Conference:
Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender
Annapolis, MD • November 17-20, 2015

Physiology and Gender
Meeting Program and Abstracts

American Physiological Society, Meetings Department
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2015 APS Conference
Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender

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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

UMMC
Women’s Health Research Center
### 2015 APS Conference: Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender
**November 17—20, 2015**
**Annapolis, Maryland**
### Week-At-A-Glance

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<th>Tuesday, November 17</th>
<th>Wednesday, November 18</th>
<th>Thursday, November 19</th>
<th>Friday, November 20</th>
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<tbody>
<tr>
<td>3:00 PM Registration</td>
<td>7:00 AM Registration</td>
<td>7:30 AM Registration</td>
<td>7:30 AM Registration</td>
</tr>
<tr>
<td>7:50—8:00 AM Welcome S. Ananth Karumanchi</td>
<td>8:00—10:00 AM Symposium I Immune System and Regenerative Medicine—Impact of Gender/Sex Heddwen Brooks</td>
<td>8:00—10:00 AM Symposium V Developmental Programming of Cardiovascular, Renal and Metabolic Diseases: Roles of Gender/Sex Javier Salazar</td>
<td>8:00—10:00 AM Symposium VIII Pregnancy and Pre-eclampsia Christine Marie-Bilkan</td>
</tr>
<tr>
<td>10:00—10:30 AM Break</td>
<td>10:00—10:30 AM Break</td>
<td>10:00—10:30 AM Break</td>
<td>10:00—11:30 AM Symposium IX Population Studies—Gender/Sex in CVD, Renal Disease, and Metabolic Syndrome Rita Tostes</td>
</tr>
<tr>
<td>12:30—1:30 PM Lunch</td>
<td>12:30—1:30 PM Lunch</td>
<td>12:30—1:30 PM Lunch</td>
<td>11:35—11:45 AM Closing Remarks</td>
</tr>
<tr>
<td>2:30—3:50 PM Symposium III Neuro Control of Cardiovascular, Renal and Metabolic Diseases: Impact of Gender/Sex Willis K. Samson</td>
<td>2:30—3:00 PM Plenary Lecture Kathryn Sandberg (Chair) Janine Clayton (Speaker)</td>
<td>3:00—5:00 PM Symposium VII Obesity, Metabolic Syndrome, Gender/Sex James R. Sowers</td>
<td></td>
</tr>
<tr>
<td>6:30—8:30 PM Welcome and Opening Reception</td>
<td>5:00—6:00 PM Career Development Session Jennifer Sasser Erica Wehrwein</td>
<td>7:00—9:30 PM Banquet and Awards Ceremony</td>
<td></td>
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</tbody>
</table>
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
The registration fee includes entry into all scientific sessions, poster socials, opening reception, and the closing conference banquet*.
*Must have a ticket for entry.

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 non-members.

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.

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
Welcome

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

Chairs:
Jane F. Rockelhoff, Univ. of Mississippi Med. Ctr.

Symposia I

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

Chair:
Heddwen 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.

8:40 AM


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 Dilatation. Kristine DeLeon-Pennell, Univ. of Mississippi Med. Ctr., Jackson. (5.11).

9:15 AM

2.5 The Effects of Testosterone and Oxidative Stress on Neuroinflammatory Signaling in Dopamine Neurons. Shakeetha Holmes, Univ. of North Texas Hlth. Sc. Sch. of Pharmacy, Denton, TX. (14.6).

9:45 AM

2.6 Sexually Dimorphic Myeloid Inflammatory and Metabolic Responses to Diet-induced Obesity. Kanakadurga Singer, Univ. of Michigan. (6.17).

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.

10:30 AM

3.1 Testosterone Therapy in Men with Testosterone Deficiency (TD): Advances and Controversies. Abdulmaged M. Traish, Boston Univ. Sch. of Med.

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. Ctr.

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 Hypercapnic 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 Penile Arteries Underlie Erectile Dysfunction Induced by Androgen Deprivation. Rheure Lopes, Univ. of São Paulo, Brazil. (4.9).

12:00 Noon

3.6 6β-Hydroxytestosterone, A Cytochrome P450 1B1-Derived Metabolite of Testosterone Plays an Important Role in Renal Dysfunction Associated with Angiotensin II-Induced Hypertension in Male Mice. Ajeeeth Pingili, Univ. of Tennessee Hlth. Sc. Ctr, Memphis. (7.13).

12:15 PM

3.7 Attenuation of Cardiac Aging and Leptin-dependent Cardioprotection in Long-lived αMUPA Mice. Edith Hochhauser, Rubin Med. Ctr., Israel. (5.9).

Poster Session I

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

Poster Board

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


5.2 A Study of the Potential Risk Factors of Cardiovascular Diseases in Young Sudanese females. L. Al-Assoom Univ. of Dammam, Saudi Arabia.

6.6 Assessment of Gender and Age-dependent Patterns of Cardiovascular Remodeling in Spontaneously Hypertensive Rats (SHR). S. Al-Ghuri, I. Kopaliani, B. Zatschler, H. Galli, M. Kasper, and A. Deussen. Tech. Univ. of Dresden, Germany.

7.7 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. Awoetodu, R. Erasmus, A. Awoetodu, and A. Namugowa, Walter Sisulu Univ., Mthatha, South Africa, and Univ. of Stellenbosch, Cape Town, South Africa.

8.8 Functional and Structural Changes in Internal Penile Arteries Underlie Erectile Dysfunction Induced by Androgen Deprivation. R. Lopes, K. Neves, M. Barbosa, V. Ollivon, S. Ruginsk, J. Antunes, L. Ramalho, F. Carneiro, and R. Tostes Univ. of São Paulo, Ribeirão Preto, Brazil.

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DAILY SCHEDULE

Poster Board 9

Poster Session II

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

Poster Board 11

Poster Board 12
5.2 Haemostatic and Rheologic Factorials as Determinants of Acute Myocardial Infections in Nigerians. E. Nwalli, and O. Ajayi. Univ. of Benin, Benin City, Nigeria.

Poster Board 13

Poster Board 14
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.

Poster Board 15

Poster Board 16
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.

Poster Board 17
5.7 Cardiac Remodeling in Female Hearts by Kv11.2 Subunit. J. Tur, K. Chapalamadugu, T. Padhaver, and S. Tipparaju. Univ. of South Florida.

Poster Board 18

Poster Board 19

Poster Board 20

Poster Board 21

Poster Session III

6.0 METABOLISM AND DIABETES
Wednes., 1:30—2:30 PM, Rhode/Severn Room.

Poster Board 22

Poster Board 23

Poster Board 24
6.3 Withdrawn.

Poster Board 25

Poster Board 26

Poster Board 27

Poster Board 28

Poster Board 29
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. S. Shaligram, G. Sangiuesa, F. Akther, M. Alegret, J. C. Laguna, and R. Rahimian. Univ. of the Pacific, and Univ. of Barcelona, Spain.

Poster Board 30

Poster Board 31

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.
DAILY SCHEDULE

Symposia V
11.0 DEVELOPMENTAL PROGRAMMING OF CARDIOVASCULAR, RENAL AND METABOLIC DISEASES: ROLES OF GENDER AND SEX
Thurs., 8:00—10:00 AM, Wye Room.

Chair: Javier Salazar, Univ. of Murcia, Spain.

8:00 AM
11.1 Effect of Estrogen in Gender-dependent Fetal Programming of Adult Cardiovascular Dysfunction. Daliao Xiao, Loma Linda Univ. Sch. of Med.

8:20 AM
11.2 Sex Differences in Cardiovascular and Metabolic Risks Due to Early Life Stress. Analia Loria, Univ. of Kentucky, Lexington.

8:40 AM
11.3 Maternal Undernutrition Significantly Impacts Ovarian Follicle Number and Increases Ovarian Oxidative Stress in Adult Rat Offspring. Deborah Sloboda, McMaster Univ., Hamilton, Canada.

9:00 AM
11.4 Reduced Sleep Time During Pregnancy-Effects on Renal Morphology and Function of Female Offspring. Guiomar N. Gomes, Univ. of Sao Paulo, Brazil. (16.5)

9:15 AM
11.5 Delayed Effects of Prenatal Hypoxia on Adult Rats Pulmonary Vessels Structure and Reactivity. Martin Vizek, Charles Univ., Prague, Czech Rep. (16.6).

9:30 AM
11.6 Sex Difference in Sensitization of Angiotensin (ANG) II-elicited Hypertension in Offspring of Hypertensive Rats. Baqijan Xue, Univ. of Iowa. (16.7).

9:45 AM
11.7 Sex Differences in Cardiovascular Responses to Stress in Adult Rats Prenatally Exposed to Dexamethasone. Tabet Hale, Univ. of Arizona, Phoenix. (16.8).

Symposia VI
12.0 NON-REPRODUCTIVE EFFECTS OF SEX HORMONES AND RECEPTORS-B
Thurs., 10:30 AM—12:30 PM, Wye Room.

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

10:30 AM
12.1 Androgen Effects on Endothelial Function in Women with Polycystic Ovary Syndrome. Nina Stachenfeld, Yale Univ.

10:50 AM
12.2 Mechanisms Involved in Cardioprotection in Females: Role of Estrogen and Estrogen Receptors (ERs). Elizabeth Murphy, NIH, NHLBI.
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<th>Poster Board</th>
<th>14.2</th>
<th>Sex Differences in the Cerebral Vascular Function and K Channel Role. M. Pabbidi, Univ. of Mississippi Med. Ctr., Jackson.</th>
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<tbody>
<tr>
<td>Poster Board</td>
<td>14.3</td>
<td>Characterizing the Gender Differences of Multidrug-resistance Peptide (MRP) Transporter Expression in Mouse Blood-brain Interfaces. K. Flores, J. L. Reinfro, and J. Manautou, Univ. of Connecticut.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>14.4</td>
<td>Sex and Genotype Differences to Epinephrine Infusions in Humans. A. Eugene, and M. Joyner. Mayo Clinic, Rochester, MN.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>14.5</td>
<td>Sex Differences in the Effect of Hypoglycemia on Baroreflex Sensitivity in Patients with Type 1 Diabetes Mellitus. J. Limberg, S. Dube, M. Mozer, A. Basu, R. Basu, and M. Joyner. Mayo Clinic, Rochester, MN.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>14.6</td>
<td>The Effects of Testosterone and Oxidative Stress on Neuroinflammatory Signaling in Dopamine Neurons. S. Holmes, and R. Cunningham. Univ. of North Texas Hlth. Sc. Ctr., Forth Worth.</td>
</tr>
<tr>
<td>Poster Session II</td>
<td>PREGNANCY</td>
<td>Thurs., 1:30—2:30 PM, Rhode/Severn Room.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>15.2</td>
<td>Vitamin D Supplementation Inhibits Blood Pressure and Uterine Artery Resistance Induced by Autonomicnobs 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.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>15.7</td>
<td>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.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>15.10</td>
<td>Up-regulation of VEGFR2 Improves Uterine Artery Myogenic Response and Maternal Hypertension Altered by Uterine Perfusion Pressure Reductions. B. Basler, 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.</td>
</tr>
<tr>
<td>Poster Session II</td>
<td>DEVELOPMENTAL PROGRAMMING</td>
<td>Thurs., 1:30—2:30 PM, Rhode/Severn Room.</td>
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<tr>
<td>Poster Board</td>
<td>16.2</td>
<td>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.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>16.3</td>
<td>Sphingosine-1-phosphate Receptor Type 3 Plays a Role in the Etiology of High Blood Pressure Programmed by Intrauterine Growth Restriction in the Male but not the Female Mouse. S. Intapad. Univ. of Mississippi Med. Ctr., Jackson.</td>
</tr>
<tr>
<td>Poster Board</td>
<td>16.4</td>
<td>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.</td>
</tr>
</tbody>
</table>
17.0 AGING AND MENOPAUSE

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


17.2 Gender Differences in Circulating Microparticles in Middle-Aged Adults. T. Bammert, J. Hijmans, C. Dow, W. Reilakvam, G. Linenberg, J. Greiner, B. Stauffer, and C. DeSouza. Univ. of Colorado, Boulder.


17.4 ET₄ Receptor Antagonism Prevents Ang II-Induced Hypertension in VCD-Treated Postmenopausal Female Mice. D. Pollow, Jr., M. J. Romero-Aleshère, and H. L. Brooks. Univ. of Arizona, Tucson.


### FRIDAY, NOVEMBER 20, 2015

#### Symposia VIII

**20.0 PREGNANCY AND PRE-ECLAMPSIA**  
Fri., 8:00—10:00 AM, Wye Room.

**Chair:** Christine Marie, NIH, NHLBI.

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<th>Presenter(s)</th>
<th>Institution</th>
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</thead>
<tbody>
<tr>
<td>8:00 AM</td>
<td>20.1</td>
<td>Mechanisms of Maternal Uterine Vascular Remodeling During Gestation</td>
<td>George Osol</td>
<td>Univ. of Vermont Coll. Med., Burlington</td>
</tr>
<tr>
<td>8:20 AM</td>
<td>20.2</td>
<td>Spontaneous Superimposed Pre-eclampsia in Dahl Salt Sensitive Rats</td>
<td>Jennifer Sasser</td>
<td>Univ. of Mississippi Med. Ctr, Jackson</td>
</tr>
<tr>
<td>8:40 AM</td>
<td>20.3</td>
<td>Vasopressin: A New Beginning for the End of Pre-eclampsia?</td>
<td>Mark Santillan</td>
<td>Univ. of Iowa.</td>
</tr>
<tr>
<td>9:00 AM</td>
<td>20.4</td>
<td>Up-regulation of VEGFR2 Improves Uterine Artery Myogenic Response</td>
<td>Brittany Balsey</td>
<td>Univ. of Akron.</td>
</tr>
<tr>
<td>9:15 AM</td>
<td>20.5</td>
<td>Effects of High-sucrose Diet on Blood Pressure Regulation During</td>
<td>Frank Spradley</td>
<td>Univ. of Mississippi Med. Ctr, Jackson</td>
</tr>
<tr>
<td>9:45 AM</td>
<td>20.6</td>
<td>Mechanisms of Renal and Colonic Potassium Retention During</td>
<td>Crystal West</td>
<td>Georgetown Univ.</td>
</tr>
<tr>
<td>10:30 AM</td>
<td>20.7</td>
<td>Impaired Flow-Mediated Dilation Before, During and After Pre-eclampsia</td>
<td>Tracey Weissgerber</td>
<td>Mayo Clinic, Rochester, MN.</td>
</tr>
</tbody>
</table>

#### Symposia IX

**21.0 POPULATION STUDIES-GENDER AND SEX IN CVD, RENAL DISEASE, AND METABOLIC SYNDROME**  
Fri., 10:30—11:30 AM, Wye Room.

**Chair:** Rita Tostes, Univ. of São Paulo, Brazil.

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Presenter(s)</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:50 AM</td>
<td>21.2</td>
<td>Gender Differences in Hypertension and Health Behaviors</td>
<td>Marie Krousel-Wood</td>
<td>Tulane Univ.</td>
</tr>
<tr>
<td>11:10 AM</td>
<td>21.3</td>
<td>Tobacco Smoking Exposure from Childhood to Adulthood and Adult Subclinical Vascular Disease</td>
<td>Shengxu Li</td>
<td>Tulane Univ.</td>
</tr>
</tbody>
</table>

#### Closing Remarks

**22.0 CLOSING REMARKS**  
Fri., 11:35—11:45 AM, Wye Room.

**Chairs:** Jane F. Reckelhoff, Univ. of Mississippi Med. Ctr; S. Ananth Karumanchi, Harvard Med. Sch.

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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
Abstracts of Invited and Contributed Presentations

2.0 Immune System and Regenerative Medicine Impact of Gender and Sex........................................13
3.0 Non-reproductive Actions of Sex Hormones and Receptors-A.....................................................13
4.0 Cardiovascular Disease....................................................................................................................14
5.0 Cardiac..................................................................................................................................................16
6.0 Metabolism and Diabetes...................................................................................................................19
7.0 Renal ....................................................................................................................................................24
8.0 Neuro Control of Cardiovascular, Renal and Metabolic Disease: Impact of Gender and Sex……27
11.0 Developmental Programming of Cardiovascular, Renal and Metabolic Diseases:
   Roles of Gender and Sex.......................................................................................................................27
12.0 Non-reproductive Effects of Sex Hormones and Receptors-B.......................................................28
13.0 Respiration.........................................................................................................................................29
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20.0 Pregnancy and Preeclampsia............................................................................................................42
21.0 Population Studies-Gender and Sex in CVD, Renal Disease, and Metabolic Syndrome.............43

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2.0 IMMUNE SYSTEM AND REGENERATIVE MEDICINE—IMPACT OF GENDER AND SEX

2.1 ESTROGEN RECEPTOR ALPHA ENHANCES LOSS OF TOLERANCE TO NUCLEAR ANTIGENS AND IMMUNE CELL ACTIVATION INDUCED BY THE SLE1 SUSCEPTIBILITY ALLELE AND IS RESPONSIBLE FOR THE SEX BIASES ASSOCIATED WITH SLE1

Karen Gould1 and Shayla Yoachim1

1Genetics, Cell Biology & Anatomy, Univ. of Nebraska Med. Ctr., 985805 Nebraska Med. Ctr., Omaha, NE, 68198-5805.

Lupus is an autoimmune disease characterized by the development of anti-nuclear autoantibodies and immune complex-mediated nephritis. ~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. Disruption of ERα 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

2.2 ROLE OF T CELLS IN THE DEVELOPMENT OF CARDIOVASCULAR DISEASE AND HYPERTENSION

Jennifer Sullivan1

1Pathology, Georgia Regents Univ., 1459 Laney Walker Blvd., Augusta, GA, 30912.

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 T 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 underlie 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., Kirabo 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.

