Sex and gender differences in cardiovascular, renal and metabolic diseases

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THE FIFTH AMERICAN PHYSIOLOGICAL SOCIETY CONFERENCE entitled, Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender Conference, is taking place in Annapolis, MD, on November 17-20, 2015. The timing of this conference is especially opportune since the number of papers published on sex and gender differences in physiology and pathophysiology is exploding, and the National Institutes of Health (NIH) is planning to release their guidelines for the incorporation of both sexes of animals in preclinical studies by year’s end. Francis Collins, Director of the National Institutes of Health (NIH), and Janine Clayton, Director of the Office of Research in Women’s Health (ORWH) at the NIH, published a paper in the journal Nature in 2014 (4), stating that the NIH would soon begin requiring the inclusion of both sexes of animals in basic science research when appropriate. As such, the National Heart, Lung, and Blood Institute and others have been in discussion with funded intramural and extramural researchers seeking advice on how to implement these changes. Therefore, this conference is especially timely and has significant potential to raise awareness and promote these areas of research.

There is mounting new evidence for the important roles that sex steroids, sex chromosomes, and gender play in mediating or predisposing individuals to cardiovascular, renal, and metabolic diseases. In just the past couple of years more than 15,000 published articles have focused on the importance of sex steroids and their receptors in nonreproductive physiological or pathophysiological conditions and sex and gender differences in physiology and pathophysiology. As more investigators are including animals of both sexes in their studies and as clinicians are performing studies that are statistically powered to find gender differences if they exist, the scientific community as a whole is discovering that there are significant differences between males and females that not only affect the normal physiology and the responses to pathological conditions, but also their response to therapeutics.

Recently, Aldhous and colleagues (1) reported that in Scottish individuals, women, whose mother, but not their father, had Type II diabetes (T2DM), had a significantly higher risk of also developing T2DM than in men whose mothers or fathers had T2DM (1). In addition, biomarkers of cardiovascular disease exhibit gender differences. For example, circulating troponin levels are used as a biomarker for myocardial infarction (MI); however, troponin levels are significantly lower in women than in men. This can lead to misdiagnosis of MI in women (7). Joyner and colleagues (11) have shown that in young men there is a direct correlation between muscle sympathetic nerve activity (MSNA) and total peripheral resistance (TPR), but not relation blood pressure, mainly because high MSNA and TPR are associated with lower cardiac output in young men. In contrast in young women, there is no relationship between MSNA and TPR because β-adrenergic vasodilator mechanisms offset the vasoconstrictor mechanisms. This changes as women age such that the relationship between MSNA and blood pressure eventually becomes linear.

In animal studies, activation of the melanocortin-4-receptor (MC4R) is a common pathway that has been found to mediate food intake and hypertension in animal models of obesity (8, 9). However, recent studies suggest that the neurons required for the expression of MC4R-mediated satiety are similar between male and female spontaneously hypertensive rats (SHR), but the neurons involved in the hypertensive actions are different (4). Similarly, both male and female pups from dams that model preeclampsia exhibit intrauterine growth restriction, but males go on to become hypertensive with puberty (10), whereas females do not become hypertensive until they stop estrous cycling, mimicking menopause in women. These studies suggest that cardiovascular diseases are programmed in utero and that their penetration may be different for male and females. Understanding how developmental programming causes cardiovascular, renal, and metabolic diseases is becoming more and more important due to the increasing obesity epidemic in the developed countries.

The roles that sex steroids play versus sex chromosomes in mediating physiology and pathophysiology of cardiovascular, renal, and metabolic systems is a wide open, exciting field of study. The development of the Four Core Genotype mice that have the gonads of one sex and the chromosomes of the other sex have allowed investigators to better address this question (2). For example, most physiological and pathophysiological changes occur as a result of the presence of sex steroids, their levels, and their receptors, rather than the presence of a specific sex chromosomal milieu. Liu and colleagues (12) used the Four Core Genotype mouse model and reported that angiotensin-converting enzyme 2 (ACE2) activity in the kidney is modulated by estradiol and the ovarian milieu, but not by testicular steroids or Y chromosome. In contrast, Chen and colleagues (5) exploited the Four Core Genotype models and showed that adiposity is due to the dosage of X chromosomes independent of the gonadal sex or the Y chromosome and that this is due to lack of X chromosome inactivation of several genes (5). Mice with 2 X chromosomes, regardless of their type of gonad, had greater adiposity and food intake during daylight hours. They also had greater weight gain on high-fat diet with higher lipid and insulin levels.

