CALL FOR PAPERS | Sex Differences in Renal and Cardiovascular Function: Physiology and Pathophysiology

Physiological and molecular mechanisms governing sexual dimorphism of kidney, cardiac, and vascular function

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IT IS WELL ESTABLISHED THAT cardiovascular disease is a leading cause of death in developed countries, but it is less well known that more women than men die of cardiovascular disease, although these deaths are delayed by ~10 yr (7, 17). It is becoming evident that there is considerable sexual dimorphism in the pathogenesis of cardiovascular disease. Thus findings from past studies, mostly in males, do not automatically apply to females. Reflecting a recognition of this sexual dimorphism, this call for papers on Sex Differences in Renal and Cardiovascular Function: Physiology and Pathophysiology produced an excellent response, with 21 original manuscripts appearing in this issue of the American Journal of Physiology– Regulatory, Integrative and Comparative Physiology, as well as several more to appear in later issues. These works encompass the field of physiological and molecular mechanisms governing sexual dimorphism of kidney, cardiac, and vascular function and include basic and translational studies.

Coronary artery disease is the number 1 cause of death in industrialized countries, and recent evidence shows that women experience higher mortality and poorer outcomes after myocardial infarction than men (10, 17). It is only in the last decade that specific guidelines for cardiovascular disease prevention in women have been formulated (19). One fundamental question is whether there are intrinsic sex differences in myocardial function. Battiprolu et al. (2) in this issue showed that even before sexual maturity, cardiac tissue from female rainbow trout tends to use glycolysis for ATP production, whereas males have a higher capacity for aerobic and lipid metabolism. Petre et al. (24) concluded that the basic mechanical performance of healthy isolated feline myocardium was not different between males and females under physiological conditions; however, under conditions of physiological stress, sex differences in myocardial function emerge that may reflect sex differences in intracellular calcium regulation in cardiac myocytes. Chronic alcohol consumption leads to cardiomyopathy, and Vary et al. (31) demonstrated sexual dimorphism in the cardiac response to heavy alcohol consumption with inhibition of protein synthesis in male (but not female) rats. This was associated with limitation of mRNA translation due to a reduction in activation (phosphorylation) of a specific eukaryotic initiation factor (eIF4G). Hunter et al. (8) investigated the susceptibility of the aging female rat heart to ischemia-reperfusion-induced injury and concluded that aging alone, independent of plasma estrogen levels, leads to reduced ischemic tolerance, although this is exacerbated by estrogen deficiency. Bupha-Intr et al. (3a) indicate that estrogen deficiency enhances calcium sensitivity of myofilaments in cardiac myocytes by a pH-dependent effect mediated by the sodium/hydrogen exchanger. Thawornkaiwong et al. (30) address the loss of cardioprotective actions of estrogen seen in diabetes and conclude that in rat heart, both estrogen and insulin are required for optimal cardioprotection, with estrogen acting to reduce cardiac β-receptor expression.

In nondiabetic chronic kidney disease (CKD), the female shows a slower rate of progression than the male (20), but this is lost in diabetic nephropathy, and Mankhey et al. (16) suggest that this is due to inadequate estrogen since supplementation attenuates glomerular and tubulointerstitial fibrosis by both reducing extracellular matrix synthesis and stimulating degradation. Rogers et al. (26) have shown that estrogen regulates (reduces) the angiotensin AT₁-receptor level in renal cortex, as well as upregulating the estrogen receptor-α, both likely to be renal protective actions during CKD. Sullivan et al. (28) examined reactive oxygen species production in the renal inner medulla in the spontaneously hypertensive rat (SHR) as a potential explanation of the blunted pressure-natriuresis relationship observed in male compared with female SHR. However, whereas urinary excretion of hydrogen peroxide was increased in male SHR compared with female rats, medullary hydrogen peroxide production was not. In fact, evidence suggested medullary antioxidant capability was increased. Possibly this represents a compensatory response by the renal medulla to offset increased superoxide production elsewhere. Yameleyeva et al. (32) report that in the female mRen2 rat, ovarioectomy greatly exacerbates the hypertension with an associated decline in renal endothelial nitric oxide synthase (NOS) and increased renal neuronal NOS (nNOS) abundance. Interestingly, this increased nNOS may be pathogenic since “selective” nNOS inhibition with L-ornithine prevented the ovarioectomy-induced rise in arterial pressure. Perucca et al. (23) conducted a retrospective analysis of a number of clinical studies and make the novel observation that urine osmolarity is greater in men than women in health and during development of CKD. This will likely explain the...
greater susceptibility of men to development of urolithiasis, and, if related to greater activity of antidiuretic hormone, could also contribute to the increased rate of progression of CKD.