2.3 ESTROGEN AND ITS EFFECTS ON WOMEN WITH LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is an autoimmune disorder that predominantly afflicts women of childbearing age. Women with SLE have a marked increase in the risk for developing hypertension, cardiovascular, and renal disease. Because of the strong bias towards women, estrogens are commonly implicated in the pathogenesis of SLE. Indeed, numerous studies in experimental models of SLE show that removing estrogens, or their receptors, early in life has a profound effect to delay the production of autoantibodies, renal pathology, and mortality. However, the role of estrogens and how they impact SLE disease progression and the associated cardiovascular risk factors like hypertension remain surprising unclear in adult women. Recent data from our laboratory suggest that there may be distinct temporal effects of estrogen in an established experimental mouse model of SLE (female NZBWF1 mice). Whereas early life (8 weeks of age) removal of estrogens by ovariectomy causes the expected delay in the onset of autoantibody production and renal injury, removal of estrogens in adulthood (30 weeks of age) exacerbates the hypertension and renal injury associated with SLE without impacting autoantibody production. Further studies are needed in women to better understand the role of estrogens in their disease progression, and experimental animal models may be useful to understand the complex role that estrogens have in this disease.

3.0 NON-REPRODUCTIVE ACTIONS OF SEX HORMONES AND RECEPTORS—A

3.1 TESTOSTERONE THERAPY IN MEN WITH TESTOSTERONE DEFICIENCY (TD): ADVANCES AND CONTROVERSIES

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Testosterone (T) deficiency is a medical condition which has been recognized for more than a century. Since 1940s T therapy was reported to improve overall health in hypogonadal men with no serious adverse effects. Data from a number of recent studies demonstrate that T therapy is associated with: a) reduced body weight and waist circumference in overweight and obese men, b) increased lean body mass, c) reduced body fat mass, and d) improved in glycemic control, e) improvements in lipid profiles, f) improvement in metabolic syndrome components, including blood pressure, reduced inflammation, and g) improved sexual function. T therapy is also shown in several studies to be associated with amelioration of diabetes and reduced mortality. A recent meta-analysis revealed no increase in cardiovascular (CV) risks in men receiving T therapy. However, few studies, with serious methodological and analytical flaws, suggested that T therapy is associated with increased CV risk. A thorough and critical analyses of these studies showed that the risks purported are unsubstantiated.

Also recent studies showed that no evidence exists that T therapy increases the risk of prostate cancer. In summary, there is no convincing evidence-based data to suggest increased CV risks with T therapy. In fact, the literature is replete with studies demonstrating beneficial effects of T therapy on CV and overall health. Reference: Morgerntaler A, Miner MM, Caliber M, Guay AT, Khera V, Trainis AM. Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin. Proc. 2015 Feb;90(2):224-51.

3.2 ESTROGEN REGULATES ADIPOGENESIS AND LIPID SYNTHESIS THROUGH MEMBRANE AND NUCLEAR ERALPHA

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Estrogen has multiple, usually favorable metabolic effects, including suppression of appetite and adipogenesis, lipid synthesis, and stimulation of fatty acid oxidation and glycose homeostasis. The mechanisms are often incompletely understood and the collaboration or participation of various estrogen receptor cellular pools and isoforms is poorly understood. We have recently focused on the ability of estrogen to act through membrane ERalpha to inhibit all forms of lipid synthesis in the liver (in-vivo) and isolated hepatocytes (Science Signaling, 2013). These and other studies to be mentioned defines a new concept in ERalpha regulation or participation of various estrogen receptor cellular pools and isoforms is poorly understood. We have recently focused on the ability of estrogen to act through membrane ERα to inhibit all forms of lipid synthesis in the liver (in-vivo) and isolated hepatocytes (Science Signaling, 2013). These and other studies to be mentioned defines a new concept in ERalpha regulation or participation of various estrogen receptor cellular pools and isoforms is poorly understood. We have recently focused on the ability of estrogen to act through membrane ERα to inhibit all forms of lipid synthesis in the liver (in-vivo) and isolated hepatocytes (Science Signaling, 2013). These and other studies to be mentioned defines a new concept in ERalpha regulation or participation of various estrogen receptor cellular pools and isoforms is poorly understood. We have recently focused on the ability of estrogen to act through membrane ERα to inhibit all forms of lipid synthesis in the liver (in-vivo) and isolated hepatocytes (Science Signaling, 2013). These and other studies to be mentioned defines a new concept in ERalpha regulation or participation of various estrogen receptor cellular pools and isoforms is poorly understood. We have recently focused on the ability of estrogen to act through membrane ERα to inhibit all forms of lipid synthesis in the liver (in-vivo) and isolated hepatocytes (Science Signaling, 2013). These and other studies to be mentioned defines a new concept in ERalpha regulation or participation of various estrogen receptor cellular pools and isoforms is poorly understood. We have recently focused on the ability of estrogen to act through membrane ERα to inhibit all forms of lipid synthesis in the liver (in-vivo) and isolated hepatocytes (Science Signaling, 2013). These and other studies to be mentioned defines a new concept in ERalpha regulation or participation of various estrogen receptor cellular pools and isoforms is poorly understood. We have recently focused on the ability of estrogen to act through membrane ERα to inhibit all forms of lipid synthesis in the liver (in-vivo) and isolated hepatocytes (Science Signaling, 2013).
3.3 GPER AND VASCULAR FUNCTION

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While estrogen receptors ERα and ERβ are known to induce transcriptional effects, a new membrane-bound, G protein-coupled estrogen receptor (GPER) was recently identified as a possible mediator of estrogen's nongenomic effects. A growing body of evidence from our lab and others shows that GPER elicits many of the beneficial actions of estrogen in the cardiovascular system. Using the mERz2 congenic model of angiotensin II-induced hypertension, we showed that activation of GPER alone emulates the protective effects of estrogen on blood pressure via regulation of the vascular renin-angiotensin system and vascular tone. Further studies to determine the signaling mechanisms for GPER in the vasculature found that this receptor induces nitric oxide release from endothelial cells and activates the cyclic AMP pathway in smooth muscle cells. In salt-sensitive hypertension, GPER counteracts proteinuria and oxidative stress in the kidney and opposes vascular remodeling in large conduit vessels. GPER expression and function is reduced in males and aging females, which has important clinical implications. We hope that research on the cardiovascular effects of estrogen and the receptors and mechanisms involved will lead to improvements in hormone therapy for postmenopausal women. (NIH 103471). Lindsey et al 2009. Endocrinology. 150:3753-58. Lindsey et al 2011. Hypertension. 58:665-671. Lindsey et al 2011. J Cardiovasc. Pharmacol. 57:598-603. Lindsey et al 2013. Am J Physiol Endocrinol Metab. 305(1):E113-8. Lindsey et al 2014. Steroids. 81:99-102.

4.0 CARDIOVASCULAR DISEASE

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

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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 passaged 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 CM0001, a broad-based matrix metalloproteinase (MMP) inhibitor, and AG1478, an epithelial growth factor receptor (EGFR) selective inhibitor, we demonstrated that 2ME2 mediated phosphorylation of ERK1/2 is depended on the activation of MMPs and transactivation of EGFR receptor. Furthermore, marimastat, 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 -1 (GPER-1) with the selective agonist G1 elicited similar signaling pathway and down-regulated the AT1R expression. Moreover, immunoprecipitation studies show 2ME2, G1 and phosphate EGFR at tyrosine 1173, which is a critical residue on EGFR to interact with Src homology 2 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 the 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

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Objectives: Primary prevention of cardiovascular disease (CVD) relies on the identification of individuals at increased risk of developing cardiovascular events. Circulating biomarkers mirroring the (subclinical) disease process are valuable tools for CVD risk prediction. Evidence is accumulating that the clinical presentation and the mechanisms for CVD development and progression differ between men and women. To what extent this is reflected in biomarker profiles is unknown. We performed a systematic review of sex-specific data on established and emerging biomarker levels and their association with CVD in the setting of primary prevention. Methods: PubMed MEDLINE and Embase were searched on 25th February 2014 and updated on 15th January 2015. Biomarkers included represented pathophysiological pathways of lipid metabolism, inflammation, kidney function and of the heart. Data on pathophysiological characteristics, sex-specific biomarker levels, biomarker association with future CVD events and clinical value were extracted. Results: Only 55 studies out of 5,374 publications provided sex-specific information. The majority of these 55 studies only corrected for sex in multivariable models without presenting sex-specific results. All the biomarkers under study show a similar direction of the association with CVD between men and women. The magnitude of the association between the biomarker and outcome varied by study and sex. The cardiac specific biomarkers troponin and B type natriuretic peptide (BNP) show the most prominent differences in baseline levels between men and women. Troponin was more likely to be detected in men and women have higher levels of BNP. The predictive values of troponin levels are similar between men and women however for BNP the data is inconsistent with one study reporting a stronger association for men. The additional clinical utility of novel biomarkers was reported in seven publications, only one of which was stratified by sex. Conclusions: Sex-specific data on biomarkers for CVD in the general population exists but is under-reported. There is inconsistency in sex-specific differences in levels of traditional biomarkers in their relation to CVD. To improve personalized cardiovascular diagnosis and care for men and women, reporting sex-specific data on clinical utility of biomarkers is crucial and should be encouraged in publications of sufficiently powered studies. This project has received funding under the Marie Curie grant agreement No 289903 via EUTRAIN.

4.3 LOSS OF THE Y CHROMOSOME IN MEN UNDERGOING CAROTID ENDARTERECTOMY

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Introduction: The Y chromosome has long been considered genomic wasteland with few genes only implicated in sex determination. However, recent studies found Y-chromosomal dosage-sensitive whole-genome regulators, an immunoregulatory role for Y, and a relation between loss of Y (LOY) and a higher risk of cancer and mortality. Given the involvement of immune cells in atherosclerosis, we hypothesized that LOY is associated with specific cardiovascular disease (CVD) phenotypes in men undergoing carotid endarterectomy (CEA). Materials and Methods: LOY was quantified in blood from raw intensity genotyping data in a cohort of 368 men within the Athero-Express biobank study. Atherosclerotic plaques were dissected, and the culprit lesions were used for histological characterisation and the measurement of various inflammatory proteins. We tested LOY for association with measures of cardiovascular disease severity and inflammatory atherosclerotic plaque phenotypes (macrophage content, IL6, IL10, IL12, TNFα, IFNγ and TGFβ) levels. In addition, we assessed the association of LOY with secondary major cardiovascular events during 3-year follow-up. The study was conducted in accordance with the declaration of Helsinki. Results: Out of 368 CEA patients, 61 exhibited LOY. Loss of Y in blood was negatively associated with age (p=0.031/10yr, r2=0.08, p=2.2×10^-8). Loss of Y was not associated with history of coronary artery disease, stroke, contralateral carotid stenosis or peripheral arterial disease of the lower limbs. Likewise we found no association of LOY with macrophage content or inflammatory cytokines in the plaque. Interestingly, LOY was independently associated with secondary major cardiovascular events during three-year follow-up (p=0.032) in a Cox regression model corrected for confounders. Conclusion: LOY in circulating blood cells is independently associated with secondary major cardiovascular events in a severely atherosclerotic population.
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 Halijerna 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

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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), which operates in acute phase responses. Elevated GDF-15 serum levels are an established risk factor 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 by ELISA in a subset of 1064 patients from the Amsterdam 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: 99042 [52094, 173273]), p value for difference 0.241). High levels of GDF-15 were associated with increasing age, reducing renal function, and a history of diabetes. However 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=0.02 in men) and more precisely for peripheral events (Quantile 4; HR 3.41 95% CI 1.11-10.47, p=0.003 in women vs. HR 0.68 95% CI 0.40-1.17 p=0.16 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

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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 different selected age, sex and ethnic groups. Aim and objective: 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 concomitant medication and female undergoing carotid endarterectomy. Plasma 25-OH-vitamin D was determined using HPLC method. Statistical analysis: Data were analyzed using SPSS 20. Data were normally distributed. Multivariate linear regression model was used to predict the relationship between multiple risk factors and haemodynamic parameters. The following haemodynamic parameters were used separately as a dependent variable: resting pulse rate, maximum pulse rate, resting diastolic blood pressure, maximum diastolic blood pressure, resting systolic blood pressure, maximum systolic blood pressure. The independent variables were body weight, waist circumference, VO2max, plasma 25-OH-vitamin D. Results: Mean age was 20.8±2.4 years, mean weight= 58.1±14.8 Kg, mean BMI= 23.0±4.8 Kg/m², mean VO2max= 33.7±11.0 ml/kg/min, mean plasma 25-OH-vitamin D= 15.10±0.73 ng/ml. Multivariate linear regression model revealed significant positive linear relationship between body weight and resting diastolic (y1), and resting systolic blood pressure (y2) with p and R2 values (0.041, 0.006) (0.121, 0.107) respectively, and for age, y3=-0.244x+127.1 x: p<0.01, R2=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.

4.6 ASSESSMENT OF GENDER- AND AGE-DEPENDENT PATTERNS OF CARDIOVASCULAR REMODELING IN SPONTANEOUSLY HYPTERTENSIVE RATS (SHR)

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Cardiovascular diseases are the leading cause of death worldwide. Whereas men are more prone to develop hypertension disorders, the death rate due to cardiovascular events is much higher among women. Despite this disparity, experimental and clinical long-term studies are still lacking to better understand the contribution of gender to age-dependent progression of hypertensive cardiovascular diseases. Here, we investigated the impact of gender in progression of cardiovascular remodeling in female and male SHR 5-, 14-, 29- and 36-week-old female and male SHR, age and gender matched with Wistar Kyoto rats (WKY) were studied. Animals were handled with permission (No: 24-015842-4/1-012-16) of institutional committee and the local authorities. Systolic blood pressure (SBP) was measured weekly with the tail-cuff method. Vessel function of aortic rings was quantified using Mulvany Myograph. Structural changes of aorta and heart were assessed by histological staining and CARS microscopy. Compared to WKY, all SHR showed significantly (P<0.001) higher SBP, except age of 5 weeks. Interestingly, at 14 weeks, SBP of female SHR was ~40 mmHg lower than that of male SHR. At this age, isolated aorta of female SHR showed significantly (P<0.001) lower vasoconstrictive response to norepinephrine stimulation compared to male SHR. While 5- and 14-week-old SHR showed normal endothelial function, this was deteriorated in male SHR at 29 weeks. In female SHR endothelial function was still preserved until 36 weeks. At 36 weeks SMC relaxation was strongly impaired. This was associated with distinct alterations in vessel structure. A massive degradation of elastin and increased degree of fibrosis was observed particularly in male SHR to a lesser degree in female SHR. Advanced functional and structural changes in aorta were accompanied by concentric hypertrophy of the heart, starting at 29 weeks in male and at 36 weeks in female SHR. Cardiac fibrosis was much stronger in male than in female SHR at the age of 36 weeks. An age-dependent upregulation of ACE2 and AT1 receptor expression was found in female as compared to male SHR. This study shows that the SHR model is a valuable tool to address 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 DEIVERED FROM PERIPHERAL PULSE WAVE ANALYSIS USING RADIAL APPLANATION TONOMETRY IN HIV POSITIVE PATIENTS FROM MITHATHA DISTRICT OF SOUTH AFRICA

Kofo Awoteshu1, Raj Ensmmans2, Abobala AWotedu3, and Ambrose Narrugowa1


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),
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<0.002). The HIV positive participants also had higher ejection duration index (ED %) with no evidence that HIV was being observed in those that were not on treatment (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, sub-endocardial variability ratio, ejection duration index, arterial stiffness, cardiac function.

4.8 FUNCTIONAL AND STRUCTURAL CHANGES IN INTERNAL PUDENDAL ARTERIES UNDERLYING ERECTILE DYSFUNCTION INDUCED BY ANDROGEN DEPRIVATION

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, 3Dept. Biodynamics of the Human Body Movement, Univ. of São Paulo, Avenida 24 A, 1515, Rio Claro/São Paulo, 13506-900, Brazil, 4.9 EFFECTS OF AEROBIC EXERCISE TRAINING ON RENIN-ANGIOTENSIN SYSTEM COMPONENTS IN HYPERTENSIVE WOMEN

The renin-angiotensin system (RAS) plays a major role in the pathogenesis of hypertension mainly through the classic axis, composed by angiotensin-converting (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-AT1-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 been demonstrated that menopause hormone therapy increases cardiovascular risk. Thus demonstra-

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ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS

EFFECTS IN THE MYOCARDIUM OF MALE AND FEMALE ENDOTHEXIC MICE

Jong Hoob1,2, Karwul Ariz3, Deborah Stiwik1, and Wilson Coleman1


miRNA-126 (0.19±0.04 vs 0.18±0.03), miRNA-145 (0.008±0.002 vs 0.009±0.001) and miRNA-150 (0.029±0.014 vs 0.071±0.021) were not significantly different between the men and women. In summary, circulating expression of specific vascular-related miRNAs is not influenced by gender in middle-aged adults.
CAECAL TRANSPLANTS (ΔCa). No data is available about the effect of cGMP in septic female (F) hearts. We studied M and F C57BL16 mice (WT) as well as mice deficient in sGC activity (sGC−/−). Lipopolysaccharide (LPS) administration (ip) induced an inflammatory shock syndrome and cardiomyopathy. Consistent with previous data, LPS-induced mortality was more pronounced in sGC−/− males (60%) for a dose of 20 μg/LPS, n = 8 males) vs. female WT mice (100%, n = 4 males). We measured sarcomere shortening (SS) and ΔCa in isolated, extracellularly paced cardiomyocytes (5 Hz), at 37°C, 14h after challenge with 25 μg/LPS. WT M mice had decreased SS and ΔCa to 60 ± 7 and 78 ± 4% of baseline (65), respectively, (n > 60 cells from 8 mice for all groups, 60/8). In sGC−/− M, the decrease in SS and ΔCa was more pronounced than in WT (to 26 ± 3 and 53 ± 3% of control, respectively, n>60/8). In WT F, LPS induced a decrease in SS (to 41 ± 6% of baseline, n>20/4), but not in ssCa2+, suggesting a myocardial dysfunction. SS decrease was less in sGC−/− F mice (61 ± 10%, n=20) than in WT F. In conclusion, cGMP-suppressed sGC 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, cGC contributes to the development of myocardial dysfunction. Different therapeutic approaches may thus be required in septic M and F patients. Funded by K08GM096802 (NHI, to LAH).

