Sex Differences in Cardiovascular Disease and Hypertension: Involvement of the Renin-Angiotensin System

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The incidence and the progression rate of cardiovascular disease and hypertension (CVDH) is markedly higher in men than in age-matched, premenopausal women. After menopause, this relationship no longer exists, and the incidence as well as the rate of progression of CVDH are very similar in women and men. Sex differences in CVDH have also been reported in animal models, including the spontaneously hypertensive rat and Dahl salt-sensitive rats, and ischemia-reperfusion injury. Although the mechanisms underlying these sex differences in the incidence and progression of CVDH are largely unknown, the role of sex hormones in modulating the activity of several regulatory systems, including the renin-angiotensin system (RAS), has been suggested. In addition, genetic differences, especially with respect to the RAS, have also been implicated in mediating sex differences in the incidence and progression of CVDH.

In the current issue of Hypertension, Okumura et al describe the relationship between the differential expression of angiotensin II type 2 (AT2) receptors in mediating vascular remodeling induced by polyethylene cuff placement around the femoral artery in the wild-type (Agrt2+/-) and AT2 receptor null (Agrt2−/−) mice. The major findings of this study are: (1) AT2 receptor expression is enhanced in the injured artery of the Agrt2−/+ and this is more pronounced in the females; (2) In the Agrt2+/- mice, no significant differences in the expression of the AT1 receptor are observed in either males or females; (3) The degree of vascular injury, as evidenced by increases in neointimal formation, DNA synthesis, expression of monocyte chemoattractant protein-1, production of superoxide anion, and NADPH oxidase activity in the injured artery, is greater in males than females and is more pronounced in the Agrt2−/− than the Agrt2+/- mice; (4) Administration of the AT1 receptor antagonist valsartan (1 mg/kg per day) decreases vascular injury more so in female than male Agrt2+/- mice; (5) Sex differences in the protective effects of valsartan are less pronounced in the Agrt2−/− mice. This study provides evidence that sex differences in the degree of vascular injury, being more pronounced in males than females, may be partially explained by the enhanced expression of AT2 receptors in the female femoral arteries. This study also provides evidence that AT2 receptors mediate a protective effect of angiotensin II in vascular injury.

The fact that females are more protected from developing CVDH compared with males has gathered much interest in examining the contribution of sex hormones to the progression of these disease processes. Studies examining the effects of sex hormones in CVDH have provided novel insights into the mechanisms of their action but also raised controversies as to whether female sex hormones are protective and whether male sex hormones may, in some cases, exert adverse effects in their target organs. The role of estrogens in particular has been controversial. Although the initial reports from the Women’s Health Initiative (WHI) study showed some adverse effects of the combined conjugated equine estrogen plus progestin therapy on stroke and coronary artery disease, other clinical studies have shown that women with hysterectomy have a higher prevalence and incidence of CVDH, suggesting that the lack of ovarian hormones is associated with a greater rate of CVDH. Accumulating experimental data in the Dahl salt-sensitive rat and in the renal wrap hypertensive model also support the hypothesis that estrogens may indeed be beneficial in attenuating CVDH. The discrepancies between the findings of the WHI indicating adverse effects of estrogens and experimental data suggesting beneficial effects of estrogens stress the importance of further examining the contribution of estrogens in CVDH.

On the other end of the spectrum are the male sex hormones. The fact that the male gender is a risk factor for the incidence and progression of CVDH suggests that male sex hormones may contribute to the development and progression of these disease processes. For example, castration in the spontaneously hypertensive rat reduces hypertension. However, it is possible that it is the balance between estrogens and androgens that govern risk factors in CVDH. Collectively, there is compelling evidence that sex hormones, most likely via interaction with other regulatory systems including the RAS, play an important role in the pathophysiology of CVDH.

The study of Okumura et al adds important information to our pool of evidence that the severity of vascular injury is greater in males than females. The authors suggest that the underlying cause for this sex difference may be the lower expression of AT1 receptors in the injured arteries of male rats. This suggests that the AT1 receptors exert a protective effect in vascular injury, especially in females. The concept that AT1 receptors exert protective effects in CVDH has also been suggested by others. These studies suggest that the antiproliferative, antifibrotic, and blood pressure-lowering

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properties of AT\(_2\) receptors contribute to its beneficial effects in CVDH. The involvement of AT\(_2\) receptors in mediating sex differences in CVDH have also been suggested. Polymorphisms in the AT\(_2\) receptor have been linked to premature coronary artery disease in males.\(^{11}\) Differential expression and activity of other components of the RAS have also been implicated in mediating sex differences in CVDH. Ovariectomy increases the expression of AT\(_1\) receptors in mesenteric vessels of spontaneously hypertensive rats\(^{32}\) and in the adrenal gland of Sprague-Dawley rats,\(^{13}\) whereas it decreases AT\(_2\) receptors in the kidney of Wistar-Hanover rats.\(^{14}\) These studies also show that estradiol supplementation decreases AT\(_1\) and increases AT\(_2\) receptor expression. Much less is known about the effects of testosterone in regulating AT\(_1\) and AT\(_2\) receptors. In the rat epididymus, castration decreases the expression of AT\(_1\) receptors,\(^{15}\) whereas in renal proximal tubules extracted from dihydrotestosterone-treated rats, no differences in AT\(_1\) receptors are observed.\(^{16}\) These studies clearly demonstrate an interaction between sex hormones and the RAS; however, further studies are needed to determine the precise physiological significance of these interactions, especially in humans.

Jugdutt et al suggested that the attenuation of myocardial injury associated with AT\(_1\) receptor blockade is associated with upregulation of AT\(_2\) receptors.\(^{17}\) The study by Okumura et al\(^{5}\) similarly suggests that the beneficial effects of AT\(_1\) receptor blockade are not just mediated through abolishing the effects of AT\(_1\) receptors but, in fact, by angiotensin II–induced upregulation of AT\(_2\) receptors, especially in females. These findings may suggest that the benefits of AT\(_1\) receptor blockers (angiotensin receptor blocker [ARB]) and angiotensin-converting enzyme (ACE) inhibitors may be gender specific. The reports on sex differences in the efficacy of ACE inhibitors have been conflicting. Although some studies report similar effects in women and men,\(^{18}\) one study reported a marginally more beneficial effects of ACE inhibitors in women.\(^{19}\) Interestingly, side effects associated with ACE inhibition such as coughing occur more frequently in women than men.\(^{20}\) The efficacy of ARB seems to be equal in men and women;\(^{21}\) however, gender-specific analysis of side effects have thus far not been performed. Furthermore, the efficacy of ARB in postmenopausal women, in whom the estrogen modulation of the RAS is lost, has not been performed. Given the evidence that estrogen regulates the RAS, it could be predicted that ARB would be particularly beneficial in postmenopausal women. Future studies need to be conducted to examine this hypothesis.

The significance of the study by Okumura et al\(^{5}\) is 2-fold. First, it demonstrates the importance of the RAS, in particular, AT\(_2\) receptors in mediating sex differences in vascular injury. Second, and, in my personal opinion more important, it stresses the importance of examining the mechanisms underlying sex differences in CVDH. Future studies in this direction will not only contribute to our understanding of why females have a lower incidence of CVDH compared with males but may also lead to the development of gender-specific therapeutics that may offer protection against disease processes that show clear sex difference in their etiology and progression.

References

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