Sex and the renin-angiotensin system: inequality between the sexes in response to RAS stimulation and inhibition

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Sullivan JC. Sex and the renin-angiotensin system: inequality between the sexes in response to RAS stimulation and inhibition. Am J Physiol Regul Integr Comp Physiol 294: R1220–R1226, 2008. First published February 20, 2008; doi:10.1152/ajpregu.00864.2007.—The purpose of this review is to examine sex differences in response to stimulation and inhibition of the renin-angiotensin system (RAS). The RAS plays a prominent role in the development of chronic renal disease, and there are known sex differences not only in the expression level of components of the RAS but also in how males and females respond to perturbations of the RAS. In men, renal injury increases in parallel with increased activation of the RAS, while in women, increases in ANG II do not necessarily translate into increases in renal injury. Moreover, both epidemiological and experimental studies have noted sex differences in the therapeutic benefits following angiotensin-converting enzyme inhibitor and angiotensin receptor blocker treatment. Despite these differences, RAS inhibitors are the most commonly prescribed drugs for the treatment of chronic renal disease, irrespective of sex. This review will examine how males and females respond to stimulation and inhibition of the RAS, with a focus on renal disease.

...transforming growth factor-β; nuclear factor-κB; janus kinase/signal transducers and activators of transcription; angiotensin-converting enzyme inhibitors; angiotensin receptor blocker

THE RAS IS A KEY SYSTEM IN controlling blood pressure and body fluid volume, and overactivation of the RAS has been shown to play a critical role in the development and progression of renal injury. The RAS is known to be influenced by the sex chromosomal complement of the animal and gonadal hormone milieu, with plasma renin activity (PRA), angiotensin-converting enzyme (ACE) activity and expression, and AT1 receptor expression levels being greater in kidneys from males compared with females. Sex differences in these aspects of the RAS have been very nicely reviewed elsewhere (25, 42, 62).

Despite these well-acknowledged differences between the sexes in the RAS, inhibitors of the RAS, including ACE inhibitors and angiotensin receptor blockers (ARBs), are the most commonly prescribed pharmaceutical treatments for renal disease. Although both ACE inhibitors and ARBs have been shown to block the development of renal injury in male experimental animals (33, 37, 52, 70), less is known regarding the effects of RAS inhibition on renal injury in females. This review will begin with a discussion of what is currently known regarding sex differences in response to RAS stimulation and inhibition followed by highlighting the potential pathways and molecular mechanisms, which may contribute to sex differences in response to perturbations of the RAS.

Males and Females Respond Differently to RAS Stimulation

Exogenous ANG II and activation of the endogenous RAS. There is a limited amount of data available regarding the effects of exogenous ANG II on blood pressure and renal function. In response to graded infusions of ANG II, healthy normotensive men and women have been reported to have similar increases in blood pressure (27, 44) although Gandhi et al. (27) found that the duration of the pressor response was significantly longer in men than in women. The authors noted that differences in the systemic clearance of ANG II were unlikely to contribute to this observation, however, as plasma ANG II levels were identical in men and women during steady-state infusion of ANG I. With respect to the kidney, systemic infusion of angiotensin peptides (at 3, 10, and 20 ng·kg⁻¹·min⁻¹ for 10–20 min) produced a greater decrease in renal perfusion among women compared with men (27). Miller et al. (44) have reported that in response to systemic ANG II infusion (0.5, 1.5, 2.5 ng·kg⁻¹·min⁻¹ for 30 min), men maintained glomerular filtration rate (GFR), while women experienced a fall in GFR. Furthermore, this effect was more pronounced among the women with higher plasma 17β-estradiol levels, suggesting a role for estradiol in modulating renal functional responses to ANG II. It could be hypothesized that among women, ANG II induces a greater degree of preglomerular constriction with no effect on glomerular filtration or tubular function, thereby protecting the glomerulus from higher systemic pressures. In response to chronic ANG II treatment, male experimental animals have a more robust increase in blood pressure compared with females. This has been demonstrated in C57BL/6J mice (1.2 mg·kg⁻¹·day⁻¹ for 7 days) and Sprague-Dawley rats (0.7 mg·kg⁻¹·day⁻¹ ANG II for 10 days) (68, 80, 82). With regard to the sex of the animal, renal function was not examined in either of these studies; however, in many cases, increased blood pressure correlates with greater injury. Greater blood pressure responses to exogenous ANG II in males may be related to the presence...
of testosterone, as castration has been shown to decrease the pressor response to acute ANG II infusion in male New Zealand genetically hypertensive rats (4.2 ml/h) (65).