Sex-specific differences in vascular function have been extensively studied, with vascular contraction being greater in intact males compared with intact females. These differences have in large part been attributed to the impact of the sex hormones (estrogen, progesterone, and testosterone), which have been shown to influence vascular function significantly (11). Work now concentrates on understanding the cellular and molecular pathways involved. Paul et al. (22) report that the sex difference in aortic contractility may be related to actions of estrogen on both vascular endothelial and smooth muscle cells. They report an estrogen-induced shift in the COOH-terminal myosin heavy chain isoforms SM1-to-SM2 ratio, and while estrogen reduces the contractile response to KCl-depolarization, it evokes an unexpected increase in sensitivity to norepinephrine-induced contraction. Loss of female hormones have been strongly linked to vascular injury and the development of atherosclerosis (18) although this is controversial given clinical data suggesting negative cardiovascular actions with estrogen replacement (5). Benton et al. (3) investigated the interaction of diabetes and loss of ovarian hormones on atheroma formation in a mouse model of type 1 diabetes. Ultrastructural studies suggested that estrogen deficiency increases vascular permeability by promoting endothelial disruption, thus contributing to atheroma formation (3). These studies suggest that estrogen may play an important role in maintaining cell adhesion molecules. Following vascular injury, the estrogen receptor-β (ER-β), is upregulated (3). Rayner et al. (25) are searching for regulatory proteins that associate with ER-β to determine its biological action. Here they report the finding of a novel protein, NM23-H2, that interacts with ER-β and suggest it plays an important role in the regulation of estrogenic effects in the vascular wall. Furthermore, the results contain hints that there may be sex differences in the protein’s expression that warrant further investigation. Whereas much emphasis is placed on the protective actions of female hormones on the cardiovascular system, there is also some evidence that the androgens can be damaging. Iliescu et al. (9) report that androgens exacerbate hypertension in the SHR via an NADPH-oxidase-dependent mechanism involving increased p47phox and gp91phox subunits (9). There are some conditions in which female sex is a cardiovascular risk factor, notably the development of cardiovascular disease in systemic lupus erythematosus (SLE). Using a mouse model of SLE, Ryan and McLemore (27) reported development of an early endothelial dysfunction in females preceding the development of hypertension. This promises to be a useful model for investigation of the causes of cardiovascular injury during SLE, as well as interactions with sex hormones.

Much less emphasis has been directed at understanding the regulation of the venous side of the circulatory system. Venous reserve plays an important role in maintaining venous return and therefore arterial pressure. Orthostatic tolerance is maintained by alteration in venous compliance of the lower limbs. Women are much less tolerant of orthostatic stress, and the study of Lindenberger and Lanne (14) demonstrates that while the venous compliance response to lower-body negative pressure was not different in men and women, when differences in calf capillary fluid filtration were subtracted from the equation, significance differences were noted. The impact of estrogen on the venous microcirculation was discussed as a possible explanation of the differences in capillary fluid filtration.

There is now compelling evidence that events occurring during fetal life can have life-long consequences for the health of the adult. This concept was first described by Barker et al. (1) who observed an inverse relationship between birth weight and cardiovascular disease in a cohort of middle-aged men. Of concern is the accumulating evidence now suggesting that altered fetal development can occur independently of low birth weight (4), suggesting that the health implications are much greater than predicted by the proportion of babies suffering growth restriction. In this issue, the study of Maduwege dera et al. (15) suggests that the renal sympathetic innervation density was increased in offspring prior to the development of hypertension in the absence of decreased birth weight. This is of particular interest given the strong evidence in humans that the renal sympathetic nerves play a role in the initiation and maintenance of essential hypertension (6). Furthermore, the study of Ojeda et al. (21) highlights evidence that there are sex-specific differences in the fetal programming of hypertension in that in many models, male and female offspring are not equally affected. In their model, young male and female offspring have increased blood pressure, but only males remain hypertensive as adults. This persistent hypertension in the males was apparently related to androgen-induced activation of the renin-angiotensin system (21). An interesting corollary to this study would be to determine whether the increased blood pressure in young female rat pups that does not progress into adulthood might become overt in aged females as estrogen levels decline.

The nervous system exerts important control over cardiovascular functions, and the clinical studies of Lavi et al. (13) suggest that aging, rather than decreased estrogen levels, contribute to increased cardiovascular risk in postmenopausal women, due in part to a shift from parasympathetic to predominantly sympathetic control of the circulation. These changes are similar to those seen in aging men, suggesting independence from sex hormones. Men generally exhibit greater autonomic responses to stress compared with women, and Kimmerly et al. (12) have investigated central nervous system control of baroreceptor unloading (using the physiological challenge of lower negative body pressure), which is greater in men than in women. Forebrain activity was assessed using functional magnetic resonance imaging with blood oxygen level-dependent contrast (BOLD) in conjunction with muscle sympathetic nerve activity (MSNA) recordings to investigate this sex-dependent difference in autonomic control. Their findings demonstrated differential regional alterations in BOLD signals in the forebrain in response to lower-body negative pressure in association with changes in heart rate and MSNA and the responses were greater in men than women (12). Although these results do not represent direct evidence that differences in forebrain activation are responsible, the enhanced sympathetic outflow in men, in response to lower-body negative pressure and baroreceptor unloading, certainly add weight to the postulate that central processing is controlled differently in men and women.
The Future

We live in an aging society, with life expectancy far greater today than a century ago. The challenge for modern medicine is how to increase the number of disease-free years as people age and improve quality of life in later years. The process of aging is associated with the deterioration of the body, including the cardiovascular system. It has become apparent that to improve diagnosis and treatment for both men and women the differences in circulatory control must be addressed. Despite the cost in terms of housing and time, longer-term studies in older cohorts of animals are required to examine the impact of age and sex on cardiovascular health. The impact of the menstrual cycle on physiological function and drug therapy should also be taken into consideration.

REFERENCES


