenkins).
18.0 PLENARY LECTURE

18.1 STUDYING BOTH SEXES: A NEW FRONTIER FOR DISCOVERY

Janine Clayton

The National Institutes of Health (NIH) funds basic, translational, and clinical research. From basic research to clinical care, studying both sexes is a guiding principle to aid in experimental design, hypothesis-generating, data-testing, and expanding understanding and deriving knowledge toward turning discovery into health for both women and men. Numerous factors prompted the development of new NIH policy, announced in May 2014, to ensure that sex is considered a basic biological variable in NIH-funded preclinical research. These included scientific progress emerging from NIH-funded laboratories, congressional interest and support, and ongoing NIH efforts to enhance reproducibility and transparency in preclinical research. Starting with applications with receipt dates beginning January 25, 2016, NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex. Selecting an appropriate preclinical model that considers the role of sex in the context of a specific research question of interest, especially for studies that model human physiology and pathology, is central to the scientific inquiry process. Reference: Clayton, J.A. & Collins, F.S. 2014. NIH to balance sex in clinical studies that model human physiology and pathology. Science. 343:1245826.

18.2 PREGNANCY AND PRE-ECLAMPSIA

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Preeclampsia is a pregnancy-specific hypertensive disorder that is considered a syndrome rather than a disease. It is characterized by hypertension, proteinuria, and other clinical features, which present in the second half of pregnancy or at delivery. It is estimated that 5-7% of all pregnancies in the United States are complicated by preeclampsia. While the cause of preeclampsia is unknown, research has suggested a potential role for placental dysfunction and abnormal angiogenesis. Recent studies have indicated that the placenta plays a critical role in regulating maternal-fetal blood flow and nutrient delivery. The placenta is a site of inflammation, and studies have shown that inflammation in the placenta may contribute to the development of preeclampsia. Therefore, understanding the mechanisms underlying placental inflammation and inflammation in the maternal circulation is crucial for developing new therapeutic strategies for the prevention and treatment of preeclampsia.
21.3 VASOPRESSIN: A NEW BEGINNING FOR THE END OF PREECLAMPSIA?

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Despite being in the medical literature for over 2000 years, the diagnosis and treatment for preeclampsia has essentially remained unchanged. To date, the only cure for this potentially devastating hypertensive disease in pregnancy is an often preterm delivery. It affects 5-7% of all pregnancies claiming the lives of 76,000 mothers and 500,000 children each year. The ability to predict, prevent, and treat preeclampsia is hampered by its unclear and multifactorial pathogenesis of which the initiating, first trimester mechanisms are uncertain. We have demonstrated that maternal plasma copeptin, a stable protein byproduct of arginine vasopressin (AVP) synthesis and release, is a robust predictor of the development of human preeclampsia as early as the 6th week of gestation. These data from our lab and others suggest an early role of AVP in the pathogenesis of preeclampsia. Our group demonstrated that chronic infusion of AVP throughout mouse pregnancy phenocopies all the vascular, renal, obstetric, and immune phenotypes in human preeclampsia. Early immune dysregulation is an early, initiating mechanism of preeclampsia. AVP is a hormone active in many vascular, renal, growth, and immune mechanisms. Given its early dysregulation in human preeclamptic pregnancies and its ability to recapitulate all the phenotypes of human preeclampsia in mice, we contend AVP is a novel, mechanistic connection between the known early and mid-gestation molecular processes that cause preeclampsia.