Sex differences in how males and females respond to exogenous ANG II are likely related to the observation that among women, there appears to be discordance between activation of the RAS and blood pressure. While in men, the degree of hypertension and renal injury closely parallels increases in RAS activation, the same relationship is not seen in women. In response to lower body negative pressure experiments, which are known to activate the RAS, circulating renin, PRA, and ANG II levels have been shown to peak during the luteal phase of the menstrual cycle when plasma 17β-estradiol levels are highest (13). Despite increased RAS activation during the luteal phase, mean arterial blood pressure fell in response to incremental increases in lower body negative pressure, and vasoconstrictor responses to RAS activation were blunted (13). Furthermore, in healthy postmenopausal women, plasma angiotensinogen and ANG II levels increase with 1 mo open-label oral estradiol treatment (2 mg/day) despite a fall in blood pressure (30). Therefore, the systemic effects of acute ANG II were comparable in men and women; however, there were sex differences in renal functional responses to acute ANG II and in blood pressure responses to chronic ANG II treatment. This may be related to the fact that the highest sensitivity to the vascular effects of ANG II are found in the kidney (5). To date, there have not been any studies to examine the effects of chronic ANG II on renal functional responses in females; however, it would seem reasonable to hypothesize that, similar to the effects seen on blood pressure, females would not develop the same degree of renal injury as seen in males.

Potential mechanisms accounting for sex differences in response to RAS stimulation. Although sex chromosomal complement is known to influence the RAS, the molecular basis for physiological/pathophysiological differences in response to RAS activation in males and females is unknown. There are, however, several potential explanations that deserve comment.

**Differential ANG II metabolism: ANG II vs. ANG (1–7).** Interestingly, our laboratory and others have noted that when ANG II levels have been assessed in males and females, be it in the plasma (27, 44, 67, 82) or in the kidney (67, 82), levels have been reported to be either comparable or greater in females, yet tissue responsiveness to exogenous ANG II is less pronounced in females (55). It could be hypothesized that this is related to differential metabolism of ANG II in males and females. Classically, the RAS was viewed as a linear system with renin catalyzing the formation of ANG I (ANG 1–10) from angiotensinogen and ACE-converting ANG I to ANG II (ANG 1–8). However, in recent years, additional members of the RAS family have been identified, and the view of the RAS has become dramatically altered. In particular, ANG (1–7), ACE2, and neprilysin are rapidly gaining attention based on their ability to antagonize classical RAS signaling. To date, there is a scarcity of data in the literature regarding the effects of male sex hormones on these components of the RAS. Therefore, this review will focus on how sex chromosomal complement and female gonadal hormone milieu influence this “nonclassical” RAS.

Very little is known regarding the effect of sex of the animal on ANG (1–7) sensitivity/production. Infusion of ANG (1–7) (24 μg·kg⁻¹·h⁻¹) for 1 wk has been shown to reduce blood pressure in male and female Dahl rats on a high-salt diet. However, after 2 wk of ANG (1–7) treatment, a blood pressure-lowering effect was only evident among female rats, suggesting that females are more sensitive to the depressor effects of ANG-(1–7) compared with males (20). Only one study to date has examined basal ANG (1–7) levels in males and females. Reyes-Engel et al. (54) examined ANG (1–7) peptide levels in plasma from young, healthy men and women, and men were found to have higher ANG (1–7) levels compared with women.

