Why Can’t a Woman Be More Like a Man?
Is the Angiotensin Type 2 Receptor to Blame or to Thank?

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In *Pygmalion*, Henry Higgins asked, “Why can’t a woman be more like a man?” But when it comes to hypertension, Henry actually should have asked, “Why can’t a man be more like a woman?” Women have lower blood pressure (BP) and a lower incidence of hypertension than aged-matched men through much of their lives. We need to understand why, because a better understanding of what protects the female from this potentially devastating disease ultimately could lead to new therapeutic treatments for both men and women. According to the American Heart Association, hypertension is a disease that afflicts >73 million people and kills >50,000 people per year in the United States alone. Uncontrolled hypertension leads to heart failure, myocardial infarction, stroke, and renal failure. Surprisingly, we still do not know the cause of essential hypertension, although it accounts for >90% of all cases of hypertension.

In this issue of *Hypertension*, using a model of angiotensin II (Ang II)--induced hypertension, Sampson et al suggest that the angiotensin type 2 receptor (AT2R) provides a major clue for solving the mystery of sex differences in hypertension. Ang II infusion is a widely used experimental model of hypertension, because inhibitors of Ang II synthesis and action have been very effective clinically to treat hypertension. Although most hypertensive patients respond to Ang II synthesis inhibitors and angiotensin type 1 receptor (AT1R) blockers, indicating that essential hypertension is primarily Ang II dependent. Thus, the mechanisms uncovered in this experimental model are likely to be clinically relevant. At high doses, Ang II (400 to 800 ng/kg per minute) can elicit a “rapid direct pressor” response in a matter of hours. At low doses, Ang II (100 to 200 ng/kg per minute) increases mean arterial pressure (MAP) gradually over a period of days resulting in a “slow pressor” response without a direct pressor effect.

The majority of hypertension research to date has been conducted in male animals, as is typically found in biomedical research. Thus, we do not know to what extent the mechanisms uncovered in the male also apply to the female. What we do know is that there are significant differences in BP control between males and females. Women have lower BP and a lower incidence of hypertension than men up through their mid-50s. With increasing age, the incidence in women approaches and eventually surpasses that in men for reasons that have been ascribed to menopause and to the loss of hypertensive men in the aging population because of sex differences in cardiovascular mortality.

Although experimental studies of hypertension rarely include both sexes, the few reports that do suggest that sex differences in hypertension are a robust phenomenon that is observed in many experimental models of hypertension, including genetic models such as the spontaneously hypertensive rat and the Dahl and Sabra salt-sensitive rats, transgenic models, such as the mRen(2).Lewis rat, and induced models, including aldosterone infusion, deoxycorticosterone acetate-salt, and co-treatment with fructose and insulin. Sex differences are also observed in the Ang II infusion model of hypertension. The female C57Bl6 mouse has lower MAP than the male after infusion of Ang II at a high dose (800 ng/kg per minute). Furthermore, Ang II infusion at 700 ng/kg daily by SC injection for 10 days increases BP in the male Sprague-Dawley rat without having any BP effect in the female. Sampson et al support these previous findings by showing that a 2-week infusion of Ang II at 400 ng/kg per minute increased MAP by nearly 2-fold in the male Sprague-Dawley rat (Δ, 42 mm Hg) compared with the female (Δ, 24 mm Hg). No differences were found in basal BP, as was seen previously in both mice and rats, suggesting that sex differences in BP are detectable only under pathological conditions.

Sampson et al measured MAP after a very low Ang II dose (50 ng/kg per minute) and found a fascinating result. Although this low dose had no effect on MAP in the male, it significantly decreased MAP in the female, and this effect was prevented by co-infusing the animals with PD123319, an antagonist of the AT2R. These authors also found markedly higher AT2R mRNA expression in the female rat kidney (300-fold) and left ventricle of the heart (6-fold) compared with the male. This sex difference in AT2R expression resulted in significantly higher mRNA ratios of the AT2R to the angiotensin type 1 receptor subtypes AT1aR and AT1bR in the female heart and kidney compared with the male. This study suggests that the Ang II--induced vasodilatory effect observed in females is attributable to the AT2R, and, conversely, that the lack of effect in males may be a result of their lower levels of AT2R expression in these key target tissues. Thus, the vasodilator/vasoconstrictor balance is greater in the female compared with the male, partly because of the difference in the ratio between the AT2R and AT1R (Figure, panel A). This study extends the findings of a previous report, which suggested that sex differences exist in the vasodilator/
vasoconstrictor balance in the renin-angiotensin system because of differences in the ratio of the heptapeptide Ang-(1-7) to Ang II.5