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 cardiac muscle caused by obstruction in coronary artery through either atheroclerosis, a thrombus or spasm. The causative factors have been well documented and its risk has been reduced to the barest minimum in advanced countries of the world while in developing countries such as Nigeria, the advancement of MI as a major cardiovascular problem is moderately recent. Therefore, researches into the responses of rheologic and fibrinolytic parameters with a view to indicate their possible use as management indicators and as possible factorials in its pathogenesis.

METHODS: We investigated longitudinally, 10 acute myocardial infarction (AMI) patients (females and 5 females) together with 20 age and sex-matched apparently healthy subjects as controls. Blood samples were taken at the admission and fibrinolytic parameters with a view to indicate their possible use as management indicators and as possible factorials in its pathogenesis.

RESULTS: Concentration (DDC), Euglobulin lysis time test (ELT) and Plasma viscosity (PV) were decreased D-dimer levels, PFC, ESR and PV in AMI patients on admission compared to control group. Significant reductions (P<0.05) of thrombosis in Nigerians with AMI and their reduction during treatment are positive clinical implications. For thrombosis in Nigerians, the probability of inducing hyperfibrinogenaemia coupled with hypofibrinolysis as risk factors for developing MI is remarkably high. Therefore, researches into the responses of rheologic and fibrinolytic parameters with a view to indicate their possible use as management indicators and as possible factorials in its pathogenesis are required.

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

The risk of developing atrial fibrillation (AF) is more prevalent in men than women, with a 2:1 male predominance. 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-related 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 stimulation (EPS) to compare the inducibility of AF in adult male and female C57Bl/6J 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 ion currents in left atrial myocytes isolated from mice of both sexes. The density of Na+ current (INa) in male mice: 20.3 ± 2.1 pA/pF, n=11; females: 19.1 ± 2.2 pA/pF, n=13; total K+ current (IK) at -30 mV; males: 20.5 ± 2.8 pA/pF, n=13; females: 21.4 ± 1.0 pA/pF, n=26; p<0.05) is similar between both sexes. Also, qPCR data revealed that the mRNA expression level of the underlying Na+ and K+ ion channels in left atria of male and female mice was comparable. However, relative mRNA levels of connexin 40 and 43 (Cx40 and Cx43) were more than 3 times lower in the left atrial tissues obtained from male mice. These changes in Cx40 and Cx43 and its association with a slower atrial conduction in males that could promote AF. In conclusion, our study suggests that atrial ion currents are comparable between males and females however, our results suggest that there might be an important role for lower connexin expression in male mice. These findings contribute to explain the cellular mechanisms responsible for the higher incidence of AF reported in men. This research was funded by the Canadian Institutes of Health Research.
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, myocyte loss, fibrosis, and cardiomyopathy. Studies have shown that these negative effects may also manifest in 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 (Taconic Biosciences, Inc.) were infected intraperitoneally with a low dose of 500 T. cruzi H1 (Yucatán, Mexico) blood trypomastigotes (bt) 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 (past 50 DPI) and entered into the chronic phase of disease. By 70 DPI, ECG revealed a significant delay in the conduction of electrical impulses from the sinoatrial (SA) node to the atrioventricular (AV) node (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 murine 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 steroid receptors and steroid metabolizing enzymes 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 receptors (ERα, ERβ) were determined by qRT-PCR. Cardiac fibroblasts express 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 of ERα, ERβ, AR, 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 potent 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 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 males and females. Fundings: AHA 13B31GIA14720053.

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 additional 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 arrythmias. These symptoms can be caused by cardiac remodeling leading to re-polarization defects. Potassium channels play a major role in maintaining the re-polarization reserve and the KβV1 subunits are uniquely positioned to modulate Kv-1 (Kv4 and KβV1) channels. The present study investigates the physiological function and roles of KβV1. We utilized a KβV1−/− deficient female mouse line (KβV1−/− KO) and noted enhanced heart rate, systolic dysfunction, and electrical defects. This report clearly demonstrates that the KβV1 subunit is involved in cardiac growth and electrical remodeling. Funding source: NIH R01HL02171-01A1.

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

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1Research Heart Ctr., Cedars-Sinai Med. Ctr., 127 S. San Vicente Blvd., A9305, Los Angeles, CA, 90048, 2Diabetes & Obesity Res. Inst., Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles, CA, 90048, 3Biomedical Imaging Res. Inst., Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles, CA, 90048. 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 (A:BL: 162±11%, P<0.02), ketone bodies (A:BL: 238±168%, P<0.001), and myocardial triglyceride content (A:BL: 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 (A:BL: -19.3%, P<0.05), but remained unchanged in the female subjects (A:BL: 4.2%, P=0.19). Sex specific analysis also revealed significantly greater elevations in ketone bodies in females than males (A:BL: 423±561% vs. 187±399%, respectively), despite a similar increase in circulating free fatty acids (A:BL: 147±14% vs. 213±29%, female vs. male, respectively). Because ketone bodies are known to be anti-inflammatory, we speculate that pre-menopausal 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 men 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. 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 (A:BL: 162±11%, P<0.02), ketone bodies (A:BL: 238±168%, P<0.001), and myocardial triglyceride content (A:BL: 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 (A:BL: -19.3%, P<0.05), but remained unchanged in the female subjects (A:BL: 4.2%, P=0.19). Sex specific analysis also revealed significantly greater elevations in ketone bodies in females than males (A:BL: 423±561% vs. 187±399%, respectively), despite a similar increase in circulating free fatty acids (A:BL: 147±14% vs. 213±29%, female vs. male, respectively). Because ketone bodies are known to be anti-inflammatory, we speculate that pre-menopausal 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.
Cardioprotection is mediated through endogenous leptin, suggesting a protective pathway distinct from that elicited under CR. This study was funded by the Israel Science Foundation.

5.10 THE CHARACTERIZATION OF AUXOTONIC TWITCH OF RIGHT VENTRICULAR CARDIOMYOCYTES FROM NON-FAILING AND FAILING HEARTS OF IMPUBLERAL 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.

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

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Survival after myocardial infarction (MI) is impaired 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 (3-7 months old; n=95) 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 (7.1%; 2 out of 26) compared to males (67.6%; 34 out of 51; p<0.05). 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 puberty, 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 APS "Guiding Principles in the care and Use of Animals". RV cardiomyocytes were obtained from non-failing males/females (NF-m, NF-f) and monocrotaline-treated males/females (MCT-m, MCT-f; n=4 in each group. Auxotonic twitches (>20 cells/group) were measured at 25°C and 1 Hz pacing rate under different preload using carbon fiber technique. Data presented as mean±SE, difference is significant at P<0.05. At low preloads (~110% of slack length, L0), end-systolic tension was two-fold larger in males vs. females in NF or MCT and was significantly larger in MCT-m/MCT-f vs. NF-m/NF-f (by 42.6±14.70%/1.7±1%, respectively). The normalized rate of tension development did not differ in NF-m vs. NF-f (12.2±0.3 vs. 12.3±0.2 1/s) but was significantly lower in MCT-m vs. MCT-f (12.0±0.1 vs. 12.7±0.2 1/s). 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±1.0% and 16.5±0.7%). These proportions in general remained under increased preloads (115-130% L0). End-systolic tension was higher in MCT-f vs. NF-f (by 7.5±1.28%, significant) and in MCT-m vs. NF-m (by 17.6±3.5%). The normalized rate of tension development was significantly lower in NF-m vs. NF-f (10.6±0.3 vs. 11.2±0.2 1/s) and in MCT-m vs. MCT-f (11.8±0.2 vs. 12.8±0.1 1/s). 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 impuberal male and female rats with monocrotaline-induced RV heart failure display similar changes from those observed in the same-sex healthy animals. The gender-specific differences were found both at low and physiological preloads. In contrast to adult animals, 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.
1East Carolina Diabetes & Obesity Inst., East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, Kinesiology, East Carolina Univ., 115 Heart Dr., Greenville, NC, 27834, Physiology, East Carolina Univ., 600 Moye Blvd, Greenville, NC, 27834. 17β-estradiol (E2) is a key regulator of energy and glucose homeostasis. Menopause comes with a significant decline in E2 production and increases a woman’s risk for developing cardiovascular disease and type-2 diabetes, while hormone replacement therapy decreases the incidence of type-2 diabetes. Mitochondrial function in skeletal muscle (SM) has been linked to the control of insulin sensitivity. To examine the potential underlying mechanism(s) by which E2 regulates insulin sensitivity in SM, young sexually mature (12 week-old) C57BL/6J-female mice were studied 2 weeks after ovariectomy (OVX-2w) followed by 2 weeks of E2 treatment (OVX+E2, 1μg/day) administered via a subcutaneous miniosmotic pump. Control groups included normally cycling females (NC) in the Proestrus stage (high physiological E2 levels) and an ovx group implanted with a saline control pump (OVX-ctl). E2 treatment effectively reversed fasting hyperglycemia developed in the OVX-2w and OVX-ctl groups (+25%, p<0.0001 and +12%, p<0.05 vs NC), decreased fat mass by 48% (p<0.01 vs OVX-ctl) and restored ex vivo-simulated mitochondrial glucose uptake back to NC values (p<0.05 vs OVX-2w and OVX-ctl). In permeabilized fibers from red gastrocnemius, maximal state-3 respiration with carbohydrate-derived substrates (pyruvate/malate) was reduced in OVX-ctl (-26%, p<0.05 vs NC) but fully restored in the OVX+E2. Surprisingly, maximal state-3 fatty acid-supported respiration was reduced in OVX-ctl (p<0.05). Spectrophotometric assessment of the relative specific activities of OXPHOS complexes in isolated mitochondria revealed a significantly impaired Complex I activity in the OVX-2w and -ctl groups (p<0.05, p<0.005 vs NC) that was fully restored in the OVX+E2. While Complex II and III activities were not altered, transfer of electrons between Complex I and III, as well as between II and III, was also decreased in OVX-ctl (p<0.005 and p<0.05 vs NC, respectively), but completely restored in OVX+E2. Mitochondrial membrane fluidity was decreased in OVX-2w and -ctl (p<0.05 vs NC), but restored in OVX+E2. Expression of OXPHOS complexes and citrate synthase activity were not affected across all groups. These findings provide evidence that E2 restores mitochondrial function in skeletal muscle via non-genomic pathways, by promoting electron transfer efficiency between complexes III and IV, thus offering new insights into the mechanism(s) by which menopause sets, and E2 therapy reverses a pro-diabetic state. NIH DK096907.

6.3 WITHDRAWN

6.4 INCREASED OREXIGENIC INNERVATION OF DOPAMINE NEURONS REDUCES PROLACTIN SECRETION IN OBSESE FEMALE RATS

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1Biology, Washington & Lee Univ., 204 W. Washington St., Lexington, VA, 24450, 2Neuroscience, Washington & Lee Univ., 204 W. Washington St., Lexington, VA, 24450. Obesity adversely affects reproductive health in women causing menstrual irregularity, anovulation, miscarriages, and decreased conception. This suggests that an inactivation of estrogen receptors in the hypothalamus, specifically within the arcuate nucleus (ARC) and the olfactory bulb (OB), results in a decrease of prolactin (PRL) levels, a hormone critical for lactation and maintenance of pregnancy. Data from studies demonstrate that 17β-estradiol (E2) is a key regulator of energy and glucose homeostasis. Menopause comes with a significant decline in E2 production and increases a woman’s risk for developing cardiovascular disease and type-2 diabetes, while hormone replacement therapy decreases the incidence of type-2 diabetes. Mitochondrial function in skeletal muscle (SM) has been linked to the control of insulin sensitivity. To examine the potential underlying mechanism(s) by which E2 regulates insulin sensitivity in SM, young sexually mature (12 week-old) C57BL/6J-female mice were studied 2 weeks after ovariectomy (OVX-2w) followed by 2 weeks of E2 treatment (OVX+E2, 1μg/day) administered via a subcutaneous miniosmotic pump. Control groups included normally cycling females (NC) in the Proestrus stage (high physiological E2 levels) and an ovx group implanted with a saline control pump (OVX-ctl). E2 treatment effectively reversed fasting hyperglycemia developed in the OVX-2w and OVX-ctl groups (+25%, p<0.0001 and +12%, p<0.05 vs NC), decreased fat mass by 48% (p<0.01 vs OVX-ctl) and restored ex vivo-simulated mitochondrial glucose uptake back to NC values (p<0.05 vs OVX-2w and OVX-ctl). In permeabilized fibers from red gastrocnemius, maximal state-3 respiration with carbohydrate-derived substrates (pyruvate/malate) was reduced in OVX-ctl (-26%, p<0.05 vs NC) but fully restored in the OVX+E2. Surprisingly, maximal state-3 fatty acid-supported respiration was reduced in OVX-ctl (p<0.05). Spectrophotometric assessment of the relative specific activities of OXPHOS complexes in isolated mitochondria revealed a significantly impaired Complex I activity in the OVX-2w and -ctl groups (p<0.05, p<0.005 vs NC) that was fully restored in the OVX+E2. While Complex II and III activities were not altered, transfer of electrons between Complex I and III, as well as between II and III, was also decreased in OVX-ctl (p<0.005 and p<0.05 vs NC, respectively), but completely restored in OVX+E2. Mitochondrial membrane fluidity was decreased in OVX-2w and -ctl (p<0.05 vs NC), but restored in OVX+E2. Expression of OXPHOS complexes and citrate synthase activity were not affected across all groups. These findings provide evidence that E2 restores mitochondrial function in skeletal muscle via non-genomic pathways, by promoting electron transfer efficiency between complexes III and IV, thus offering new insights into the mechanism(s) by which menopause sets, and E2 therapy reverses a pro-diabetic state. NIH DK096907.

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

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1Biology, Washington & Lee Univ., 204 W. Washington St., Howe Hall, Lexington, VA, 24450, Neuroscience, Washington & Lee Univ., 204 W. Washington St., Howe Hall, Lexington, VA, 24450, Biochemistry, Washington & Lee Univ., 204 W. Washington St., Howe Hall, Lexington, VA, 24450. Currently, 60% 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 2% sucrose solution and food containing 60% carbohydrates from fat. After three weeks of diet consumption, HFHS rats 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 10 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 ovarioectomized, 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

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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 prostatic 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 prefed 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 (HFD) and high-protein (HPD) 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.
6.7 A HIGH-FAT DIET IMPACTS GLUCOSE AND BLOOD PRESSURE IN FEMALE AND MALE DAHL SALT-SENSITIVE RATS

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There 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 DSS (n=4-6). At baseline, females had a lower BP (125±1 vs. 132±2 mmHg; p=0.008) and were smaller than males (220±4 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 telemetry device 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: 2043±206 vs. 2381±216; p=0.05). Rats 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±0.2 vs. 103±3 mg/dL; p=0.45). The HF diet also significantly increased BP in both female (145±8) 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 fat-induced 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 DS1 for the glucose implants and technical support.

6.8 HIGH FRUCTOSE INTAKE EXACERBATES THE IMPAIRMENT OF MESENTERICAL 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 8 weeks. Control rats received no sugar supplement. Blood pressure was measured every 2 weeks by tail-cuff method (LE-5001, Panlab, Harvard).

Aim and objective: The aim of this study was to determine the impact of fructose ingestion on vascular reactivity in female rats. Sprague-Dawley rats were divided into three groups. Group 1 was fed a high-fat diet (60% fat diet for 46 days). Group 2 was fed a high-sucrose diet (60% sucrose diet for 46 days). Group 3 was fed a high-glucose diet (60% glucose diet for 46 days).

Results: The effects of fructose ingestion on vascular reactivity, in female rats, were compared with glucose and sucrose ingestion. The results showed that fructose ingestion significantly decreased the sensitivity of smooth muscle to NO in female rats, whereas glucose and sucrose ingestion did not have any significant effect on vascular reactivity. These results suggest that high fructose intake may exacerbate the impairment of vascular reactivity in female rats compared to glucose and sucrose ingestion.

6.9 THE IMPACT OF HIV INFECTION ON BODY COMPOSITION, LIPID PROFILE, ADIPONECTIN LEVEL AND RESTING ENERGY EXPENDITURE IN MTATHA DISTRICT, A SEMI URBAN SOUTH AFRICAN COMMUNITY

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Aim and objective: The aim of this study was to determine the impact of the highly active antiretroviral therapy (HAART) on body composition, lipid profile, and resting energy expenditure. Methods: This was a descriptive and comparative study made up of 81 participants recruited from the public clinics in Mtatha, South Africa. They were categorized into the following three equal groups: 27 HAART treated HIV participants (group A), 27 HAART naïve HIV participants (group B) and 27 healthy non HIV patients (group C). Anthropometric measurements were used to determine basal metabolic index (BMI) and body composition indices. Biochemical tests such as analysis of serum lipids and adiponectin were performed.

Results: The participants with normal nutritional status (BMI of 18.5-24.9 kg/m²) in the three groups had significant variation in the following parameters: resting energy expenditure, (REE) adiponectin level, lipid profile and ideal weight. (P<0.05 Conclusion: The treatment of HIV infection with first line antiretrovirals reduces the level of adiponectin, increased the lipid profiles with the exception of HDL, making them more susceptible to atherosclerosis. Key words: HIV infection, Highly Active Antiretroviral Therapy (HAART), adiponectin, Lipid profile, Resting Energy Expenditure (REE).

6.10 ALTERATIONS IN FATTY ACID SIGNALING PATHWAYS DIFFERENTIALLY AFFECT FAT INTAKE IN MALE AND FEMALE MICE

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Excessive dietary fat intake has been linked with the current epidemic of obesity. The pathway underlying the recognition of fatty acids, the prototypical fat stimulus, by chemosensory cells in the oral cavity and the digestive system has been at least partially elucidated. This transduction pathway for polyunsaturated fatty acids (PUFAs) involves PUFAs binding to C36D and/or fatty acid activated GPCRs, and downstream activation of PLCγ, IP, and TrpM5. To determine the contribution of this pathway to dietary fat intake, we have utilized several model organisms that lack individual elements in this pathway and monitored food intake and body composition on high fat, high sucrose diet and control diets. Our initial study looked at the effects of TrpM5 deletion (TrpM5−/−) in mice compared to wild-type mice (TrpM5+) 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) or the fatty acid transport protein, CD36, which are implicated in the fatty acid pathway. Since both pre- and post-ingestively, the sweet (carbohydrate-sensing) pathway involves the same transduction elements, we compared the same metrics on a high sucrose diet. Despite the importance of TrpM5 in this pathway, no differences were seen, tying this phenomenon to high fat diets. The effects of TrpM5 deletion were gender specific – female mice lacking TrpM5 show similar levels of fat intake, body fat and body weights on a high fat diet as wild type females. As with males, no differences in food intake or body composition between TrpM5−/− and TrpM5+/+ female mice were seen on high sucrose diets. Our data are consistent with the interpretation that alterations in fatty acid signaling, pre- and post-ingestively, lead to specific changes in the intake of dietary fat in male mice and that the effect is gender specific. We are currently exploring the mechanistic nature of these gender differences in fatty acid signaling pathways and their regulation. Supported by NIH DC013194 and NIH DCO131318 (TAG).