In female experimental animals, Brosnihan et al. (9) have demonstrated the ability of 17β-estradiol to promote ANG (1–7) production. Using ovariectomized transgenic rats expressing the mouse (Ren2) gene, they showed that 17β-estradiol replacement shifted the balance of the vasoconstrictor-vasodilator effects of RAS activation by favoring the formation of ANG (1–7) to potentiate a depressor blood pressure response to acute ANG (1–7) injections (100–600 nmol) compared with vehicle-treated females. With regard to the kidney, ANG (1–7) protein levels and the intensity of ANG (1–7) staining have been shown to progressively increase in the renal proximal and distal tubules during pregnancy in experimental animals compared with nonpregnant controls (10). Although 17β-estradiol levels do not increase with pregnancy in rats, levels of other female sex hormones, including prolactin, progesterone, and relaxin do increase, suggesting that multiple gonadal sex hormones may contribute to the balance of ANG II to ANG (1–7) in females (28). Among pregnant women, where circulating 17β-estradiol and other ovarian hormone levels do increase, urinary ANG (1–7) levels have been shown to increase throughout pregnancy, thereby also supporting a role for the female gonadal hormone milieu to mediate an increase in ANG (1–7) (74). More work is needed to fully characterize the effects of both female and male sex hormones on ANG (1–7) formation and sensitivity.

Gonadal hormone milieu has also been shown to modulate enzymes involved in the generation of ANG (1–7). ACE2 is a newly identified monooxygenase that directly catalyzes the production of ANG (1–7) from ANG II, or indirectly via ANG I (24, 72, 75). Neprilysin is a peptidase that directly converts ANG I to ANG-(1–7), and neprilysin plays a major role in ANG-(1–7) formation in the circulation, vascular endothelium, and kidney (1, 11, 77, 81). Female gonadal hormones potentially positively regulate enzymes responsible for the production of ANG (1–7). In experimental animals during pregnancy, ACE2 immunostaining and enzymatic activity are enhanced compared with nonpregnant controls (10, 36). Neprilysin activity has also been shown to be increased in the uterus in midpregnancy and following 17β-estradiol treatment, suggesting that 17β-estradiol increases neprilysin activity in the uterus (47, 49), although neprilysin activity was not altered by estradiol treatment in the kidney cortex or medulla of female rats (47).

Sex differences in ACE2/neprilysin expression and activity may result in sex differences in the ratio of ANG II to ANG (1–7). Some studies suggest that the G protein-coupled receptor mas is the endogenous receptor for ANG 1–7 (17, 23), and the mas receptor stimulates NO and prostaglandin production in cultured endothelial cells, transfected Chinese hamster ovary cells, and canine coronary arteries (8, 31, 64), accounting for the vasodilatory, antiproliferative, antithrombotic, diuretic, and
natu reinc propey of ANG 1–7 (8, 31, 61, 71). NO is an important regulator of renal function, and deficiencies in NO are associated with the development of renal injury. The female gender has been associated with increased renal NOS activity and NO production (69, 76). Therefore, a sex difference in bioavailable NO may contribute to sex differences in ANG II-mediated renal disorders (for a review, see Ref. 42). Nothing is known regarding the effect of sex chromosomes or the gonadal hormone milieu on mas receptor expression in the kidney. Preliminary studies suggest, however, that estradiol treatment reduces transcription of the mas receptor in human coronary artery endothelial cells (29). Therefore, increased ANG (1–7) in females may act to enhance the activation of counter-regulatory pathways resulting in a blunting of the deleterious effects of ANG II.

