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REVIEW ARTICLE

The relationship between estrogen and renin angiotensin system components in the context of hypertension

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Abstract

Hypertension is recognized as a significant risk factor for the development of cardiovascular diseases (CVD), stroke, and kidney diseases. Although hypertension is influenced by numerous factors, the renin-angiotensin system (RAS) is widely acknowledged as a critical regulator of normal blood pressure (BP) stability and a significant contributor to the development of hypertension. RAS has different peptides and receptors that exert their effects via two alternative and classical pathways. In females, estradiol exhibits protective effects on the cardiovascular and renal systems. It may modulate BP regulation via its influence on the RAS, affecting the levels of crucial substrates, enzymes, receptor expression, and protein production. Sex disparities in hypertension are apparent in various hypertensive animal models. This review explored the connection between estrogen and RAS components in the context of hypertension.

Keywords Hypertension · Renin-angiotensin system · Sex differences · Estrogen

Introduction

According to the World Health Organization, hypertension is defined as having systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg [1], which is recognized as a significant risk factor for the development of cardiovascular diseases (CVD), stroke, and kidney diseases [2–5]. It is projected that the number of individuals with hypertension worldwide will surpass one billion by the year 2025 [6]. Premenopausal women tend to have a lower risk of developing hypertension than age-matched men. However, it is essential to note that the incidence of hypertension increases significantly in postmenopausal women (Post-MW) [7, 8]. Hypertension is a condition that is influenced by various factors, and the renin-angiotensin system (RAS) is widely recognized as a critical regulator of normal blood pressure (BP) stability and a significant contributor to the development of hypertension. Some studies documented the relative contributions of circulating versus intrarenal RAS in regulating renal function and arterial blood pressure (ABP) control [9–12]. Recent biomedical research in animal models of hypertension and numerous clinical trials involving drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or mineralocorticoid receptor blockers to treat hypertension [2, 3, 5, 13]. This review explored the connection between estrogen and RAS components in the context of hypertension.

The renin-angiotensin system (RAS)

RAS has been acknowledged for over a century since the discovery of renin by Tigerstedt and Bergman in 1898 [14]. It serves a vital function in maintaining normal BP levels and ensuring proper electrolyte balance [15]. Angiotensin II (Ang II) is a highly potent biological substance produced by the RAS [15]. Ang II has a more significant binding affinity for the Ang II type 1 receptor (AT1R), which is located mainly in the kidneys, vascular smooth muscle, lungs, and liver, and a lower affinity for the Ang II type 2 receptor (AT2R), which is mainly expressed during the prenatal period and later in childhood [16]. AT2R is exclusively expressed in the kidneys, heart, and blood vessels in adults [16]. Both receptors have antagonistic properties and are

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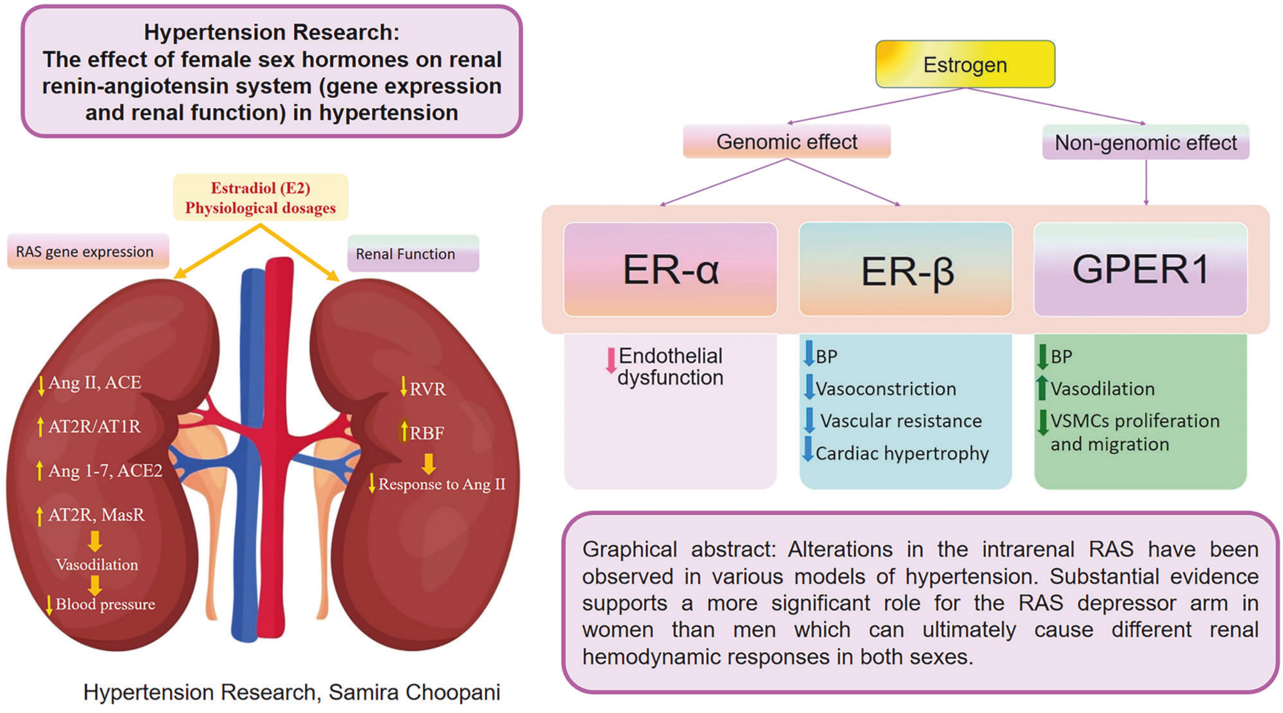
Graphical Abstract