6.11 WITHDRAWN

6.12 A PILOT STUDY EXPLORING METABOLIC DYSFUNCTION IN TRANS-SEXUAL WOMEN: NOVEL INSIGHT FROM MAGNETIC RESONANCE SPECTROSCOPY
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Standard 75g oral glucose tolerance test (OGTT). Hepatic steatosis was assessed by
ual women, who had undergone bi-lateral orchiectomy (n = 4) or had not (n = 8).
completely understood. To begin to address this question, we recruited 12 trans-sex-
gender and/or female hormone treatment leads to metabolic impairment remains in-
pose fat distribution after sex re-assignment surgery, suffer from increased metabolic
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However, previous studies do not consistently show in-
centrations before and after weight loss are examined. Percentage of weight lost,

Results: Previous studies that involve caloric

OBESITY MODULATE BUPRENORPHINE-INDUCED RESPIRATORY DEPRESSION IN MICE

Sex, Leptin Status, and Obesity Modulate Buprenorphine-Induced Respiratory Depression in Mice

Opiates cause sex-specific differences in modulation of pain (Pain 155:398, 2014; 

Methods: Previous studies that involve calorie

bution of the renal sodium transporters via real-time PCR using custom-

Leptin sensitization in lean animals similarly in-

It appears greater weight loss is needed for women than males. Exercise may help reduce the amount of weight loss

Male (M) versus Female (F) differences in VE (saline vs 0.3 mg/kg bupe) were

In mice, leptin modulates increases in opiate-induced adverse events associated with female sex and obesity (Anesthesiology 122: 659, 2015). Support: 5R01-HL065272-12 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

Anne-Cécile Huby1,2 and Eric J. Belin de Chantenelle1

Physical chemistry, fat deposition and metabolic changes, in females than males, for the same level of

Moreover, 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, VLCAD 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 (11SDG80006 to EJB) 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 solution in 1% salt solution and a powdered 8% 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 customized PCR arrays (QIAGEN). Results demonstrated that mean blood pressure (MBP,
mmHg) was not different between females and males in the control period (72.3 ± 2.6 and 73.4 ± 1.3, respectively). No change in MBP occurred after the first week of F+S diet; however, at the end of the second week, MBP increased in both females and males (86.4 ± 2.2 vs 77.2 ± 1.0, respectively, p<0.01 from control week) with the female MBP > male MBP (p<0.01). At the end of the 4th week of F+S consumption, female MBP and male MBP were not different (90.1 ± 3.2 vs 89.4 ± 2.6, respectively).

Sex differences in mRNA expression of renal sodium transporters were observed with female kidneys showing significantly higher expression of NCC, NKCC2, NHE3, and each of the three ENaC subunits whereas higher expression of Na+-phosphate transporter was found in male kidneys. Moreover, females consistently demonstrated lower sodium excretion-to-sodium intake ratio (%) compared to males during the period (60.4 ± 4.4 vs 74.8 ± 3.7, respectively, p<0.01) that consuming the F+S diet for two weeks increased blood pressure in both female and male 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+S diet and studies are underway to test this proposal. This study was funded by NIH-sponsored Oklahoma INBRE summer research program (PA-12-313).

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 toward the use of male to study obesity-induced metabolic dysfunction because of similar protection in female mice. We have investigated dietary obesity in a mouse model and have directly compared inflammatory responses in males and females. Objectives: 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 leucocyte 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 (HFD). Females had higher body weight increases 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 responses after monocyte transfer experiments into female host and bone marrow transplantation. Conclusion: Sex differences in high fat diet induced inflammatory activation are due to cell intrinsic differences in hematopoietic responses to obesity cues. This work was supported, in whole or in part, by American Heart Association Scientist Development Grant 14SDG1790004 and Department of Pediatrics Janette Ferrantino Investigator Award.

6.18 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

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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 prorenin receptor (sPRR) in cardiovascular patients suggest that plasma sPRR might be a potential biomarker of RAS activation. While women with T2D exhibit disproportionately greater burden 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 (Ct; BMI<30), 66 obese (Ob; BME=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 Ct (16.5 ± 0.4ng/mL) and Ob (16.6 ± 0.5 ng/mL, P < 0.0001). Urine Albinum/Creat ratio showed a similar trend (Ob: 31.0 ± 4, Ob+T2D: 53.1 ± 3 vs. Ct: 24.9±2 mg/gCr; P < 0.0001). Plasma sPRR levels negatively correlated with WHR in the Ob+T2D group (r=−0.462, P = 0.0395) but not with Ct or Ob patients. Control lean men exhibited significantly higher plasma sPRR levels compared to women (18.1 ± 0.8 vs. 15.4 ± 0.4 ng/mL; P=0.01). Interestingly, the sPRR differences among groups of same sex were greater in Ob+T2D women compared to Ct (20.7 ± 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 of 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 CaTS).

6.19 SEX DIFFERENCES IN RENAL GENE EXPRESSION IN A DIET INDUCED OBESITY MODEL OF DIABETIC NEPHROPATHY (DN)

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DN is a serious and common complication of diabetes mellitus. Our objective was to identify novel genes differentially regulated in the early stages of DN using an unbiased approach. To this end, male (M) (n=10) and female (F) (n=6) C57Bl/6 mice were fed high fat diet (HFD). Assessments for glucose metabolism were performed as well as evaluations of inflammatory responses in leucocyte activation in bone marrow, blood, and adipose tissue as well as pre-adipocyte populations. BM cells were cultured from male and female animals and stimulated with LPS to investigate potential sex differences. The array included the 9 most upregulated and 11 most downregulated genes; of the 22 genes with the greatest fold increase or decrease, only 2 (Lipg, Sk7a12) have been previously been studied in a diabetic context. We then utilized a Taqnaq real-time (RT) PCR array to confirm our initial findings and examine potential sex differences. The array included the 9 most upregulated and 11 most downregulated genes; of the RNA Seq and of interest to our group (primarily sensory receptors and G proteins). These arrays (31 genes + 18S control) were used to filter F samples (n=3 CD, n=3 HFD), and a second cohort of M samples (n=3 CD, n=3 HFD). All of the 9 genes significantly upregulated with HFD by RNA Seq were also upregulated in the M samples by RT-PCR (Aplt2a, Ccl28, Ctnx3, Cyp2b10, Lhx2, Popdc3, Ptpn5, Sorcs1, Synpr; p<0.05). However, of the remaining 22 genes (downregulated + other genes of interest) only 3 were confirmed in M by RT-PCR (Gpr12, Gpr146, Tprn1; p<0.05). Furthermore, none of the genes were altered in F by HFD diet (vs. CD). When comparing M vs. F, we found that 10 of the 31 genes were differentially expressed between the sexes both on CD and on HFD (Bmnt, Ccl28, Ctnx3, Cyp2b10, Lhx2, Popdc3, Sk22a29, Sorcs1, Synpr; p<0.05); 6 additional genes (Aplt2a, Cyp2a5, Gpr12, Gpr146, Ptpn5, Tprn1; p<0.05) were altered between M and F on HFD but not CD. These data demonstrate that our RNA Seq data regarding upregulation were more reproducible than those regarding downregulation, and that changes are sex-specific. The fact that the 9 upregulated genes in M do not change in F (which do not develop metabolic syndrome) implies that renal changes are downstream of metabolic changes, and not non-specific alternations due to an alteration in diet. Thus, we have identified novel renal genes associated with DN, and have demonstrated sex differences in renal gene expression both in control conditions and in DN.

6.20 LEPTIN-MEDIATED ALDOSTERONE SECRETION CAUSES HYPERTENSION IN OBESE FEMALES

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animal weight gain, with animals fed a high fat diet without supplemental estrogen and ovariectomized with basal levels restored in half the animals by implantation of a slow releasing estradiol pellet. Using RNA purified from hypothalamus, pituitary, adrenal cortex, and kidney of ovariectomized Long Evans rats, we investigated alterations in gene expression levels with diet and estrogen treatment. We recently discovered that female rats display lower proximal tubule (PT) Na reabsorption compared to males, i.e. Na+H+ exchanger isoform 3 retracted 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+Cl-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-dependent activation of NCC and ENaC. ENaC activation drives potassium (K) secretion in principal cells. Dietary K rapidly decreases 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 compared to 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 volume and urinary K excretion were similar between sexes. Food consumed during the 3 hr meal was similar in all four groups. After the 2%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 mEq/L, [Na]: 133±1 vs. 135±1 mEq/L, Osm: 296±3 vs. 306±2 mOsm. Differences appeared independent of the estrous cycle (vaginal smear). After the 2%K meal, plasma K increased in both sexes: to 4.6±0.1 mEq/L in females and to 5.8±0.4 mEq/L in males, associated with 7 fold increases in urinary K (mmol/hr): from 0.12±0.03 to 0.9±0.1 in females, and from 0.01±0.03 to 0.13±1.2 in males. Plasma Na (mEq/L) was unchanged in both sexes after meals, but urinary Na excretion (mmol/hr) 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 TGFß 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 hypertrophy 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 TGFß 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 80 days followed by a new treatment for an additional 40 days (groups: veh, E2, E2+veh). TGFß levels were measured by competitive enzyme-linked immunosorbent assay (ELISA), and 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: eGFR: 0.36 ± 0.04 mL/min/1.73 m2; E2: eGFR: 0.39 ± 0.05; E2+veh: 0.36 ± 0.04; p=0.07). There was no difference in the glomerulosclerosis index (GI) as assessed by Periodic acid-Schiff staining (veh:GI= 1.76 ± 0.12; E2:GI=1.79 ± 0.13; E2+veh:1.83 ± 0.15; p=0.94). Renal interstitial collagen formation assessed by Comassie’s trichrome staining also revealed no changes (veh:COL= 9.20 ± 0.34%; E2:COL= 8.60 ± 0.47%; E2+veh: 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:4.73 ± 0.93%; E2:2.19 ± 0.23%; E2+veh: 3.76 ± 0.60%; p=0.02). Additional immunofluorescence studies revealed upregulation of renal cortical transforming growth factor B (TGFß) by long-term E2 treatment (veh:2.102 ± 0.58%; E2+veh:2.10 ± 0.50%; E2+veh: 1.42 ± 0.32%). These results indicate that long-term E2 treatment may promote an increase in TGFß and concomitant renal injury in ovariectomized rats. 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.H.L.

7.3 ALTERATIONS IN 20-HETE PRODUCTION CONTRIBUTING TO END ORGAN DAMAGE IN DAHL RATS

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It is well documented that a sexual dimorphism exists in the regulation of blood pressure in both the human population as well as experimental animal models, such that males have higher blood pressures than females of the same age. While there is a clear discrepancy in the development of hypertension and progression of renal injury in many rodent models, evidence of a sex difference is lacking in the Dahl S rat. While the current reports present conflicting data, we hypothesize that alterations in CYP450 expression and 20-HETE production contribute to the relative resistance of female Dahl S rats to target organ damage compared to males. Consistent to what we have previously reported, the time course for the development of proteinuria and renal injury were significantly reduced in female Dahl SSR rats challenged with a high salt diet relative to male rats. In addition, arterial cortical 20-HETE production was elevated in female (120±42 pmol/min/g) versus male rats (45±11.78 pmol/min/g); whereas, no difference was noted in the outer medulla (19.6±1.8 vs 17.15±3.9 pmol/min/g). Introgenesis of the CYP4A1 gene into the Dahl S genetic background, resulted in significant elevations in 20-HETE production both on low salt and high salt diets. Furthermore the rise in mean arterial pressure was attenuated in CYP4A1 overexpressing rats in both sexes (191±9mmHg in CYP females vs 61±9 in Dahl S females; 20±5mmHg in CYP males vs 50±5mmHg in Dahl S males). Moreover, the degree of glomerular injury was reduced in CYP rats, both male and female, compared to Dahl S rats in response to a high salt diet. Therefore, increases in the CYP gene expression and 20-HETE production prevent the rise in mean arterial pressure and kidney injury in male Dahl S rats. AHA 14SDG20160020.

7.4 APOPTOTIC CELL DEATH IN RENAL ISCHEMIA-REPERFUSION 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 (N=5-6). 24 hours later, kidneys and plasma were collected to quantify apoptotic cell death via TUNEL assay and assess renal injury by measuring plasma creatinine (Cr). Control female SHR have more apoptotic cells compared to male (M: 1.6±0.6; F: 5.0±1.0 cells per area; p=0.04). Following IR, apoptotic cells significantly increased in each sex, however the sex difference was abolished (M: 12.0±3.9; F: 18.3±3.9 cells per area; effect of treatment: p=0.01; effect of sex: p=0.1). IR induced injury was confirmed with an increase of Cr in both sexes (M: 0.22±0.06 vs. 4.1±0.6; p=0.01; F: 0.25±0.16 vs. 2.3±0.6; p=0.04). These data do not support the hypothesis that more apoptotic cell death that occurs in females following IR contributes to less IR injury compared to males. More studies will need to be performed to measure what the ratio of apoptotic cell death to total cell death is in each sex. Better understanding of the type of cell death in IR may offer novel insight into treatments for acute kidney injury in both sexes.

7.5 WITHDRAWN

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

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We have engineered transgenic (TG) mice with these haplotypes (Hap -6A: -6A/- , Hap -6A/-217A: -532T/C, -793A/G, -1074T/C, and -1178G/A). Hap -6A/-217A is associated with hypertension. Studies have shown that SNPs in the promoter of the hAGT gene are associated with hypertension. Importantly, these SNPs can further modulate the gene of interest in various physiological/environmental settings like gender or high-sodium diet. In this regard, the human angiotensin gene (hAGT) gene has polymorphisms in its 2.5kb promoter that form two haplotype (Hap) blocks: -6A/G (+1670A/G, -1562C/T, -1561T/C) and -217A/G (-352T/C, -793A/G, -1074T/C, and -1178G/A). Hap -6A/-217A is associated with human hypertension whereas Hap -6G/-217G reduces cardiovascular risk. We have engineered transgenic (TG) mice with these haplotypes (Hap -6A/-
217A and Hap-6G, -6G/-217G) so as to examine the transcriptional regulation of the hAGT in an in vivo setting. This study is designed to study the effects of a high-sodium diet on the transcriptional milieu of hepatic and renal tissues with consequent effects on the hAGT expression in our two haplotypes. Male and female TG mice were placed on 4% Na+ for a period of 8 weeks. High-salt diet upregulates the hAGT expression in both liver and kidney tissues (p<0.05); however, this effect is observed only in male mice with high salt diet treatment. Interestingly, the hAGT activation observed was significantly greater in -6A haplotype mice compared to -6G males. High-salt increased the expression of transcriptional regulators including, CEBPβ, HNF4 and GR. This effect was also limited to the males of our two TG lines suggestive of a gender-dependent effect of Na+ on the cellular transcriptional apparatus. Complementary ChIP assay confirmed enhanced transcription factor (TF) binding to the chromatin of male -6A TG mice as compared to their -6G counterparts after high salt diet treatment. Thus, for the first time we show an effect of high-salt on cellular transcriptional apparatus that is gender-dependent, with consequent activation of the hAGT in male TG mice only. Crucially, increased TF affinity of the chromatin in -6A TG mice leads to higher salt-induced AGT levels in this haplotype. These observations could partly account for increased salt-sensitivity of adult males that, in turn, is governed by the ‘risk’ haplotype. Identifying these -6A haplotype individuals will help guide therapeutic lifestyle changes in patients with essential hypertension.

7.10 DIFFERENT RESPONSE TO DOPAMINE OR TO BRADKININ INHIBITION IN OVARIECTOMIZED ADULT WISTAR RATS UNDER HIGH SODIUM INTAKE

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In previous work, we have shown that ovarectomized (oVx) adult Wistar rats develop high blood pressure upon high sodium intake (HS). Among other facts, oVx rats have a lower sodium excretion and renal overexpression of total and dephosphorylated Nr, K+-ATPase (NKA) compared with intact female (IF) (1, 2). oVx rats also have a decreased expression of dopamine D1 receptor (D1R) (2) and a higher urinary kallikrein excretion than IF rats (3). With the aim to compare the relative contribution of dopamine and bradykinin-kinin systems to the deranged regulation of sodium balance and blood pressure control in ovariectomy, we studied IF and oVx rats on HS after both dopamine or bradykinin blockade. Ovariectomy was performed in Wistar rats at 60 days of life and rats were studied 90 days post oVx. The rats received 1% NaCl in drinking water on the final 5 days. D1R (SCH 23390, 1mg/kg bwt/day, sc) or bradykinin B2 receptor (HOE 140, 1µg/100 g bwt/day, sc) were blocked the last two days. In IF rats, D1R blockade caused a decrease in urinary sodium (UnaN = 3.14±0.03 vs 1.65±0.09 mmol/100g bwt/day, p<0.01), in volume excretion (V = 11.52±0.06 vs 6.13±0.19 ml/100g bwt/day, p<0.01), higher mean blood pressure (112±2 vs 140±2 mmHg, p<0.05) and no change in 20-HETE synthesis (4µmol/100g bwt/day) compared to untreated rats. In opposition, D1R blockade did not cause any change in oVx rats. In IF rats, the bradykinin receptor (B2R) blockade had no effect on hydro-electrolyte excretion or NKA phosphorylation. In oVx rats, B2R blockade decreased urinary sodium (UnaN = 2.13±0.24 vs 1.48±0.33 mmol/100g bwt/day, p<0.05) and volume excretion (V = 8.50±1.66 vs 6.22±1.67 ml/100g bwt/day, p<0.05), while NKA phosphorylation state remained unaltered. No changes in glomerular filtration rate following D1R or B2R blockade were observed. Present results show that, as already described (2), dopamine system is unresponsive in oVx HS rats, whereas bradykinin through B2R, contributes to maintain sodium excretion in rats with absence of ovary hormones and HS intake. Funding source: UBACYT 20020120100379BA, Buenos Aires University, Argentina to FRI.