Previous studies in male AT2R knockout mice suggest that this receptor contributes to BP control.6 Compared with their wild-type littermates, male AT2R knockout mice exhibit slightly higher systolic BP and induce a more rapid and pronounced increase in BP in secondary models of hypertension, such as volume-expansion–induced hypertension produced by deoxycorticosterone acetate-salt. Controversy exists, however, over the role of the AT2R in modulating the effectiveness of AT1R blockade at lowering BP in male rat models of renin-dependent (eg, 2-kidney, 1-clip) and -independent (eg, the spontaneously hypertensive rat) hypertension, because Ang II hypersensitivity in the absence of the AT2R may simply reflect AT1R upregulation. It is indeed a pity that female AT2R knockouts were not investigated in these studies, because one might predict that they would exhibit an even greater difference in BP and a greater degree of Ang II hypersensitivity compared with their wild-type littermates, because females have higher AT2R expression in 2 critical organs involved in BP control. Studies of peripheral overexpression of the AT2R also support a role for this receptor in BP regulation. Although a single intracardial injection of an adenovirus containing the AT2R into male Sprague-Dawley rats did not affect the MAP, the effectiveness of an AT1R antagonist was greater in the AT2R-overexpressing animals compared with those expressing a control vector.7 It is again unfortunate that females were not studied in this model, because the potentiating effect of the AT2R during AT1R antagonism may have been even greater in the female than in the male given the higher expression of the AT2R in the female.

Interpretation of the AT2R knockout studies must include the caveat that compensatory changes occurring during development could impact BP regulation, whereas interpretation of the AT2R overexpression studies must contend with potential confounding effects, such as increased promiscuity of the receptor for non-AT2R signaling cascades. In the Sampson et al study, expression of the AT2R in the rat heart and kidney is not modulated experimentally; it is naturally higher in the female than in the male. This study suggests that the greater magnitude of Ang II–induced hypertension in the male is because of less attenuation of AT1R-mediated vasoconstrictor signal transduction by AT2R-mediated vasoactive signaling pathways, such as through bradykinin, NO, and cGMP (Figure, panel B).8

This study is particularly exciting, because not only do the data provide direct evidence of a vasodilatory role for the AT2R in BP control in the female, it also provides a potential

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**Figure.** Schematics of AT1R and AT2R action. A, Sex differences in the AT1R:AT2R ratio and the vasodilator/vasoconstrictor balance. B, AT1R and AT2R signaling cascades. PLC indicates phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; CaM, calmodulin; BK, bradykinin; eNOS, endothelial NO synthase; and, sGC, soluble guanylate cyclase.
mechanism for why female rats have lower BP than males in a model of Ang II–dependent hypertension. These findings could, therefore, partly explain why a woman cannot be more like a man when it comes to BP control. These studies also support the idea that increasing AT2R activity could be a valuable therapeutic approach for treating hypertension. It will be of interest to determine whether sex differences in MAP also exist when circulating Ang II is increased under physiological conditions, such as during a low-sodium or -potassium diet or under pathophysiological conditions that elevate circulating Ang II, such as in response to hemorrhage. In this latter case, men may have the advantage over women because of less AT2R-mediated vasodilation.

The higher levels of AT2R expression in the female heart and kidney compared with the male may be because of gonadal hormone regulation of the AT2R. Armando et al9 showed that intact female mice have higher AT2R expression in the kidney compared with ovariectomized females. There is less known about androgenic regulation of the AT2R, although studies in the rat urinary bladder suggest that testosterone downregulates the receptor.

An especially intriguing aspect of the AT2R is its location on the X chromosome. Thus, XY men obtain their AT2R from their maternal X chromosome, whereas AT2R expression in XX women is a 50:50 mixture of their father’s and mother’s X chromosomes. Female mosaicism of the X chromosome has major implications for human health and disease and is the leading cause of female protection from X-linked genetic disorders. Interestingly, Zivkovic et al10 reported recently a functional polymorphism (−1332A/G) in the AT2R in which the G allele impairs AT2R protein expression and is associated with essential hypertension in male patients of Caucasian origin. Is this association between a gene haplotype/genotype and hypertension also observed in women or is it a sex-specific effect found only in men? We need to find out!

X chromosome mosaicism is not the only genetic difference between males and females. Although the second X chromosome is inactivated in XX cells, the inactivation is incomplete, and ∼17% of genes on the X chromosome escape X inactivation.11 Thus, not only will it be important to assess the role of gonadal steroid regulation of AT2R action and the impact of AT2R mosaicism in BP control, we also need to determine whether the higher AT2R expression in the female is a result of escape from X inactivation.

Lastly, this article clearly illustrates the importance of comparing experimental data in both sexes. If the authors had only studied the male rat, they might have incorrectly concluded that, under their experimental conditions, the AT2R does not modulate BP in both sexes. The majority of articles published in hypertension research do not conclude by saying that factor Z contributes (or not) to hypertension in the male animal. Instead, the implicit assumption made is that factor Z contributes (or not) to hypertension in both sexes, although factor Z has only been studied in the male. Eliza Doolittle told ‘enry ‘iggins, “Just you wait!” We too should just wait until potential mechanisms of BP control are investigated in the female before inappropriately extrapolating from studies performed only in the male.

Sources of Funding
This work was supported by National Institutes of Health grants HL-57502 and AG-19291 to K.S.

Disclosures
None.

References
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Hypertension. 2008;52:615-617; originally published online August 18, 2008; doi: 10.1161/HYPERTENSIONAHA.108.115063

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