Sex steroids affect males and females differently. For example, obese men have reduced levels of testosterone, hence the television advertising boom asking the question, “Do you have low T?” Animal studies show that testosterone supplements in...
obese male Zucker rats cause a significant reduction in body weight, increase in activity levels, reduction in inflammatory mediators, and improvement in insulin resistance and glucose levels (6). Despite these improvements in metabolic syndrome and inflammation, testosterone caused an increase in blood pressure. In contrast, metabolic syndrome and elevated blood pressure accompany the elevated testosterone levels observed in women with polycystic ovary syndrome (3). Furthermore, in female animals, testosterone supplements cause an increase in food intake, insulin resistance, modest hyperglycemia, and elevated blood pressure (18). Whether estrogens affect males and females differently has not really been studied mainly due to the lack of a corresponding medical condition. However, with the increase in the number of transsexual individuals, this question may become more important for their health care. Thus studies are needed to determine why sex steroids have opposite effects on some systems and yet similar effects on other systems.

Immune system function also shows sex differences with different cohorts of T cells being more dominant in kidneys of females than males (14, 15), thus mediating differences in cardiovascular disease risk and mechanisms of injury. Females also are protected from ischemia-reperfusion, acute kidney injury compared to males, but this protection in females is independent of both nuclear and cell membrane estrogen receptors (10), suggesting either nonreceptor-mediated activity of estrogens or X-chromosomal effects contribute to protection of women from acute kidney injury.

Finally, studies on the gender differences in the responses to medications, especially those used to treat cardiovascular and renal diseases, has been slow to advance. This topic is well covered in a recent review by Stolarz and Rusch (15), in which the authors point out that in women there is a 1.5- to 1.7-fold higher risk of adverse drug events in women than men, and that there are gender differences in the absorption, distribution, metabolism, and excretion of drugs used to treat cardiovascular abnormalities.

Therefore, more research is needed to describe, understand, and determine the mechanisms responsible for the sex and gender differences in cardiovascular, renal, and metabolic diseases to improve health outcomes in both men and women in our society. This is also a field that is ripe for animal studies to lay the foundation for future translational research that will become even more important as additional sex and gender differences are found or novel physiological and pathophysiological roles for sex steroids and chromosones are uncovered.

Thus the scientific program for the Annapolis conference will capitalize on the newest scientific research on the influence of sex and gender in cardiovascular, renal, and metabolic diseases with major topic areas including the roles of the immune system and regenerative processes play in cardiovascular diseases; nonreproductive actions of sex hormones and their receptors in cardiovascular, renal, and metabolic diseases; neurocontrol of cardiovascular, renal, and metabolic diseases; developmental (perinatal) programming of later-in-life cardiovascular, renal, and metabolic diseases; obesity and metabolic syndrome and the effects on cardiovascular and renal diseases; and population studies in cardiovascular, renal, and metabolic diseases and the contribution of gender.

Speakers invited to present at the Gender in Physiology conference in Annapolis are the leaders in the fields of sex and gender differences in cardiovascular, metabolic, renal, and immune system function; changes with aging; sex steroid use; and developmental programming of disease. Dr. Janine Clayton will lead a discussion on the new NIH guidelines that are to be put into place for the January 25, 2016 applications in which sex as a biological variable will be factored into research designs, analyses, and reporting in both vertebrate animal and human studies.

To increase the exposure of the findings presented at the conference, the American Journal of Physiology, Regulatory, Integrative and Comparative Physiology (AJP-RIC), will publish minireviews by invited speakers and selected minireviews or original articles from conference participants. In addition, AJP-RIC is announcing a Call For Papers, from which accepted papers will be included in an electronic Table of Contents (eTOCs) along with the manuscripts from the conference and appear as they are published. Submission of manuscripts detailing research related to sex and gender differences in physiology and pathophysiology of biological systems is encouraged and will be entered into the traditional journal peer-review system for potential publication as well.

REFERENCES