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7.11 PARTICIPATION OF CYP4A ω-HYDROXYLASE/20-HETE IN BLOOD PRESSURE REGULATION OF HYPERANDROGENEMIC FEMALE RATS

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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-hydroxyeicosatetraenoic acid (20-HETE) synthesis in rats. In particular, evidence from our laboratory indicates that CYP4A2 expression is elevated in the renal vasculature of hyperandrogenemic female Sprague-Dawley rats. Dahl Salt Sensitive (DS) rats have a deficiency in CYP4A ω-hydroxylase/20-HETE system in the kidneys compared with either Dahl Salt Resistant (DR) or SSββ‰ consomic strain rats. 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 hyperandrogenic 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 DS rats, DR and SSββ‰ control rats wereimplemented with dihydrotestosterone (DHT; 7.5mg/90µl) or placebo pellets (6/48g). 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±4 vs. DHT: 95±1 mmHg, p<0.05) and female SSββ‰ 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 SSββ‰ females, and with DHT there was a more robust increase in MAP in female SSββ‰ 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 ω-hydroxylase/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-R01HL66072, P01HL51971 (JFR), 14POST18640015 (ROM).

7.12 MULTIPLE ESTROGEN RECEPTOR SUBTYPES SELECTIVELY INFLUENCE FLUID INTAKE IN FEMALE RATS

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Estradiol (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 GPR30. In addition to the complexity offered by the existence 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. In support of this hypothesis, we found that angiotensin II (AngII)-stimulated fluid intake was decreased (p<0.05) after treatment with an estradiol-BSA conjugate that can only activate receptors on the cell surface. Follow up studies to test if ERα, ERβ, and GPER-1 in mediating the anti-diuretic effect of E2 are blocked with E2 and AngII analogues to consume fluid, we found unexpected receptor-selective effects on AngII-stimulated water and saline intake. Specifically, we found that AngII-stimulated water intake was decreased after selective activation of ERα and that AngII-stimulated saline intake was decreased after selective activation of ERβ or GPER-1 (p<0.05). Furthermore, analysis of drinking microstructure revealed differences in the underlying behavioral difference in the respective effects of ERα and ERβ on water and saline intakes. This analysis found that the ERα-mediated decrease in water intake was a function of a selective decrease in burst number (p<0.05), suggesting a change in post-ingestive feedback. In contrast, the ERβ-mediated decrease in saline was a function of a change in burst size (p<0.05), suggesting a change in the osmolarity of the fluid. Although activation of ERβ and GPER-1 similarly affected saline intake, without a concomitant effect on water intake, the decrease in saline intake after GPER-1 treatment was mediated by a change in burst number (p<0.05), unlike the change in burst size that was underlying the ERβ-mediated change in intake. Together these findings demonstrate that specific ERs selectively influence water 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 REINAL DYSFUNCTION ASSOCIATED WITH ANGIOGENIN II-INDUCED 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 natriorexigenic 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 normally occurring after daily ANGII administration is not induced if the 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 vasoconstrictor mechanisms. 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 vasoconstriction 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 DESENSITIZATION 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-induced hypertension is greater in 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, c-fos 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 plasma renin activity, 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 and female rats. Am J Physiol Regul Integr Comp Physiol. 15:304(2):R121. 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, 968.11.

12.3 MATERNAL UNDERNUTRITION SIGNIFICANTLY IMPACTS OVARIAN FOLLICLE NUMBER AND INCREASES OVARIAN OXIDATIVE STRESS IN ADULT 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/fetus/neonate makes adaptations in response to early life cues, resulting in adjustments in homeostatic systems that are maladaptive in postnatal life.

Contrast to nicotine exposed animal model, the data in maternal hypoxia rat model indicated that estrogen may counteract heightened reactive oxygen species production, leading to protection of females from development programming of hypertensive phenotype in adulthood. Contrast to nicotine exposed animal model, the data in maternal hypoxia rat model indicate that estrogen is not directly responsible for the sex dimorphism in fetal programming of heart ischemic vulnerability but suggest a novel mechanism of estrogen in protecting female hearts against ischemia and reperfusion injury. (Supported by NIH/HL11861, NIH/DA032510, and by the regents of the University of California Tobacco Related Disease Research Program grant #22X2T-0022).

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

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

Nina Stachenfeld1

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 gondotropin-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 6-11. 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 vasocorstrictor and ETBR mediates vasodilation in women with and without AE-PCOS, but vasodilation is blunted in women. Only ETBR are expressed in the endothelium, so our data suggest peripheral microvascular endothelial dysfunction in AE-PCOS. We have also demonstrated that the androgenic milieus is a key element to this endothelial dysfunction, and that the androgen effects on the endothelium are mediated by the ETBR 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 ovariectomized 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 (csERα-KO) mice, and found that EDC treatment significantly decreased infarct size and improved functional recovery compared to the vehicle-treated csERα-KO mice, suggesting that the protection is not mediated by plasma membrane ERα. To induce hypertrophy, male and female mice were treated with androgens 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 csERα-KO and their WT littermates. The reduction in hypertrophy observed in the WT females was not altered by ablation of ERS. 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 ERS, suggesting that ERS 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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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/fetus/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. Developmental adaptation 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 and ovarian function. But the underlying ovarian mechanisms regulating the relationship between the early life developmental environment and postnatal reproductive dysfunction remain unclear.
Increased circulating volume, pressure overload and mineralocorticoid excess contribute differently to cardiovascular pathophysiology in women and men, in male and female rodents. In order to understand sex-specific differences, we evaluated the impact of sex hormones, the influence of sex hormones on heart rate variability, and sex differences in response to pressure overload and/or mineralocorticoid excess lead to pathological myocardial hypertrophy. Estrogen receptor alpha and beta activation have different effects on myocardial function. Female sex plays a protective role against myocardial hypertrophy and ischemia. Increased circulating volume, pressure overload and/or mineralocorticoid excess lead to pathological myocardial hypertrophy. Estrogen receptor alpha and beta activation have different effects on myocardial function. Female sex plays a protective role against myocardial hypertrophy and ischemia.

Diet and environmental stressors, including inhaled pollutants, have been implicated in the development and progression of metabolic diseases. Since metabolic processes linked with higher incidence of respiratory infections, especially in women and children. As with other air pollutants, oxidative stress is believed to play a major role in the etiology of CS-related lung pathologies. We are developing models to study respiratory infections and the mechanisms of health benefits derived from the more efficient CS. Previously, we infected neonatal Fischer (FIS) rats with a rat-adapted influenza virus, and showed that acetyls, FIS pups developed minimal lung changes. We have also assessed oxygen (O2)-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 O2-exposed neonatal FIS, SD, and W rats to determine which strain’s susceptibility was most susceptible to early life oxidative insult. Smaller litters in time-pregnant FIS rats were noted in each group size. FIS were 30-40% smaller than SD or W pups. Subsets of female (F) and male (M) 14- and 21-d-old (pre- and weaning) pups were exposed to air, O2, 1.0 ppm O2:2h. 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 rats, no age/stage differences were apparent for lung UA, total protein, or glutathione (GSH) peroxidase/reductase (per g wet lung wt). At 14-d, FIS rats had 62% more GSH than SD or W rats, respectively. GSH decreased in all strains from 14-21 d. Lung SOD also decreased in all strains from 14-21 d, with FIS rats having 25-35% more than SD or W rats. Post-O2, FIS 14-d rats of all strains had small GSH decreases (120%); while M pups were unchanged. Relatedly, F SD and W rats had decreased GSH (30-36%), SOD (15-26%), and UA (22-42%); while levels in F FIS were unchanged or increased. M 14-d rats had minimal changes. Conversely, F 21-d rats post-O2 showed minimal change while M pups had increased SOD (25-31%); and M SD pups had increased GSH peroxidase/reductase (18%). In summary, FIS rats appear relatively resistant to lung insult, while neonatal 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.)

 Estradiol Prevents Cardiorespiratory Dysfunctions Induced by Chronic Intranasal 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 evidences showing that hormonal replacement therapy can reduce apnea frequency, the potential protective roles of sex steroid hormones against the cardio-respiratory dysfunctions induced by SDB and CIH are unknown. We tested the hypothesis that estradiol protects female rats against the cardio-respiratory dysfunctions induced by CIH. Sprague-Dawley rats (230-250g) were randomized (OVX) and implanted with osmotic pumps delivering vehicle or estradiol (E2 - 0.5 mg/kg/day) for 21 days. After 14 days of recovery, the rats were exposed to CIH (21% ± 10% O2; 24 cycles/ hour) or air (RA) for 7 consecutive days. At the end of CIH exposure, mean arterial pressure (MAP - tail-cuff) was measured, and the rats were placed in a whole body plethysmograph to record ventilation, breathing stability (Poincaré-plots), apnea frequency, and metabolic rate (O2 consumption and CO2 production rate) for 4 consecutive hours. All parameters were analyzed during sleep (determined by visual examination of the recordings). Then, the rats were exposed to hypercapnia (5% CO2 + hypoxia) and hypoxia (12% O2 – 5 min each) to assess chemoreflex function. Shams-operated rats treated with vehicle and exposed to RA were used as a control group for the effects of endogenous estradiol. Compared to OVX-Ra rats, OVX-CIH rats had higher MAP (93.4 ± 0.8 vs 105.2 ± 2.0 mmHg, p<0.0001), high instability of respiratory frequency, high frequency of apneas during sleep (9.5 ± 1.5 vs 16.2 ± 0.9 apneas/hour, p=0.001), and a lower metabolic rate. The responses of respiratory frequency, minute volume, hypoxia and hypercapnia were more responsive in the OVX-CIH rats compared to OVX-Ra. In OVX-E2-CIH rats, MAP was lower (90.3 ± 2.5 mmHg), apnea frequency was reduced (5.5 ± 0.6 apneas/hour), metabolic rate higher, and respiratory responses to hypoxia and hyper-
13.4 POTENTIAL ROLE OF ESTROGEN IN 15-HYDROXYEICOSATETRANOCIC ACID PRODUCTION AND ACTIVITY IN HUMAN PULMONARY ARTERY ENDOTHELIAL 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 arachidonic acid is metabolized to a variety of compounds that effect pulmonary vascular function. Key enzymes in the biosynthetic pathway of arachidonic acid are altered by estrogen. Our central hypothesis is that estrogen has a dual effect to increase 15-hydroxyoxygenase (LO) gene transcription, and phosphorylation of 5-LO, which together result in increased production of the proliferative compound, 15-hydroxyeicosatetraenoic acid (HETE). Human pulmonary artery endothelial cells (HPAEC) from a male donor were incubated with estrogen (17β-estradiol, 1 µM; 18 hrs). 15-LO and 5-LO protein expression increased compared to untreated cells. However, there was no evidence of 5-HETE production when cells were incubated with 15-LO and 5-LO inhibitors (10 µM), ERK1/2 inhibitor, FR180204 (1 µM) or the estrogen receptor antagonist, ICI182780 (1 µM) proliferation was attenuated. In summary, these studies suggest a novel mechanism whereby estrogen regulates the arachidonic acid pathway which may potentially contribute to alterations in vascular function in sex-based diseases like PAH. Supported by HL093191 and AHA-01514212. Reference: Gilbert NC, Ruiz Z, Nezu DB, Wright MT, Bartlett SG, Boeglin WE, Brasil AR, Newcomer ME.

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13.5 MUSCULAR AND CARDIORESPIRATORY ADAPTATIONS TO TREADMILL TRAINING WITH AGING ARE BLUNTED IN FEMALE COMPARED TO MALE MICE

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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 attenuate these aging-associated decreases in strength and fitness in both male and female mice. In vivo plantarflexor maximal force and fatigue (% of max, respectively) with no age differences in TM groups. In female mice there were no differences in fatigue resistance among all groups. In treadmill pre-tests, young groups ran longer than aged groups (p<0.05). Treadmill test time was not increased in any SEXP group. Similar increases in treadmill test time after TM training occurred in young and aged male mice with respective 1,059±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 505±173 seconds, respectively (p<0.05). These findings suggest treadmill training is more effective in attenuating age-associated reductions in muscle force and cardiorespiratory fitness in male than female mice. Funded by NIH R15AR060469.

13.6 EFFECT OF EXERCISE ON RED BLOOD CELL VARIABLES IN HIGHLY TRAINED FEMALE ATHLETES

Dhika Akther1

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 change 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 conducted 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, hemoglobin concentration, were measured. The mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, were determined by equations. Statistical indices were computed for each group and for each variable. Subgroup 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 hemoglobin (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, were determined by equations. Statistical indices were computed for each group and for each variable. Subgroup analysis was done by unpaired Student’s ‘t’ test. Conclusions: 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 submature sports. Key words: Female athletes, exercise, RBC, PCV, MCV, MCH, MCHC.
capnia and hypoxia-capnia 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 capnia in PRKO males are probably related to other types of progesterone receptors, or to allopregnanolone, 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 SYNTHESIS IN CONTROLLING MITOCHONDRIAL RESPIRATION OF LARGE CEREBRAL ARTERIES IN FEMALE AND MALE RATS

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We have found that mitochondrial 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 synthesis (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 (pM/min/μg protein) in isolated, large cerebral arteries (middle cerebral artery, circle of Willis, and basilar artery) 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 (pM/min/μg protein) including basal respiration (96.9 ± 15.2), ATP production (33 ± 5.3), proton leak (63.6 ± 10.5), maximal respiration (147.2 ± 21.6), and spare respiratory capacity (50.4 ± 8.4) were significantly (p < 0.05) elevated in females compared with males (36.3 ± 8.5, 15.1 ± 4, 21.2 ± 4.6, 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 both 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 (224.3 ± 25.8 and 125.6 ± 20.2, respectively) compared with vehicle. The ratios of phosphorylated eNOS and total nNOS and phosphorylated nNOS and total nNOS were significantly higher in the female (2.2 ± 0.6%, 0.12 ± 0.2%, respectively) compared with the males (0.08 ± 0.2%, 0.5 ± 0.2%, respectively). Thus, NOS inhibition enhanced mitochondrial respiration in cerebral arteries from female and male 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

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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 electrophysiologic 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 pressure from 40 to 140 mmHg in 20 mmHg steps, whereas the diameter decreased in male MCAs (% change in diameter from 40 to 140 mmHg: Females 16±8, Males 26±4, p<0.05, n=5-8). Female MCAs have -1.76 fold lower diameter at 40 mmHg compared to age matched males in the presence of calcium (Females 8±5, Males 14±3.13 mm, p<0.05). In contrast, passive dilation was similar (diameter at 40mmHg compared to age matched males in the presence of calcium (Female MCAs) ~0.8 fold lower in the female SD rats compared to males (mV: Females -22±3, Males -27±3, n=4). Together these results suggest that female MCAs 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 exaggerated vasoconstriction. In conclusion, these results may identify a mechanism 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 (13SDG100006) to Malikkarjuna R. Pabbidi.

14.3 CHARACTERIZING THE GENDER DIFFERENCES OF MULTIDRUG-RESISTANCE PEPTIDE (MRP) TRANSPORTER EXPRESSION IN MOUSE BLOOD-BRAIN INTERFACES

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The choroidplexus (CP) epithelium and the capillary endothelium (blood brain barrier, BBB) are blood-brain interfaces with transporters that play important roles in clearing the brain of unwanted substances and preventing the entrance of potentially harmful material into the brain. Previous research has shown gender-specific patterns of the multidrug resistance peptide (MRP) efflux transporters, part of the ATP-Binding cassette (ABC) gene family. This is best documented in liver and kidney, where Mrp1, Mrp3 and Mrp4 have higher expression in females and Mrp5 and breast cancer resistance protein (Bcrp/ ABCG2), have higher expression in males. However, little is known about the MRP gender differences and their function in the brain. The aim of this study was to examine differences in mRNA and protein expression for ABC transporters in the brain and CP of naive wild type (WT) male and female C57 mice. We hypothesized that renal and hepatic gender-specific patterns of these transporters would also be present in the brain blood interfaces, mRNA and protein levels were measured by quantitative polymerase chain reaction (qPCR) and western blotting, respectively. Immunoblot analysis on CP and brain showed that Mrp4, Mrp6 and Bcrp are expressed in a gender specific pattern, and their expression correlates with the expression in the kidneys, supporting our hypothesis. In contrast, Mrp1 and Mrp2 expression had no gender pattern. Our findings indicate for the first time that significant differences in expression of these transporters at the blood-brain interfaces exist between male and female. These results will be helpful for understanding the physiological roles of individual transporters at both the blood-CSF barrier (CP) and BBB. Physiological barriers are known to influence many pharmacokinetic processes. Therefore, it is important to determine how gender can affect transport, metabolism and drug distribution. (Supported by NSF and NIH).