Graphical abstract: Alterations in the intrarenal RAS have been observed in various models of hypertension. Substantial evidence supports a more significant role for the RAS depressor arm in women than men which can ultimately cause different renal hemodynamic responses in both sexes.

part of a family of receptors that bind to G proteins. AT1a and AT1b receptors (AT1aR and AT1bR) are subtypes of AT1R [17]. Although these subtypes are similar in their capacity to bind to and activate ligands, they differ in their tissue distribution, chromosomal localization, genomic structure, and how they are controlled in the transcription process [17]. Most actions of Ang II on AT1Rs involve cellular dedifferentiation and proliferation, vasoconstriction, cardiac contractility, increased renal tubular sodium reabsorption, secretion of aldosterone, vasopressin, and endothelin, as well as salt appetite, thirst, and activation of the sympathetic nervous system, all of which can elevate ABP and contribute to the development of hypertension [18]. Activation of AT2Rs by Ang II, opposes the prohypertensive, progrowth, and proliferative effects of AT1R activation. It leads to vasodilation and increased natriuresis [19–23]. Ang 1-7 is a biologically active derivative of Ang I and Ang II, which are enzymatically cleaved by ACE2 [24, 25]. The Mas receptor (MasR), is the target of Ang 1–7, causing vasodilation and natriuresis, as well as increasing the production of nitric oxide to decrease inflammation and fibrosis [26, 27]. In return, Ang 1-7 can bind to AT2R [7]. Plasma renin activity was reduced by an infusion of Ang 1-7, which may have contributed to its antihypertensive effects [28]. Thus, the RAS has some components with opposite effects to those of the classic axis (renin/ACE/Ang II/AT1R), these components are called alternative pathways (ACE2, AT2R, Ang 1–7, MasR, and alamandine) with antihypertensive effects (Fig. 1) [29–31]. However, the classic axis still plays a predominant role in regulating ABP, cardiovascular and kidney function, and the pathogenesis of hypertension [32–38].

Intrarenal RAS

The RAS can operate both systemically and locally. The systemic RAS is the classical, circulating endocrine system that operates throughout the body. Local or tissue RAS refers to the presence of RAS components and their local production within specific tissues and organs such as the heart, blood vessels, kidney, brain, adipose tissue, adrenal gland, pancreas, liver, reproductive system, lymphatic tissue, placenta, and eyes [39]. In comparison to the circulating levels, the intrarenal levels of Ang II are greater, and the medulla contains more Ang II than the cortex [40]. Researchers have used radiolabeled Ang II to provide direct evidence of the local synthesis of Ang II [41]. All essential components of the RAS, including angiotensinogen (AGT), renin, and ACE, are synthesized in the kidney to facilitate the local production of Ang II [15, 18, 26, 42–44]. Navar et al. previously demonstrated that circulating Ang II is absorbed by the kidney or proximal tubule through AT1aR-mediated processes [41, 45–51]. The thick ascending limb of the nephron also exhibits significant levels of AT1Rs [52]. The