Intrarenal RAS. In addition to the systemic RAS, there is an intrarenal RAS (for a review, see Ref. 26). To date, potential sex differences in the intrarenal RAS have not been explored; however, sex differences at the tissue level may contribute to how males and females respond to exogenous ANG II. Miller et al. (44) suggest that high 17β-estradiol plasma concentrations (>300 pmol/l) may actually activate the intrarenal RAS. The functional consequences of this are unknown, as 17β-estradiol has also been shown to blunt acute ANG II blood pressure responses (10, 20, and 50 pmol) in female transgenic (mRen2)27 rats (9) and to attenuate ANG II-induced hypertension in female C57BL/6J mice (80). More studies are needed to characterize the intrarenal RAS in males and females and more fully explore the effects of exogenous ANG II on renal function.

AT1 receptors. Known sex differences in the RAS components may favor a greater pressor response to ANG II in males compared with females. Activation of AT1 receptors mediate most of the well-known biological functions of ANG II, including vasoconstriction, sodium reabsorption, mesangial cell proliferation, vascular hypertrophy, inflammation, and increased oxidative stress (7, 71). There are numerous reports in the literature that males have greater AT1 receptor expression in the kidneys compared with females, at both the RNA and protein levels (for a review, see Refs. 25 and 62). In addition to decreased receptor density in kidneys of females compared with males, Rogers et al. (56) have recently shown that specific AT1 receptor binding is ~40% lower in glomeruli from female Sprague-Dawley rats compared with males, and this is dependent on the presence of 17β-estradiol. Therefore, a decrease in AT1 receptor activation in females may contribute to a smaller pressor response in response to ANG II.

Signal transduction pathways. It is tempting to speculate that sex differences in the activation of different signaling pathways in the kidneys of males and females downstream of the ANG receptors could contribute to sex differences in the development of renal pathologies. For example, transforming growth factor-β (TGF-β), nuclear factor-κB (NF-κB), and JAK/STAT have all been implicated in ANG II–induced renal injury, and all have been suggested to be influenced by sex chromosomes complement (3, 4, 6, 60, 63). Very little attention has been paid to potential sex differences in intracellular signal transduction pathways. However, given the central role played by signal transduction pathways in the activation of specific transcription factors to ultimately determine the phenotype expressed by a cell/organism, this area needs to be more closely examined in light of sex differences in numerous pathological conditions, including chronic renal disease.

Genetic polymorphisms. There is evidence to suggest that the genetics of hypertension may differ in males and females. In the Prague hypertensive hypertriglyceridemic rats, blood pressure in the male rats was controlled by two loci on chromosomes 1 and 5 through the systemic nervous system and influenced by the RAS (73). In females, however, blood pressure was controlled by loci on chromosomes 3 and 7 and was independent of the RAS (73). Within the RAS, genetic polymorphisms in ACE, angiotensinogen, and the AT1 receptor have been more closely linked with the development of cardiovascular complications in men (25, 79). In contrast, a strong association has been found for the ACE2 gene A/G polymorphism at nucleotide 8790 in intron 3 with hypertension in female Chinese patients with metabolic syndrome and myocardial infarction, with no association in men (83, 86). These findings make it tempting to speculate that ACE2 may play a larger role in modulating cardiovascular-renal health in women, although, in ACE2 knockout mice, males develop severe renal injury with age, while female mice do not (50). Additional studies are needed to more fully characterize the role of the nonclassical RAS pathway in cardiovascular-renal health in males and females.

Males and Females Respond Differently to RAS Inhibition

Historically, the majority of epidemiological and experimental data collected on disease progression and the effectiveness of therapeutic interventions in hypertension and chronic renal disease has been collected in males. Few clinical trials examining the health benefits of RAS inhibition have reported data for both sexes separately, even when women have been included. In addition, the endpoint reported in most clinical trials testing the efficacy of ACE inhibitors and ARBs in men and women have not focused on renal function; therefore, little is known regarding the effects of RAS inhibition on renal injury per se. However, because the kidney is critical in the long-term regulation of blood pressure, an increase in blood pressure likely reflects impairment in renal function.