14.4 SEX AND GENOTYPE DIFFERENCES TO EPIPHRINE INFUSIONS IN HUMANS

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Objective: We sought to identify any differences relative to gender and/or genotype on the cardiovascular responses to exogenous infusions of low dose epinephrine (5ng/kg/min). Methods: Subjects: Ten males (mean ± SD: age=27.8±6.6, height=178.5±8.0cm, weight=83.9±12.4kg, BMI=26.3±2.3kg/m², BSA=2.0±0.2) and fourteen females (mean ± SD: age=26.3±5.9, height=164.3±7.0cm, weight=60.8±6.2kg, BMI=22.5±2.1kg/m², BSA=1.7±0.1) were studied. Three males were homozygous for Arginine (Arg/Arg) and 7 males were homozygous for Glycine (Gly/Gly) at position 16. In the female cohort, eight females were Arg/Arg and six females were Gly/Gly, at position 16. Procedure: A 1-hour epinephrine infusion was dosed at 5ng/kg/min was administered. BP was measured using an arterial catheter and HR via EKG. Stroke volume and cardiac output were estimated via ModelFlow and TPR was calculated. Plasma samples were collected at time: -10, 0, 30, 45, 60, 90, 120, 180 and 240 minutes and catecholamines measured using HPLC. Statistics: ANOVA with repeated measures was performed controlling for both gender and genotype during the epinephrine infusion at time(s): 0, 30, 45, and 60 minutes. All data were analyzed using the R software package with significance set if P was <0.05. Results: At baseline, mean values for MAP, HR, CO, SV, and TPR differed between sexes and genotype. At 30-minutes, mean values for MAP, HR, CO, and SV differed by sex as well as genotype. Significant, sex by genotype interactions were noted for MAP, SV, and TPR, while significant sex differences were identified for MAP, CO, and SV throughout the infusion. Conclusion: Our results indicate that the cardio-
vascular responses to epinephrine infusions are influenced by both sex and [I2-aden- ergic 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

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>Baseline (t=00)</th>
<th>30-min</th>
<th>A Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>82±7</td>
<td>82±8</td>
<td>0</td>
</tr>
<tr>
<td>Females</td>
<td>81±9</td>
<td>77±10</td>
<td>4</td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>79±9</td>
<td>77±12</td>
<td>2</td>
</tr>
<tr>
<td>Gly/Gly</td>
<td>82±8</td>
<td>81±7</td>
<td>1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
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</tr>
<tr>
<td>Males</td>
<td>60±12</td>
<td>62±11</td>
<td>2</td>
</tr>
<tr>
<td>Females</td>
<td>70±14</td>
<td>74±11</td>
<td>4</td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>67±12</td>
<td>70±12</td>
<td>3</td>
</tr>
<tr>
<td>Gly/Gly</td>
<td>65±15</td>
<td>68±13</td>
<td>3</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.4±0.7</td>
<td>7.7±1.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

When compared to euglycemia, male subjects exhibited significant reductions in sCBRS to rising blood pressure, a measure of parasympathetic control, is reduced during hypoglycemia in male patients with T1DM. These changes are not observed in women. In contrast, the rise in heart rate during hypoglycemia in women – while similar to that observed in men – appears insufficient to maintain blood pressure, suggesting impaired sympathetic control in women with T1DM. Funding: NIH DK090541, NIH HL120570.

14.6 THE EFFECTS OF TESTOSTERONE AND OXIDATIVE STRESS ON NEUROINFLAMMATORY SIGNALING IN DOPAMINE NEURONS

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1Pharmacology & Neuroscience, Univ. North Texas Hlth. Sci. Ctr. at Fort Worth, 350 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 hydrogen peroxide (tBHP) 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 Raman1, Nirmal Vijayavel1, Colleen Kerring1, Jennifer Echeverria1, Jared Dickinson, Chad Carroll, Taben Hale1, and Siddhartha Angati1

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 NFκB/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 NFκB. DOX and TLR4 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 levels using standard western blotting. Although COX2 was considered an inducible enzyme, it has been shown to be expressed under basal conditions. In cortex and pial arteries from vehicle-treated rats, measurable levels of COX2 and TLR4 protein were detected. However, contrary to our hypothesis, levels of COX2 and TLR4 were decreased following DOX. In pial arteries, DOX elicited a reduction in both the COX2- and TLR4- bands. While the COX2 bands were not observed at the highest dose (12 mg/kg), the TLR4 bands were. In conclusion, although others have suggested the involvement of the NFκB 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

Michelleersa, Lev A. Reves2, Apollonia For2, and Jorge M. Segarra2
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The objective was to determine if cerebral blood flow regulation is affected throughout the menstrual cycle in young, healthy women with normally 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. Beat-by-beat blood pressure, heart rate, end-tidal CO₂, and transcranial Doppler ultrasonography of the anterior and middle cerebral arteries were measured for each subject. Results from the sit-to-stand maneuver indicate a significant reduction (p = 0.05) in the cerebral autoregulatory index of the middle cerebral artery during the late follicular phase (NOC: 3.7 ± 0.44; OC: 3.1 ± 0.39) compared to the menstrual phase (NOC: 4.2 ± 0.67; OC: 4.2 ± 0.60), but not a significant effect of oral contraceptives. There was a significant effect of oral contraceptives on both the resting mean arterial pressure (p = 0.02); menstruation NOC: 79.7 ± 4.9 mmHg; OC: 92.7 ± 4.4 mmHg; late follicular: NOC: 70.4 ± 6.2 mmHg; OC: 87.1 ± 5.6 mmHg; luteal: NOC: 66.1 ± 8.1 mmHg; OC: 93.0 ± 7.2 mmHg and heart rate (p = 0.027; menstruation NOC: 60.7 ± 4.3 bpm; OC: 74.3 ± 4.3 bpm; late follicular: NOC: 66.4 ± 1.5 bpm; OC: 70.1 ± 1.5 bpm; luteal: NOC: 65.8 ± 3.5 bpm; OC: 72.8 ± 3.5 bpm), but no effect of menstrual cycle phase. There was also a significant effect on the decrease in mean flow velocity of the middle cerebral artery when going from a sitting to standing position, but there was a trend for a greater drop in steady-state flow velocity when standing in women on oral contraceptives (menstruation: NOC: 0.90 ± 0.43; OC: -6.7 ± 3.8; late follicular: NOC: -3.5 ± 3.4; OC: -5.4 ± 3.0; luteal: NOC: -0.35 ± 3.6; OC: -5.8 ± 3.2%). While more data is necessary to interpret the findings, the preliminary results may indicate reduced cerebral vasodilation in women on oral contraceptives. However, this data is from a small number of young women. Additional participants are needed to support these findings.

15.0 PREGNANCY

15.1 PLACENTAL ISCHEMIA INCREASES SENSITIVITY TO PENTYLENETERAZOL-INDUCED SEIZURES AND CEREBROSPINAL FLUID INFLAMMATION

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Eclampsia is diagnosed in pregnancy when women 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 utero-placental perfusion pressure, increases susceptibility to seizures, cerebral edema, cerebrospinal fluid (CSF) cytokines/chemokines, and plasma neurokinin B (NKB). Pentylenetetrazol (PTZ) was administered and UARI assessed by Doppler sonography and MAP was measured on GD14. Consistent with previous studies, MAP was increased in AT1-AA-infused pregnant rats (123.3±7.4 mmHg, n=3) compared to normal pregnant rats (101.2±1.2 mmHg, n=9, p=0.0005). MAP was reduced with VD2 treatment in AT1-AA-infused rats (105.0±2.3 mmHg, n=4, p=0.04) and AT1-AA+VD3 rats (110.4±1.5 mmHg, n=6, p=0.06). Our data indicated that UARI was increased in AT1-AA rats (0.55±0.02, n=4) compared to NP (0.44, 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 (74.91±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 (241.0±187.7 pg/ml, n=3). Our preliminary data demonstrate that Vitamin D supplementation improves uterine artery vascular resistance and sFlt1 which are possible mechanisms for improved hypertension induced by AT1-AA during pregnancy. This study was funded by NIH grants ROIHD067541 and T32HL105324.
Gi/o inactivation with pertussis toxin (PTX). In contrast, PTX had no effect on day 15 in Rgs2-/- mice. Examination of uterine artery tone showed augmented myo-

during pregnancy. Impaired uterine artery blood flow is not known. Here we determined whether the loss of RGS2, a

euglycemic hyperinsulinemia have significant effects to increase blood pressure during pregnancy through different pathways. Thus, elevated circulating metabolic factors such as leptin and insulin may contribute to the development of hypertension in PE women. Funding: 14POST18970005, HIL051971, and T12HL105324.

15.4 THE INCREASED ENDOTHELium-DEPENDENT VASODILATORY RESPONSE OF HEALTHY PREGNANCY IS ABSENT IN THE PREECLAMPTIC DAHL SALT-SENSITIVE RAT
Ellen Gillis1, Taylor Coleman2, Frank Sandler1, Joey Grauner3, Michael Garrett1, Michael Ryan1, and Jennifer Sasser3

Pharmacology & Toxicology, Univ. of Mississippi Med. Ctr., 2500 N. State St., Jackson, MS, 33216.

Preeclampsia is a hypertensive disorder of pregnancy associated with renal injury and endothelial dysfunction. More specifically, in preeclampsia there is an absence of the well-characterized increase in endothelium-dependent vasorelaxation that occurs during normal pregnancy. Previously, our laboratory identified the Dahl salt-sensitive (Dahl S) rat strain as a spontaneous model of preeclampsia exhibiting hypertension and renal injury during late pregnancy; however, it is unknown whether this model also presents with endothelial dysfunction. Thus, in the present study, we hypothesized that the Dahl S rat would exhibit impaired endothelium-dependent vasodilation during late pregnancy. Vascular rings were isolated from carotid arteries and third-order mesenteric arteries from pregnant Dahl S rats on gestational days 17-18 and age-matched virgin female rats (n=4/group). Endothelium-dependent vasorelaxation to acetylcholine and endothelium-independent vasorelaxation to the nitric oxide donor sodium nitroprusside were assessed. There was no significant difference in acetylcholine sensitivity (logEC50) in the pregnant rats compared to their virgin controls in carotid arteries (−6.5±0.51 M vs. −6.3±0.13 M, respectively) or mesenteric arteries (−6.7±0.07 M vs. −6.7±0.06 M, respectively). However, the maximum response to acetylcholine (at −log4.5 M) was significantly impaired in carotid arteries from pregnant Dahl S rats compared to virgins (85±1% vs 91±1%, p<0.05), with a similar trend observed in the mesenteric arteries (85±10% vs 91±8%). There were no differences in sensitivity or maximum vasorelaxation to sodium nitroprusside in pregnant or control rats in either vascular bed, indicating no changes in the vascular smooth muscle response to exogenous nitric oxide. These data support our hypothesis that the increased endothelium-dependent vasodilatory response that is characteristic of healthy pregnancy is absent in the Dahl S rat and that this failure of the normal cardiovascular adaptation to pregnancy contributes to the increased blood pressure and preeclamptic phenotype in the Dahl S rat.

15.5 DECREASED UTERINE ARTERY BLOOD FLOW AND ENHANCED MYOGEnIC TONE IN RGS2-DEFICIENT MICE
Li He1, Elizabeth Owens2, and Patrick Osei-Owusu3


Uterine artery blood flow is critical to maintaining uteroplacental perfusion for delivery of nutrients and oxygen to the fetus during pregnancy. Impaired uterine artery blood flow is implicated in several pregnancy complications including fetal growth restriction, small for gestational age, and preeclampsia. The etiology of abnormal uterine artery blood flow is not known. Here we determined whether the loss of RGS2, a GTPase activating protein for Gi/11 and G­ii class G proteins that regulates vascular smooth muscle contraction, affects uterine artery blood flow during pregnancy. We used Doppler ultrasonography to assess uterine artery blood flow prior to and at three stages of gestation in wild-type (WT) and Rgs2-null (Rgs2-/-) mice. Ex vivo microscroscopy was used to examine myogenic tone in pressurized uterine artery segments.

We found that baseline uterine artery blood flow velocity was markedly decreased while peak systolic velocity-to-least diastolic velocity ratio (PS/2D; WT: 2.45±0.18 vs. Rgs2-/-: 3.85±0.64, p<0.05), resistive index (RI; WT: 0.58±0.04 vs. Rgs2-/-: 0.71±0.03, p<0.01) and pulsatility index (PI; WT: 0.90±0.06 vs. Rgs2-/-: 1.25±0.11, p<0.01) were all increased in non-pregnant Rgs2-/ mice relative to WT controls. During pregnancy, PS/2D and PI remained elevated and increased between gestational day 15 in Rgs2-/- mice. Examination of uterine artery tone showed augmented myogenic response in both Rgs2+/+ and Rgs2-/- mice, which was reduced to WT level following Gi/o inactivation with pertussis toxin (PTX). In contrast, PTX had no effect on myogenic response in WT uterine arteries. The data together indicate that RGS2 deficiency decreases uterine artery blood flow by increasing myogenic tone at least partly through prolonged Gi/o activation. Thus, mutations that decrease vascular RGS2 expression may be a predisposition to decreased uterine blood flow. Targeting Gi/o 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
Frank Sandler1, Ana Pale1, and Joey Grauner3

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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 pregnancy 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 NIH11 standard chow; mated at 17 weeks old, and supplemented with high dietary fat intake in drinking water with the non-selective NOS inhibitor L-N^Sup data-list-id=1<SUP data-listid>G</SUP>-nitroarginine methyl ester (L-NAME, 100 mg/L) starting at gestational day 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, N=10) than MC4R+/- (untreated: 337±A name=OLE_LINK2 data-list-id=1<SPAN data-listid>G</SPAN>-Nitroarginine methyl ester at G, N=16 vs. L-NAME: 332±8g; N=12) regardless of treatment (P<0.05). The same was true for visceral adipose tissue weight with MC4R+/- (untreated: 70±1.1 vs. L-NAME: 5.2±0.5g) being greater than MC4R+/- (untreated: 3±0.3 vs. L-NAME: 3.5±0.4g) (P<0.05). Fetal weight was reduced by L-NAME only in MC4R+/- (1.98±0.03 vs. 1.82±0.06g, P<0.05) not MC4R+/- (1.92±0.03 vs. 1.86±0.06g) while placental weights were similar among untreated and L-NAME-treated groups alike, respectively, (MC4R+/-: 0.50±0.01 vs. 0.50±0.03g) and (MC4R+/-: 0.56±0.02 vs. 0.55±0.02g). MAP was greater in untreated MC4R+/- vs. MC4R+/- rats (P<0.05). The effect of NOS inhibition to raise MAP was statistically higher in <A name=OLE_LINK3 data-listid>G</SPAN>-Nitroarginine methyl ester at G (ANOVA: F=27.0 vs. 130±3mmHg, P<0.0001) compared to MC4R+/- (112±A name=OLE_LINK4 data-list-id=3<SPAN data-listid>A</SPAN>-Nitroarginine methyl ester at G, N=16 vs. L-NAME: 134±6mmHg, P<0.001). GFR was reduced (P<0.05) by L-NAME similarly in MC4R+/- (1.5±0.01 vs. 1.1±0.1mL/min/100g) and MC4R+/- (1.5±0.02 vs. 1.3±0.1mL/min/100g). Circulating leptin (MC4R+/- untreated: 5.9±0.6 vs. L-NAME: 5.8±0.9ng/mL; MC4R+/- untreated: 3.6±0.3 vs. L-NAME: 3.4±0.8ng/mL) and total cholesterol levels (MC4R+/- untreated: 123±5 vs. L-NAME: 137±2mg/dL; MC4R+/- untreated: 93±5 vs. L-NAME: 113±1mg/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.
15.8 A NOVEL MASTER SWITCH FOR OVARIAN CYClicity: THE IMPACT ON CARDIOMETABOLIC HEALTH

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The increased risk for cardiovascular disease that follows menopause may reflect not only the cessation of ovarian hormone production but also previously unidentified, sex-specific factors whose presence or absence precipitates CVD. We identified a novel endogenous peptide called Phoenixin (PNX), which is robustly expressed in the hypothalamus where mRNA levels fluctuate during the estrous cycle. This plus our previous observation that knockdown of endogenous PNX levels using siRNA decreased the appearance of estrous with an average cycle length of 9 days. Taken together, PNX acts in CNS to act activate the hypothalamo-pituitary-gonadal axis. We identified the orphan G-protein coupled receptor GPR173 in vitro. We then tested whether siRNA mediated compromise of central GPR173 expression would also result in impaired estrous cyclicity. Female rats were pretreated with a control siRNA, cFos mRNA expression increased upon PNX stimulation an anesthetized blood pressure is measured via carotid catheter then resistance arterioles (0.032673ug pDNA/ 2.5mg NP) are injected into the uterine wall. On day 21 of gestation, silver clips are placed on the abdominal aorta (0.2mm i.d.) and the utero-ovarian arteries (0.1mm i.d.) are harvested for study in an isobaric arteriograph. GFR was reduced, it was not significant between Preg + ANGII rats (7.4 ±1.09 vs. 15.4 ±1.75 ml/min). No change in RVR between Preg + ANG II and Preg + AT1-AA vs NP rats (14.2 ±2.96, 14.4 ±1.48 vs. 15.4 ±1.75 ml/min). However, the RWR was drastically increased between Preg + ANGII and AT1-AA vs NP rats (18.4 ±2.91 vs. 6.4 ±0.77). Conclusion: Together, ANGII and AT1-AA drastically decreases renal function by 37%. RBF by 59%, and caused a 3 fold increase in RVR vs NP rats. These data indicate the importance of AT1-AA s to drastically enhance ANG II induced renal vascular sensitivity and reduce renal function during preeclampsia. Research Supported by T32HL105324 and RO1HD067541.

15.9 BLOOD PRESSURE RESPONSES TO ISOMETRIC HANDGRIp EXERCISE AND POST-EXERCISE ISCHEMIA IN WOMEN WITH A HISTORY OF HYPERTENsIVE PREGNANCY

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Objective: History of hypertensive pregnancy (HTNP) is considered a risk factor for cardiovascular disease. However, only some women with a history of HTNP become hypertensive later in life. An exaggerated blood pressure (BP) response to physical stressors (e.g. isometric handgrip and post exercise ischemia) is an independent marker of cardiovascular risk. Hence, the aim of the study was to compare BP responses to 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 photoplethysmography) was recorded at rest and during first phase, second third phase and final phase of isometric handgrip (HG) exercise. Blood pressures were measured simultaneously at the upper arm (7 mm Hg) and legs (with a thigh cuff). Additionally, isometric handgrip exercise was followed by 90 seconds of post-exercise ischemia on the exercising arm. BP was analyzed in three phases of 30 seconds each during cuff occlusion. Results: Women with a history of 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 (8 ± 1 and 8 ± 1 %, respectively, p<0.05). Women with a history of HTNP had a significantly higher rise in DBP during 1st cycle of cuff occlusion (12 ± 2 %) as compared to non-treated HTNP women (6 ± 2 %, p=0.028). 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, H53947.