21.4 POPULATION STUDIES-GENDER AND SEX IN CVD, RENAL DISEASE, AND METABOLIC SYNDROME

21.1 SEX DIFFERENCES IN RISK FACTORS FOR STROKE IN WOMEN

Kathryn Reynolds


Stroke is the third leading cause of death for women, and fourth-leading cause of death for men. Women account for a majority of stroke deaths (61%), and have a higher lifetime risk of stroke than men (6%). Several risk factors for stroke are sex specific, such as pregnancy and pregnancy-related conditions (including preeclampsia, pregnancy-induced hypertension, gestational diabetes, premature birth, and birth of small size for gestational age). In addition, to the need for long-term data on the impact of pregnancy-related conditions and hormonal conditions, such as polycystic ovarian syndrome, intervention trials to reduce associated risk of stroke among these groups of women are needed. In addition, oral contraceptives and postmenopausal hormone therapy may be associated with risk and use is limited by women. Other risk factors have a higher prevalence or a higher associated risk of stroke in women, including diabetes mellitus, hypertension, atrial fibrillation, depression and psychosocial stress and trauma. Effective means of reducing risk of stroke among women with these conditions are needed. For example, among patients with atrial fibrillation, risk scores that take gender into account improve risk stratification; however, rates of anticoagulation have remained lower in women than men. Relatively similar risk reductions for both men and women have been observed in the primary prevention of stroke by lifestyle factors. A female-specific stroke score should be developed and evaluated to better reflect the risk of stroke in women across the lifespan. References: Bushnell C, et al. Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45: 1545-1588.

21.2 GENDER DIFFERENCES IN HYPERTENSION AND HEALTH BEHAVIORS

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Preeclampsia is a profound hypertensive disease in females and males. The presentation will highlight gender differences across the lifespan in cardiovascular disease, hypertension, and adherence to healthy lifestyle and medication-taking behaviors to improve hypertension control and reduce CVD risk. Efforts to overcome gender-specific barriers and tailor interventions that reduce risk for poor adherence and uncontrolled hypertension have the potential for substantive impact on reducing CVD across the lifespan and improving heart disease survival. The work was supported, in part, by the National Institutes of Health: Award R01 AG022536 from the National Institute on Aging, Award K12HD043451 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development, and Award U54 GM104940 from the National Institute of General Medical Sciences for the Louisiana Clinical and Translational Science Center.

21.3 TOBACCO SMOKING EXPOSURE FROM CHILDHOOD TO ADULTHOOD AND ADULT SUBCLINICAL VASCULAR DISEASE

Shengyu Li, Marie Krousel-Wood, Paul Whelton, and Wei Chen

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Tobacco smoking has been well established as a major risk factor for cardiometabolic diseases. However, limited information is available regarding the effects of tobacco smoking exposure beginning in childhood on adult cardiometabolic conditions. The current study examined the adverse effects of tobacco smoking exposure beginning in childhood on body mass index (BMI), ankle-brachial pulse wave velocity (abPWV) and carotid intima-media thickness (CIMT) in women and men from the Bogalusa Heart Study. Among non-smoking adults, exposure to secondhand smoke (SHS) either in childhood or in adulthood was associated with increased BMI, only in women (P=0.0001), with women continuously exposed to SHS from childhood having the highest BMI compared to women with other SHS exposure statuses. Exposure to SHS either in childhood or in adulthood was associated with increased CIMT in both men and women, with individuals continuously exposed to SHS from childhood having the greatest CIMT compared to those with other exposure statuses. Despite having lower BMI, adult cigarette smokers had faster abPWV and greater CIMT in both men and women. Further, cigarette smoking significantly exacerbated the adverse effects of age and metabolic syndrome on CIMT and of blood pressure on abPWV. In conclusion, SHS exposure beginning in childhood is associated with increased BMI, arterial stiffness, and atherosclerosis; cigarette smoking in adult life increases arterial stiffness and atherosclerosis and exacerbates the adverse effects of other risk factors on arterial stiffness and atherosclerosis, in otherwise healthy adults. Support: NIH K12HD043451, 5R01ES021724, and 2R01AG016592, AHA 13SDG14650068. REFERENCES: Yan M, Li S, Ge S, Fernandez C, Chen W, Srinivasan SR, Berenson G (2015). Tobacco smoking strengthens the association between elevated blood pressure and arterial stiffness: The Bogalusa Heart Study. J Hypertens 33:266-274. Chen W, Yun M, Fernandez C, Li S, Sun D, Lai CC, Hua Y, Wang F, Zhang T, Srinivasan SR, Berenson GS (2015). Secondhand smoke exposure is associated with increased carotid artery intima-media thickness: The Bogalusa Heart Study. Atherosclerosis 240:374-379. Li S, Yun M, Fernandez CA, Xu J, Srinivasan SR, Chen W, Berenson GS (2014). Cigarette smoking exacerbates the adverse effects of age and metabolic syndrome on subclinical atherosclerosis: The Bogalusa Heart Study. PLoS One 9:e96368.
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