ACE inhibition. In young, healthy men and women, a single dose of the ACE inhibitor lisinopril (20 mg) has been shown to produce a similar decrease in blood pressure in both sexes at 24 h (59). In a bioequilivance clinical trial examining the effectiveness of a single 20-mg dose of two formulations of the ACE inhibitor enalapril in healthy men and women, it was found that at low plasma concentrations (<5 ng/ml), maximum inhibition of ACE by enalapril was less in women (84). However, when plasma concentration exceeded 5 ng/ml at 20 to 24 h after dosing, ACE inhibition was comparable in men and women. In contrast, when treated for a 20-day period at 20 mg/day, Falconnet et al. (21) reported that men had a larger decrease in ambulatory blood pressure in response to lisinopril compared with women. These data suggest that over time, the effectiveness of ACE inhibition is diminished in women. The relevance of the effects of a single dose of drug is unclear; however, as under pathological conditions, an individual would be treated for a span of time, and over time, women are reported to be less responsive to the blood pressure-lowering effects of ACE inhibition. This conclusion is supported by additional cardiovascular studies in patients with congestive
heart failure and following myocardial infarction in which ACE inhibition confers less cardiovascular benefit to women compared with men as assessed by total mortality (32). In contrast, Ruggenenti et al. (57) found that women with chronic proteinuric nephropathies have markedly better improvement in kidney survival and greater decreases in proteinuria compared with men when treated with the ACE inhibitor ramipril (titrated to maintain diastolic blood pressure below 90 mmHg). It is important to note, however, that in this study the participants ranged in age from 18 to 70, with the average age of the men being 49.5 and that of women being 48. Because hormonal status can potentially influence how women respond to inhibitors of the RAS, more studies are needed to more fully characterize the effects of ACE inhibition on renal injury in men and women.

Reduced effectiveness of ACE inhibition in females is supported in animal studies in which the depressor responses on blood pressure to the ACE inhibitor enalapril (250 mg/l in drinking water for 8–10 wk) are greater in young male spontaneously hypertensive rats (SHR) compared with females (53). Despite ACE inhibition having a greater effect on blood pressure in male SHR, urinary protein excretion was significantly reduced in female SHR and not in males. This study by Reckelhoff et al. (53) is the only study to examine the effect of ACE inhibition on any index of renal injury in male and female experimental animals. The finding that enalapril selectively reduced proteinuria in female rats may be related to the difference in the magnitude of protein excretion; protein excretion in males was 15-fold that in females, or to the fact that total protein excretion was measured as opposed to albumin. Alternatively, as both male and female SHR were given 250 mg/l in drinking water and female SHR tend to be smaller than males, depending on how much water each sex consumed, it is possible that plasma concentrations of enalapril were higher in the females, accounting for the greater effect on protein excretion. More studies are needed to specifically evaluate the effectiveness of ACE inhibition on chronic renal injury in females relative to males.

ARBs. There are limited data available regarding the effects of sex on ARB efficacy. Miller et al. (45) have reported that in healthy individuals ARB treatment (irbesartan at 75 mg/day for 4 wk) produced a similar decrease in mean arterial pressure, renal vascular resistance, glomerular filtration rate, renal blood flow, effective plasma renal flow, and filtration fraction in men and women. However, in response to exogenous ANG II concurrent with ARB treatment, hemodynamic and renal responses to ANG II infusion were abolished in women after 4 wk of low-dose ARB (75 mg), while ANG II insensitivity was not seen in men even following 4 wk of high-dose ARB (150 mg). These data suggest that healthy women were more sensitive to ARB treatment compared with men. Similarly, in patients with mild to moderate hypertension, the ARB valsartan at both 80 mg and 160 mg produced a larger decrease in diastolic blood pressure in women compared with men (43). In a recent population study by Hudson et al. (32), the efficacy of ACE inhibitors and ARBs was determined in patients with congestive heart failure. Although more patients were placed on ACE inhibitors (8,627 women and 8,484 men) over ARBs (1,596 women and 991 men), women prescribed ARBs had better survival than those prescribed ACE inhibitors, and men prescribed ACE inhibitors had better survival compared with those prescribed ARBs.