15.10 UP-REGULATION OF VEGFR2 IMPROVES UTERINE ARTERY MYOGENIC RESPONSE AND MATERNAL HYPERTENSION ALTERED BY UTERINE PERFUSION PRESSURE REDUCTIONS

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RATS

BP was recorded and a transonic flowmeter probe was placed on the left renal artery to measure RBF. Results: BP was elevated in all pregnant rats administered ANG II and/or the AT1-AA. Although GFR was reduced, it was not significant between Preg + ANGII and Preg + AT1-AA vs NP rats (15.9 ±2.0 vs. 16.0 ±0.17 ml/min) however, the GFR was further decreased in Preg + ANGII + AT1-AA rats (12.0 ±0.08). No difference was observed with the RBF between Preg + ANGII and Preg + AT1-AA vs NP rats (14.2 ±2.96, 14.4 ±1.48 vs. 15.4 ±1.75 ml/min). RBF was decreased in Preg + ANGII + AT1-AA vs NP rats (7.4 ±1.09 vs. 15.4 ±1.75 ml/min). No change in RVR between Preg + ANGII and Preg + AT1-AA vs NP rats (14.2 ±2.96, 14.4 ±1.48 vs. 15.4 ±1.75 ml/min). However, the RWR was drastically increased between Preg + ANGII and AT1-AA vs NP rats (18.4 ±2.91 vs. 6.4 ±0.77). Conclusion: Together, ANGII and AT1-AA drastically decreases renal function by 37%. RBF by 59%, and caused a 3 fold increase in RVR vs NP rats. These data indicate the importance of AT1-AA s to drastically enhance ANG II induced renal vascular sensitivity and reduce renal function during preeclampsia. Research Supported by T32HL105324 and RO1HD067541.

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

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Objective: History of hypertensive pregnancy (HTNP) is considered a risk factor for cardiovascular disease. However, only some women with a history of HTNP become hypertensive later in life. An exaggerated blood pressure (BP) response to physical stressors (e.g. isometric handgrip and post exercise ischemia) is an independent marker of cardiovascular risk. Hence, the aim of the study was to compare BP responses to
While obesity increases the risk for developing preclampsia, which is now-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 alters blood pressure during pregnancy. This could be due to the lack of high sucrose diets to use in animal models. However, it is unknown whether body weight, for example segregation of lower vs. higher body weights even within the normal weight range, is important.

**Most interestingly, MAP was greatest (P<0.05) in HSD-H (120±2mmHg) over respectively) over the NSD-L and HSD-L groups (345±7 vs. 325±12g, respectively).**

Body weights were greater (P=0.0002) in NSD-H and HSD-H (378±3 vs. 355±4g, respectively) over the NSD-L and HSD-L groups (345±7 vs. 325±12g, respectively). Most interestingly, MAP was greatest (P<0.002) in the NSD-H and HSD-H groups (82.0±4 vs. 66.0±7g, respectively) than NSD-L and HSD-L groups (59.2±2 vs. 47.2±8g, respectively). Body weight was greater in NSD-H than HSD-H (P<0.05). Visceral adipose tissue mass was greater (P<0.002) in the NSD-H and HSD-H groups (82.0±4 vs. 66.0±7g, respectively) than NSD-L and HSD-L groups (59.2±2 vs. 47.2±8g, respectively).

These data suggest that the hypertensive response to HSD 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 change in pregnancy in the setting of high circulating aldosterone and enhanced sodium reabsorption. We measured dietary K+ intake and urinary K+ excretion. K+ intake increased in MP and LP vs V (4.6±0.1 vs. 5.2±0.1 vs 3.3±0.1 mmol/24h, p=0.05) were renal K+ excretion also rose (4.3±0.1, 4.6±0.1 vs. 3.0±0.2 mmol/24h, p=0.05). We also measured the mRNA expression of BK, ROMK, H,K+-ATPase type 1 (HK1, H,K+-ATPase type 2 (HK2a), and H+ATPase in the renal cortex, outer medulla, and inner medulla of virgin (V, n=6), mid pregnant (MP, n=6), and late pregnant (LP, n=6) rats using quantitative real-time PCR. We found an increase in HK in the outer medulla in MP rats vs V and increased HK2a expression in both cortex and outer medulla of LP rats vs V. Furthermore, ROMK expression decreased in the inner medulla of MP and LP rats compared to V. BK mRNA increased in outer medulla and decreased in inner medulla at MP, and increased in cortex at LP. The expression level of the other genes tested did not differ with pregnancy stage. Although ROMK mRNA was unchanged in the CTX and decreased in the IM, the abundance detected by immunofluorescence was increased in both MP and LP vs V in the cortex and not different in the medulla. In the distal colon we found a fall in BK mRNA at MP, an increase in the H,K-ATPase mRNA at LP and an increase in distal colon HK2a protein abundance whereas IM HK2a protein abundance was too low to be detected in kidney, even in LP rats. During pregnancy the kidney is receiving negative signals with respect to K+ handling, with the changes in apical sodium channels/transporters and ROMK promoting K+ secretion, and the changes in HK1 and HK2a promoting K+ retention. Therefore the K+ retention of pregnancy is likely due to both increased collecting duct K+ reabsorption (via increased HK1/HK2a) offsetting the increased K+ secretion, as well as increased colonic reabsorption via HK2a. Future studies will determine the signaling pathways involved in these mechanisms.

**15.13 IMPAIRED FLOW-MEDIATED DILATION BEFORE, DURING AND AFTER PREECLAMPSIA: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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**Background:** Endothelial dysfunction is believed to play a critical role in preeclampsia, however it is unclear whether this dysfunction precedes the pregnancy or is caused by early pathophysiological events. It is also unclear whether vascular dysfunction resolves post-partum, or may be one mechanism linking preeclampsia with future cardiovascular disease. **Objective:** to determine whether women with preeclampsia, examined before, during and after a preconceptual pregnancy, have worse vascular function compared to women who did not have preeclampsia. Vascular dysfunction was assessed by flow-mediated dilation (FMD). **Methods and Results:** We performed a systematic review and meta-analysis of studies examining FMD before, during and after preeclampsia published before January 27, 2015. Differences in FMD were evaluated by standardized mean differences. We searched 595 abstracts identified through PubMed, EMBASE and Web of Science. 32 studies were eligible for the meta-analysis. When compared to women who did not have preeclampsia, women who had preeclampsia had lower FMD prior to the development of preeclampsia (~20-29 weeks gestation), at the time of preeclampsia, and for three years post-partum. The estimated magnitude of the effect ranged between 0.5 and 3 standard deviations. Although statistically significant, the estimated effects had wide confidence intervals due to high heterogeneity. These differences were no longer evident by 10 years post-partum. **Conclusions:** Compared to women who do not develop preeclampsia, women who develop preeclampsia have worse vascular function from 20 weeks gestation until 3 years post-partum. This meta-analysis may over-estimate the effects of preeclampsia, as the small, observational studies included have a high risk of bias.

**16.0 DEVELOPMENTAL PROGRAMMING**

**16.1 VENDOR-SPECIFIC EFFECT 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 intrauterine 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 remained 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 ovarioectomy (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 and female 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±3 vs. 36 ±7g and Females: 19±3 vs. 17±3g; 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±3 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. Dusing: AHA 15PRE24700010, Alexander: HL074927, AHA GRNT19900004, P01-HL51971, GM104357.

16.2 IS THERE A SEX DIFFERENCE BETWEEN HYPERTENSION RISK AND LOW BIRTH WEIGHT IN HEALTHY YOUNG JAPANESE ADSULTS?

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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 is 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 TG 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 in the sitting position (p < 0.01), although no significant responses were observed in men. Similar to the results of earlier studies, our results showed that healthy young men have lower HDL-C and higher TG levels compared to healthy young women. Our results also showed that healthy young men with a LBW have lower HDL-C levels compared to their counterparts with a normal birth weight. In addition, among healthy young Japanese adults, men may be less sensitive to postural changes in BP compared to women. In conclusion, we found that sex differences exist between LBW and hypertension risks in healthy young Japanese adults.

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), an established behavioural stress model, are glucose intolerant with no differences found in males. The aim of this study was to investigate the effect of ELS on adipocyte morphology and fat distribution. C57BL/6 mice were separated for 4 hours/day from postnatal day 2-5 and 8 hour/day from PDN6 to 16 with early weaning at day 17. Normally reared litters served as control (C). Upon weaning, mice were placed on a low-fat diet (LFD, 10% kcal from fat=6-10) or high-fat diet (HFD, 60% kcal from fat=910) for 16 weeks. Although MSEP did not lead to changes in body weight on mice fed a LFD, both male and female mice exposed to MSEP gained a significant amount of weight on a HFD; however, this weight gain was greater in females. EchoMRI revealed that this increase in body weight was due to increased adiposity in both genders. Although male MSEP mice showed significantly elevated fat mass through week 12, no differences were observed at week 16 compared to C (22.4±0.8 vs 20.1±0.8 g, respectivly. Female MSEP mice showed exaggerated adiposity beginning at week 4 that persists through the end of the study (18.2±1.4 vs 7.6±0.1 g, p<0.01). Because of these changes in adiposity, we examined morphological parameters from gonadal white adipose tissue in both sexes. Male MSEP mice fed a LFD have elevated cell area (3268±2808, 2643±141 µM², p<0.05) whereas no differences were present in females fed a LFD. Interestingly, when females were fed a HFD, MSEP led to hyper trophy of adipocytes (6011±503 vs 4252±282 µM², p<0.05) with increases in cell diameter (77.2±4 vs 68.4±2.8 µM, p<0.05) compared to C; however, no differences were observed in male MSEP cell area (2758±190.1 vs 2663±170 µM²) or cell diameter (51.7±2 vs 53.3±19 µM) compared to C fed a HFD. Magnetic resonance spectroscopy revealed that female MSEP mice fed a HFD have elevated levels of visceral fat compared to C (1557±235.5 vs 904.1±104.56 mm², p<0.001) with no differences in subcutaneous levels. In addition, MSEP increases ser um cholesterol levels in both genders fed a HFD; however, MSEP male mice displayed a greater response compared to MSEP female mice (p<0.05). ELS worsens the fat morphology in female mice whereas it disturbs the lipid metabolism in male mice. These data suggest that the mechanisms by which ELS affects fat partitioning and adipocyte biology as well as cholesterol levels are sex-specific.

16.4 SPHINGOSINE-1-PHOSPHATE RECEPTOR TYPE 3 PLAYS A ROLE IN THE ETIOLOGY OF HIGH BLOOD PRESSURE PROGRAMMED BY INTRAUTERINE GROWTH RESTRICTION IN THE MALE BUT NOT THE FEMALE MOUSE

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Intrauterine growth restriction (IUGR) is a risk factor for hypertension and cardiovascular (CV) disease in later life, but the underlying mechanisms remain unclear. The bioactive sphingolipid metabolic sphingosine-1-phosphate (SIP) is critically involved in CV development in the fetus, and plays a significant role in the regulation of CV health in adulthood. SIP receptor (SIPR) type 1, 2, and 3 are widely expressed in CV system and SIPR3 is involved in the control of blood pressure (BP). We previously reported in IUGR induced by reduced uterine perfusion (RUP) in the mouse programs a significant increase in BP in male IUGR mice but not in female IUGR mice as compared to same-sex control counterparts. Hypertension in male IUGR is attenuated by the SIP receptors agonist. Yet, whether regulation of SIPR3 expression is sex-specific following IUGR is unknown. In the present study we tested the hypothesis that IUGR programs sex-specific renal expression of SIPR3 in IUGR mice. C57Bl/6 mice underwent sham or RUP at day 13 of gestation with delivery at full term. IUGR offspring (from RUP dams) had a lower birth weight than control (P<0.05). Kidneys were isolated from 24 week old control and IUGR offspring after measurement of BP. Male IUGR offspring had a significantly higher BP compared to male control via carotid catheter in the conscious state (control: 121±2.2, IUGR: 125±3.7 mmHg; N=7, P<0.05). MAP did not differ between female control and female IUGR offspring (113±2.8, 117±2.8 mmHg; N=5). Kidney weight per body weight was not different between control versus IUGR same-sex counterparts. Renal SIPR3 gene expression levels were increased (2.5 fold vs. control, N=4, P<0.05) whereas SIPR3 protein levels were decreased (0.75 fold vs. control, N=4, P<0.05) in male IUGR. Renal gene and protein SIPR3 expression levels were not differ ent between female control and female IUGR. Together our data suggest that IUGR programs a sex-specific alteration in renal SIPR3 expression which may contribute to an increase in BP programmed only in male IUGR but not female IUGR mice Thus, SIPR3 signaling is a potential putative mechanism underlying the sex-specific hypertensive of IUGR mouse offspring. Dr. Intapad 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 SR (sleep restricted). At two months, half of the offspring were divided into three groups: control, SR and RUP (reduced uterine perfusion). 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 (KCA) and kidney mass (KM). The results are shown as mean± SEM and number of measurements between parenthesis; Anova, p<0.05. The SR groups presented increased BP [CS: 125±0.7(17); CO:
RT-PCR analysis of the lamina terminalis and the paraventricular nucleus tissues either hypertensive (ANG II treatment produced only a slight, but significant increase in BP in offspring of enhanced hypertensive response to sc ANG II (120 ng/kg/min, beginning at 10 weeks of age, male offspring of hypertensive dams showed an eng/kg/min, sc) during pregnancy sensitizes ANG II-induced increase in blood pressure and renal function, confirming the role of female sex hormones in regulation of arterial pressure and renal function during adult life. Financial support: FAPESP.

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 vessels of adult rats that had been exposed to PH (1 wk before and 1 wk after birth) and then lived in normoxia are more compliant and their vasconstrictor response to a high concentration of ANG II 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 cleavages in the extracts of collagenous proteins from prealveolar pulmonary vessels typical for hypoxic pulmonary hypertension (3). The presence of right ventricle hypertrophy only in males led us to question the role of sexual hormones. Rats exposed to PH were therefore gonadectomized as neonates (3). Pulmonary arterial pressure was elevated in adult pulmonary vessels of 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 blood vessels (a reliable structural marker of pulmonary hypertension) in adulthood was greater than in intact, perinatally normoxic male controls. In gonadectomized females born 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 transmural K+ currents, we tested the response of pulmonary vasculature of male and female rats exposed to PH to K+. In contrast to males, PH females have higher basal perfusion pressure and reactivity to K+ than control females. The different effects of PH in male and female rats may result from difference expression and/or activity of K+ channels. Supported by GACR 13-01710S and IGA NT/13358. References: 1. Hampa V et al. Am J Physiol Lung Cell Mol Physiol 285: L386-392, 2003. 2. Hampa V, and Herget J. Am Rev Respir Dis 142: 619-624, 1990. 3. Novotná J, and Herget J. Life Sci 62: 1-12, 1998.

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

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Prehypertension (systolic blood pressure: 120-139 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 reduced 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 reduced endothelial t-PA release in middle-aged women. Thirty-four sedentary, normoestrous, post-menopausal, middle-aged women were studied. Prehypertensive (age: 57±1 yr; BMI: 26.1±0.8 kg/m²; BP: 105/66±2/2 mmHg) and 17 hypertensive (age: 56±1 yr; BMI: 26.6±1.0 kg/m²; BP: 130/79±1/2 mmHg) women were at least one year post menopause, not taking hormone replacement, and free of overt cardiometabolic disease. Endothelial release of t-PA was determined, in vivo, in response to intrabrachial infusions of bradykinin (BK: 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-
larly in the normotensive (from 0.6±0.7 to 56.9±7.6 ng/100 mL tissue/min) and pre-
hypertensive (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 t-PA release in middle-aged women. Impaired fibrinolytic function does
not appear to contribute to the increase in vascular risk with prehypertension in
middle-aged women. Our findings suggest that mechanisms underlying prehyp-
tension-related vascular risk may differ between men and women.

17.2 GENDER DIFFERENCES IN CIRCULATING MICROPARTICLES IN MIDDLE-AGED ADULTS

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The incidence of coronary heart disease (CHD) and stroke is ~50% higher in men
compared with women between the ages of 45 and 65 years. The mechanisms respons-
ible for the gender-related difference in cardiovascular disease risk are not com-
pletely understood. We and others have reported profound gender-related differences
in vascular endothelial function in middle-aged adults. Clinical interest in circulating
microparticles (MPs) has increased due to their putative role in inflammation, vascular
health and cardiovascular disease (CVD). MPs are small vesicles (0.1-1µm) formed
by the outward blebbing of the cellular plasma membrane and released into circu-
lation by a variety of cell types. Circulating MPs originating from platelets (PMPs),
endothelial cells (EMP), monocytes (MMPs) and leukocytes (LMPs) are now recog-
nized as biomarkers of vascular injury and are predictive of vascular events. There is
currently no consensus as to the biological significance of circulating MPs. The aim of
this study was to determine whether circulating MPs, EMPs, MMPs and LMPs differ
in middle-aged men compared with women. If so, this may contribute to gender-related
disparity in CVD in middle-aged adults. Thirty healthy, sedentary, non-obese, middle-aged adults were studied: 16 males (age: 57±2 yr; BMI: 25.3±0.5 kg/m²) and 14 females (age: 55±1 yr; BMI: 24.5±0.7 kg/m²). All
women were at least 1 year postmenopausal and not taking hormone replacement therapy.
Circulating MPs were measured in platelet free plasma from peripheral blood samples.
Cellular lineage was identified by flow cytometry utilizing cell-specific antibodies:
PMPs (CD31+CD42b), EMPs (CD31+CD42d), MMPs (CD14+) and LMPs (CD14). Circulating MPs were ~200% higher (P<0.05) in females (111±28
µm/L) compared with males (37±8 µm/L). However, there were no significant
gender-related differences in circulating EMP (393±66 vs. 388±41 µm/L), MMP
(237±53 vs. 266±50 µm/L) or LMP (38±10 vs. 37±9 µm/L) concentrations be-
tween the women and men. These results indicate that aside from PMPs, there is no
influence of gender on circulating EMPs, MMPs or LMPs in middle-aged adults.

17.3 FOREARM VASCULAR CONDUCTANCE RESPONSES TO TERBUTALINE, A β2-ADRENERGIC RECEPTOR
AGONIST, DIFFER IN PREMENOPAUSAL Versus POSTMENOPAUSAL WOMEN

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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 be-

flow (FBF, venous occlusion plethysmography) and mean arterial pressure (MAP, in-
tra-arterial brachial catheter) were measured at baseline and during intra-arterial in-
fusions of terbutaline at 0.1, 0.5, 1.0, and 2.0 µg/100 ml tissue/min. These women did
not differ in body mass index or blood pressure. Baseline FBF was similar in pre-
menopausal and postmenopausal women (2.2±0.4 vs. 2.0±0.5 ml/100 ml tissue/min,
respectively; p>0.05) and rose significantly within each group at the highest ter-
butaline dose (10.7±2.1 vs. 7.1±1.9 ml/100 ml tissue/min, respectively; p>0.05); how-
ever, there were no FBF differences between the groups. Baseline forearm vascular
conductance (FVC-FBF/MAP+100) was not different between groups (2.4±0.4 vs,
1.8±0.4 ml/100 ml tissue/min/mmHg; premenopausal vs. postmenopausal,
respectively; p>0.05). Terbutaline infusion at the highest dose resulted in a significant
increase in FVC in both premenopausal and postmenopausal women (12.0±2.5 vs.
6.9±1.9 ml/100 ml tissue/min/mmHg; respectively; p<0.05). The increase in FVC
was greater in premenopausal women when compared with postmenopausal women
(interaction of group x dose, p<0.05). These data provide evidence to support that β2-
adrenergic receptor responsiveness is blunted with aging and menopause in healthy
women. Funded by AHA 14PRE18040000, NIH HIL HS3947 and HIL18154, and
NCATS ULI TR000135 (CTSA).

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

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The VCD model of menopause (4-vinylcyclohexene diepoxide, VCD) preserves the
“perimenopause” transitional period and the androgen secreting capacity of the resid-
ual 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 sensitivity (significant in-
crease in SBP and MAP), along with renal hypertrophy and cardiac fibrosis. Endo-
thelial and ET receptor signaling through ET-1, receptors, has been shown to promote renal
and Ang II hypertension in male rodents, while postmenopausal females were protected.
To determine whether ET receptors signaling contributes to the increased sensitivity
of Ang II hypertension in VCD-treated postmenopausal female mice (Meno), Ang II (800ng/kg/min, 14d) was infused with or without injections of the
ET1 receptor antagonist ABT-627 (5mg/kg, ip) (ET1). Premenopausal females received sesame oil vehicle with and without Ang (C, C/Ang II). Ang II infusion in-
duced a significant increase in systolic blood pressure in VCD-treated postmeno-
pausal mice compared to Ang II infusion in premenopausal mice (CΔ2±2
ml/mmHg, C/Ang II Δ15±2 mmHg, Meno/Ang II Δ37±6 mmHg, P<0.05 vs C, #P<0.05 vs
C/Ang II). ET1 receptor antagonism prevented this increase in blood pres-
sure in postmenopausal females (ETA14±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 ET1 receptor antagonism (Meno/Ang II 1.0±0.07 vs 6.08±0.08 in ETA treated, P<0.05). Together, these data
suggest that ET1 signaling, via ET1 receptor activation, promotes Ang II induced
hypertension and renal damage in postmenopausal females. Targeting this 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 be-

flow (FBF, venous occlusion plethysmography) and mean arterial pressure (MAP, in-
tra-arterial brachial catheter) were measured at baseline and during intra-arterial in-
fusions of terbutaline at 0.1, 0.5, 1.0, and 2.0 µg/100 ml tissue/min. These women did
not differ in body mass index or blood pressure. Baseline FBF was similar in pre-
menopausal and postmenopausal women (2.2±0.4 vs. 2.0±0.5 ml/100 ml tissue/min,
respectively; p>0.05) and rose significantly within each group at the highest ter-
butaline dose (10.7±2.1 vs. 7.1±1.9 ml/100 ml tissue/min, respectively; p>0.05); how-
ever, there were no FBF differences between the groups. Baseline forearm vascular
conductance (FVC-FBF/MAP+100) was not different between groups (2.4±0.4 vs,
example, the coronary arteries percent tone was increased to 28.9±13.7% at 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 O VX model, vasodilatory pathways involving E T B and nitric oxide re- main intact. This work is supported by NIH R15 HL09754.

17.6 CIRCULATING STEROID HORMONES HAVE NO INFLUENCE ON THE CARDIOVASCULAR BENEFICIAL EFFECT IN TRAINED HYPERTENSIVE POST-MENOPAUSAL 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 circulating sex hormones 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) 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 the 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: 406.9±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±10 and HT: 137.5±16 nmol/L) measured at postprandial state. After AET, there were no significant changes on testosterone 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 and cortisol concentrations are reduced 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: Fapesp.

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 (PMW), 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 andro- gen 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 PMW with 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 weeks of age (pellets were changed every 85 d), were aged to 22-25 months. Renal function was measured by clearance studies in euvolemic, anesthetized rats (Inactin 110 mg/kg i.p.). Catheters were placed into femoral artery (continuous measurement of blood pressure (mean arterial pressure (MAP)), femoral vein (for infusion of 50% global/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 1 ml/hr). Tracheostomy was performed and a catheter was placed into the trachea 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=0.0001), MAP (130.5±5 vs 110±4 mmHg, p=0.05), left kidney weight (1.49±0.11 vs. 0.8±0.02 g, p=0.0001) than placebo controls. Placebo treated females had normal GFR whereas DHT-treated females had a 40% reduction in GFR (0.62±0.07 vs 1.5±0.1 ml/min/kg, p<0.01) and 40% reduction in RPF (2.33±0.41 vs 4.08±0.51 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 had progressive changes in body and blood pressure may have a similar risk profile.

Conclusions: Our study suggests that the tachyphylactic effect of estradiol on BP with aging may be related to decreased aldosterone levels.

17.8 EFFECT OF ESTRADIOL REPLACEMENT IN HYPER- TENSION IN THE AGING FEMALE DAHL SALT SENSITIVE RAT

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It has been demonstrated that the prevalence of arterial hypertension as a result of an increase in blood pressure (BP) is not well controlled in women, particularly the older ones. In our model of postmenopausal hypertension, the aging female Dahl Salt Sensitive (DS) rats develop spontaneous hypertension by 12 mos of age and are no longer able to respond to treatment. 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. 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 weighted. The low estradiol (1x) increased plasma estradiol levels by about 3-fold compared to placebo (15.4±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 which lasted only 4 days (164±2 vs 154±5 mmHg; 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 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 (43.2±0.62 vs 82.0±1.45 ng/dl; p=0.05) and visceral fat (23.6±4 vs 11±3 mg/gr 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 obesity. 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 POST-MENOPAUSAL HYPERTENSION

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Hypertension in postmenopausal women is not as well controlled in men regardless of ethnicity of the cohort. Our model of postmenopausal hypertension, the aging female Dahl salt-sensitive hypertensive rats (PMR), we found that blood pressure remains 110 mm Hg despite concurrent treatment antagonists of angiotensin II AT1 receptors, endothelin ETA receptors and 20-HETE synthesis inhibitors. We have also shown that the sympathetic nervous system and the renal nerves contribute to the hypertension 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=6-8/group) underwent uninephrectomy, and two weeks...
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 perinatal 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 hypercapnia (8% inspired CO2) and hypocapnia (mild hyperventilation) as well as cerebrovascular 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±0.7, 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: 0.0±1.3, Females: 0.8±3.1 %/mmHg CO2, p<0.006). Interestingly, there was no correlation between the vasodilatory or vasoconstrictor response and measures of cerebral auto-regulation. In addition, controlling for diabetes, hyperlipidaemia or hypertension did not change the results. Conclusion: These data suggest that an impaired response to a dilatory cerebral vascular stimulus (hypocapnia) may indicate that cerebral endothelial dysfunction is present in aging. In contrast smooth muscle regulation of the vasculature remains intact since cerebral vessels were able to constrict during hypocapnia and dilate during a hyperventilatory stimulus while standing. Thus, improving endothelial function may result in improved dilation of vessels during stimuli that activate the endothelial pathways such as hypocapnia.

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

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Menopause increases adiposity and the risk of osteoporosis. Partly as a result of the carcinogenic concerns of hormone replacement therapy, increasing numbers of post-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 both dietary 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 activity as a result of actions on multiple molecular targets that impact the life cycle of adipocytes and bone precursor cells. Aged, ovariectomized (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 genistin, (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, with 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 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.
18.0 PLENARY LECTURE

18.1 STUDYING BOTH SEXES: A NEW FRONTIER FOR DISCOVERY

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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-generation and -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 cell and animal studies. Nature. 509, 282-283. NIH Guide Notice NOT-OD-15-102. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html.

19.0 OBESITY, METABOLIC SYNDROME, GENDER AND SEX

19.1 IN UTERO CONSEQUENCES OF RODENT VERTICAL SLEEVE GASTRECTOMY ON MATERNAL HEALTH AND FETO-PLACENTAL DEVELOPMENT

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Despite many similar improvements between sexes in metabolic health following surgical weight loss, female reproductive health and transgenerational effects of surgery remain unclear. Our previous work in rodents suggests that following vertical sleeve gastrectomy (VSG, a surgery which resects 80% of the stomach), offspring born to VSG dams are small-for-gestational age. When challenged with a high fat diet (HFD) during adulthood, these animals are glucose intolerant and have levels of adiposity in excess to lean and obese control offspring. In the present studies, we sought to identify the key in utero insults that may be driving these defects. Female Long-Evans rats were placed on HFD for 3 weeks and then received either sham or VSG surgery. Females exhibited similar body weight and glucose and lipid improvements as previously reported. Females were then mated with males; during the first 2 weeks of gestation, VSG animals gained weight and consumed similar calories to control dams. During gestational days 12-18 (G12-18), VSG body weight gain precipitously dropped off. Blood pressure measurements taken at G19 showed significant reductions in mean arterial pressure in comparison to lean and obese controls. Animals were euthanized on G19 for analysis of uterine contents; the number of fetuses was reduced in VSG (p < 0.05) with reduction in total fetal mass in comparison to controls. Placental-to-fetal weight ratios were increased suggestive of placental insufficiency. Genes involved in inflammation (interleukin 1 receptor antagonist, metalloproteinase 9) and hypoxia (heme oxygenase 1) were up-regulated by Affymetrix microarray analysis of harvested placental tissue. Taken together, these data indicate that gestational hypertensions is not a cause of the reduced fetal growth and that hormonal and chemokine alterations induced by the surgery may be driving reduced fetal growth. These data further support that the beneficial effects of VSG surgery in adult females may have negative consequences on gestation and beyond to their offspring.

19.2 NUTRIENT SENSING MECHANISMS IN HYPOTHALAMIC CELL MODELS: NEUROPEPTIDE REGULATION AND NEUROINFLAMMATION

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Over-nutrition, through elevated saturated fatty acids, such as palmitate, and the ensuing hypothalamic inflammation is a major perpetuating factor in the development of metabolic diseases, such as obesity and diabetes. Inflamed neurons of the CNS fail to properly regulate energy homeostasis leading to pathogenic changes in feeding and weight. Hypothalamic neurons are particularly sensitive to pro-inflammatory signals, and it is these neurons that become inflamed first upon high fat feeding. Efforts are underway to identify therapeutic targets for this inflammatory state. Omega-3 fatty acids and their receptor, GPR120, have emerged as putative targets. We have generated a wide array of novel, immortalized cell models derived from the rodent hypothalamus to study activation of fatty acid receptors at the level of the individual neuron. Signal transduction pathways, as well as gene expression of pro-inflammatory cytokines and neuropeptides, were studied upon exposure to palmitate or tumour necrosis factor α (TNFα) in the presence of the omega-3 fatty acid docosahexaenoic acid (DHA). DHA pretreatment prevents the inflammatory state through endogenous GPR120. GPR120 activates both AKT and ERK; however, the anti-inflammatory action of this omega-3 FA receptor is AKT and ERK-independent and likely involves the GPR120-TAB1 interaction. These studies provide mechanistic insights into how fatty acids act at the level of the individual hypothalamic neuron, and potential avenues to resolve hypothalamic neuroinflammation. Refs: Beldsmn et al. FASEB J, 2010; Weilhnser and Beldhs, J Neuroinflamn, 2014.

19.3 THE ROLE OF ESTROGENS AND ANDROGEN IN CONTROL OF GLUCOSE HOMEOSTASIS

Finnak Mauvais-Jarvis1

There are fundamental aspects of the control of glucose homeostasis that are regulated differently in males and females and may influence both the development of diabetes and the response to pharmacologic intervention. There are gender differences in diabetes pathophysiology and prevalence and there are more diabetic men before puberty, while there are more diabetic women after menopause. The prevalence of pre-diabetic symptoms such as impaired fasting glucose and impaired glucose tolerance also differs by sex. Some result from the action of estrogens and androgens on glucose homeostasis after puberty and in adults. In females, estrogen favors glucose homeostasis via estrogen receptors (ERs) by ameliorating insulin secretion and sensitivity. In males, testosterone is converted to estrogen and maintains fuel homeostasis via ERs and the androgen receptor, which share related functions to improve insulin secretion and sensitivity.

20.0 PREGNANCY AND PRE-ECLAMPSIA

20.1 MECHANISMS OF MATERNAL UTERINE VASCULAR REMODELING DURING GESTATION

George Osov1

The most accepted etiology of preeclampsia (PE) is that shallow trophoblast invasion of the maternal spiral arteries leads to placental underperfusion and triggers development of the maternal syndrome. This theory carries the hemodynamic prediction that, in normal pregnancy, reduced pre-placental flow resistance will also accelerate blood flow through proximal vessels and thereby increase shear stress and stimulate outward circumferential remodeling. We, and others, have shown that inhibition of endothelial nitric oxide synthase (eNOS) attenuates this process, implicating NO as the primary effector of arterial widening and supporting reduced NO signaling contributing to PE. Yet, uterine arteries and veins also lengthen considerably during pregnancy, and NOS inhibition has no effect on this axial elongation. Here, we hypothesized that axial growth may be triggered by myometrial distortion secondary to fetoplacental growth. Using a rat model, myometrial distortion was stimulated by instilling medical grade silicone into one uterine horn. The initial stretch was followed by continued myometrial expansion secondary to the accumulation of an exudate within the uterine lumen, and resulted in measurable arterial lengthening. Analysis of the exudate revealed significant increases in PDGF and VEGF, growth factors known to play a role in vascular remodeling. In summary: (1) Outward circumferential vascular remodeling is mediated primarily by endothelial NO, most likely secondary to increased shear stress due to placentation/spiral artery invasion. (2) Conversely, axial remodeling may be stimulated by placental and/or myometrial secretion of angiogenic factors such as VEGF into veins, followed by transfer into the periarterial space.

20.2 SPONTANEOUS SUPERIMPOSED PREECLAMPSIA IN DAHL SALT SENSITIVE RATS

Democracy II, Ste. 400, Bethesda, MD, 20892.
Preeclampsia is a leading cause of maternal morbidity and death worldwide, and our understanding of its pathogenesis and development of therapies for pre eclampsic women have been hindered by a lack of spontaneous animal models of the disease. Our laboratory has characterized the Dahl salt sensitive (S) rat, a genetic model of hypertension and kidney disease, as a spontaneous model of superimposed preeclampsia. Blood pressure and urinary protein excretion are elevated in the Dahl S prior to pregnancy, but both are exacerbated during pregnancy. In addition, Dahl S rats exhibit glomerulonephritis, increased placental hypoxia, decreased placental vascu larization, increased uterine artery resistance during late pregnancy, and increased soluble fms-like tyrosine kinase-1 (sFlt-1) and tumor necrosis factor-alpha (TNF-α). Furthermore, there is a greater incidence of fetal demise and intrauterine growth restriction in the Dahl S pregnancy when compared to pregnancy in the healthy Sprague Dawley strain. In summary, the Dahl S pregnancy phenotype is consistent with many of the characteristics observed in human superimposed preeclampsia; therefore this model could allow for the analysis of time-dependent changes throughout preeclamptic pregnancy, the discovery of new biomarkers for detection of preeclampsia, the identification of new therapeutic targets in populations with preexisting cardiovascular diseases, and determination of the long term cardiovascular outcomes for both mothers who have experienced preeclampsia and their offspring.

### 20.3 VASOPRESSIN: A NEW BEGINNING FOR THE END OF PREECLAMPSIA?

Mark Santilli

Dept. of OB/Gyn, Div. of Maternal Fetal Med., Univ. of Iowa, 200 Hawkins Dr., Iowa City, IA, 52242.

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 an early 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.

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

#### 21.1 SEX DIFFERENCES IN RISK FACTORS FOR STROKE IN WOMEN

Kathryn F. Rexrode


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. 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 changes, 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 are associated with risk and used exclusively 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

Marie Roussel-Wood


Hypertension is a key modifiable risk factor for cardiovascular 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 K12 HD045341 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

Shenggu Li, Marie Roussel-Wood, Paul Whelton, and Wei Chen


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 smoking (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 2R01AG106592; AHA 13SDGI4650068. REFERENCES: Yun 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, Zhung 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:e96908.
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<td>7.11, 17.7</td>
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<td>Zhou, X.</td>
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<td>Zimmerman, M.</td>
<td>7.2</td>
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<td>Zono, S.</td>
<td>6.9</td>
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**Note:** *Indicates Invited Speaker
Special Call for Papers
AJP-Regulatory, Integrative and Comparative Physiology

Sex and Gender Differences in Cardiovascular, Renal and Metabolic Diseases

The Editor-in-Chief of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology and the Physiology and Gender Conference organizers have provided an additional platform to illuminate the research from this vital conference. Original research articles related to the Physiology and Gender Differences in Cardiovascular, Renal and Metabolic Diseases are invited. These papers will be published starting in 2016 and all manuscripts accepted from this Call for Papers will be included in a unique online article collection to further highlight this important topic.

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