In experimental animals, treatment of 14- to 16-wk-old male SHR with losartan (orally 15 mg·kg⁻¹·day⁻¹ for 15 days) normalized blood pressure to levels seen in normotensive control male Wistar-Kyoto (WKY) rats in 53.3% of the animals treated (43). In contrast, under the same treatment regimen, 100% of the female SHR achieved blood pressures comparable to normotensive female WKY controls, supporting the hypothesis that females respond better to ARB treatment compared with males. Interestingly, in a separate study using similarly aged male and female SHR treated with losartan (gavage 15 mg·kg⁻¹·day⁻¹) for 15 days, systolic blood pressure was decreased by ~20 mmHg in both males and females (17). Although, because the blood pressure was greater in the male SHR before ARB treatment, the data suggest that females were more sensitive to the blood pressure-lowering effects of losartan. In contrast, in 16-mo-old SHR, female SHR exhibit a blunted depressor response to the ARB losartan (40 mg·kg⁻¹·day⁻¹ for 3 wk) compared with aged males (82). The blunted depressor response to ARB treatment in the aged female SHR compared with males may be related to an age-related decline in AT₂ receptor expression as discussed below, although this was not examined in the study. Alternatively, discrepancies in the data in the literature may relate to the dose of drug given, the strain of the animals studied, the age of the animals studied, the source of the rats, or the methods used to measure blood pressure. Despite the controversy regarding a subject’s sex chromosomal complement on the benefits of ACE inhibition and ARB treatment, the majority of the data supports the conclusion that in women ACE inhibitors have reduced efficacy and ARBs should be the drug of choice, while the opposite is true in men (32). Often times, however, the number of women included in clinical trials has been relatively small; therefore, a degree of caution needs to be used when drawing conclusions from the data. Regardless, more studies are needed to determine with confidence the effects of sex chromosomal complement on the therapeutic benefits of RAS inhibition. In particular, because RAS inhibitors are commonly used to treat chronic renal disease, studies need to be performed to examine how perturbations of the RAS influence the development of renal injury in females.

Potential mechanisms accounting for sex differences in response to RAS inhibition. ANG (1–7)/ACE2. ACE2 and ANG 1–7 levels increase in male rats treated with an ACE inhibitor or ARB and blocking ANG 1–7 synthesis increases blood pressure and end-organ damage (19, 34, 39, 66). Thus, ANG 1–7 contributes to the antihypertensive and renal protective actions of ACE inhibition and ARB treatment (35). Because the female sex already tends to be associated with enhanced ANG (1–7) production relative to males, this effect may be potentiated with perturbations of the classical RAS. In addition, genetic polymorphisms in ACE2 in women have also been shown to reduce the blood pressure-lowering effects of the ACE inhibitor captopril, while polymorphisms in ACE may influence the effectiveness of ACE inhibition in men (22, 57). A more complete understanding of the RAS profile, at both the genetic and peptide level, in men and women may lead to better treatment options for both sexes.
**Invited Review**

SEX AND THE RAS

**AT**₂ receptor. Enhanced effectiveness of ARBs in females may be related to sex differences in AT₂ receptor expression. Sex chromosomal complement influences AT₂ receptor expression, which is not surprising since the AT₂ gene is located on the X chromosome (16). In the adult kidney of the male rat, AT₂ receptors have been reported to be absent (14, 15), detected only at low levels (51), or clearly expressed within blood vessels, tubular structures, and glomeruli (41, 58). Female mice express renal AT₂ receptors in numbers substantially higher than those present in male mice in an estradiol-sensitive manner (2). The AT₁/AT₂ ratio has also been examined in kidneys and found to be less in females because of the presence of 17β-estradiol (2). ARBs selectively block AT₁ receptors; therefore, in the presence of an ARB, there is an increased likelihood that ANG II will bind AT₂ receptors. Because AT₂ receptor activation stimulates vasodilation, improves renal blood flow, and enhances pressure natriuresis, an increase in AT₂ receptor stimulation could contribute to increased ARB effectiveness in females. Indeed, Okumura et al. (48) have shown that treatment with the ARB valsartan (1 mg·kg⁻¹·day⁻¹ for 1 wk) attenuates the degree of vascular injury induced by the placement of a polyethylene cuff around the femoral artery to a greater extent in arteries from females compared with males. This effect was likely due to an exaggerated increase in AT₂ receptor expression in the femoral artery of female mice following the induction of vascular injury compared with arteries from males, as the effect of valsartan was markedly attenuated in AT₂ receptor-null mice. Losartan treatment has also been shown to selectively increase AT₂ mRNA expression in mesenteric arteries from female SHR and not in arteries from male SHR (17).

**Estrogen.** Diabetic females have been suggested to be more sensitive to ACE inhibition compared with males. In adolescents with type 1 diabetes, ACE inhibition (21 days of enalapril at 0.1 mg·kg⁻¹·day⁻¹ for 1 wk and 0.1 mg/kg twice a day for 2 wk) produced a similar decrease in mean arterial pressure in both boys and girls (12). However, GFR and filtration fraction were only altered in girls, suggesting that kidneys of diabetic girls are more sensitive to ACE inhibition compared with the kidneys of boys (12). Interestingly, during hyperglycemic clamp in these same adolescents, girls experienced an increase in glomerular filtration rate, renal vascular resistance, and filtration fraction with a decrease in effective renal plasma flow and renal blood flow. In contrast, these same parameters were not altered in boys under identical conditions. In diabetes, women tend to lose the cardiovascular and renal protective benefits normally seen compared with men. The mechanisms responsible for the loss of renal protection in diabetic women is not known; however, the Maric laboratory has shown that in female experimental animals, diabetic nephropathy is associated with a decrease in circulating 17β-estradiol levels accompanied by increases in extracellular matrix proteins and transforming growth factor β (TGFβ) (18, 40, 78). Because 17β-estradiol has been linked with maintaining cardiovascular-renal health in premenopausal women, and estradiol has been shown to inhibit TGF-β-induced collagen synthesis in cultured mesangial cells (38, 46, 85), a decrease in estradiol likely contributes to the increased susceptibility of women to diabetic renal injury. Because estrogens have also been linked to regulating the balance of RAS components, diseases that alter estradiol levels may also modulate the way in which women respond to inhibition of the RAS.

**Perspectives**

There is growing awareness that there are differences between the sexes in a number of systems involved in the regulation of blood pressure and chronic kidney disease although few studies have been performed specifically to evaluate the role of sex chromosomal complement on renal disease progression. Although the RAS has been identified as a candidate pathway contributing to sex differences in the development and progression of chronic renal disease, the molecular mechanisms responsible are still relatively unknown. The approach often taken assumes that the basis of the renal injury is similar in males and females; just the magnitude of the response differs. However, on the basis of the vast number of differences that have been identified in cardiovascular physiology, pathophysiology, and pharmacology, it is not unreasonable to propose that the pathway by which males and females develop renal disease may be distinct. For example, among males there is little doubt that activation of the classical RAS significantly contributes to the development of chronic renal disease. As outlined in this review, however, the data are not as compelling to support a role for the classical RAS in mediating hypertension and renal disease in females. This may be related to basic differences in males and females concerning the metabolism of ANG II, differential angiotensin receptor expression and activation, differential activation of signal transduction cascades, or many other differences. It is not debated that females are inherently different from males, so why cannot the pathway to disease progression also be inherently different?

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