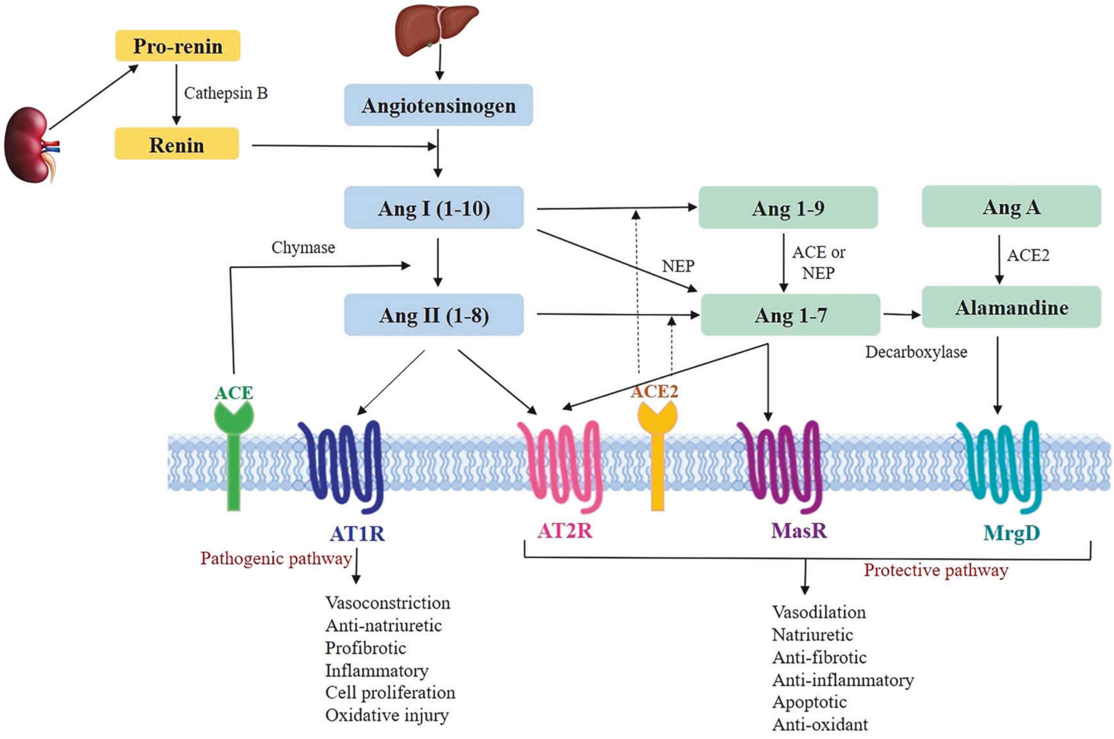


Fig. 1 Classical and alternative pathways in the renin-angiotensin system. Ang Angiotensin, ACE Angiotensin-converting enzyme, NEP Neutral endopeptidase or neprilysin, ATR Angiotensin receptor, MrgD Mas-related G-protein coupled receptor, member D, MasR Mas receptor

presence of high-density receptors specific for Ang II and Ang 1-7 has been identified in the kidney cortical nuclei of both sheep and rats [53–56]. In the kidneys, when AT1Rs are activated, it triggers the expression of sodium-hydrogen exchanger 3 (NHE3) in the proximal tubules and the ascending limb of the loop of Henle. This leads to a reduction in the pressure-natriuresis response and an increase in ABP [19, 57–60]. Ang II, suppresses renin secretion by targeting the AT1Rs on renal juxtaglomerular cells, acting as a negative feedback system that limits systemic activity [18]. Some of the topics addressed include the relative contributions of circulating versus intrarenal RAS in regulating renal function [9–12], the role of intracellular RAS [61–66], and the roles of intratubular RAS in normal ABP control and Ang II-induced hypertension [15, 42, 67, 68].

In summary, all essential components of the RAS are synthesized within the kidneys (as a local autocrine/paracrine system), playing a crucial role in renal function. Ang II and Ang 1-7 receptors are extensively distributed throughout the kidney and contribute to BP regulation by modulating NHE3 activity and renin secretion.

Estrogen

Estrogen, a lipid-soluble steroid hormone, is one of the most important female sex hormones. It is mainly synthesized by the ovaries, testes, and adrenal cortex, playing a key role in numerous essential physiological processes. In humans, four types of estrogens have been identified: estrone (E1), 17β-estradiol (E2), estriol (E3), and estetrol (E4) [69]. The word “estrogen” often refers to E2 because of its extensive presence and significant physiological roles across various tissues and organ systems [70]. E2 is crucial for the development of the reproductive system, maintaining metabolic equilibrium, regulating energy production and distribution, promoting mitochondrial biogenesis, and aiding in the synthesis of adenosine triphosphate [71]. E2 exhibits a strong binding affinity for estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β), which belong to the nuclear hormone receptor superfamily [72], and peripheral G protein-coupled estrogen receptor 1 (GPER1), has been recognized as another mediator of non-nuclear signaling [73].

Within the nuclear signaling pathway, E2 binds to the intracellular receptors ERα and ERβ, creating an E2-receptor dimer complex that subsequently moves into the nucleus. Once inside the nucleus, this complex binds to estrogen response elements or activator protein-1 and specificity protein-1 located on the promoters of E2-responsive genes, functioning as transcription factors to control gene transcription [70]. Ultimately, estrogen-mediated gene products regulate autophagy, proliferation, apoptosis, survival, differentiation, and vasodilation under normal conditions.

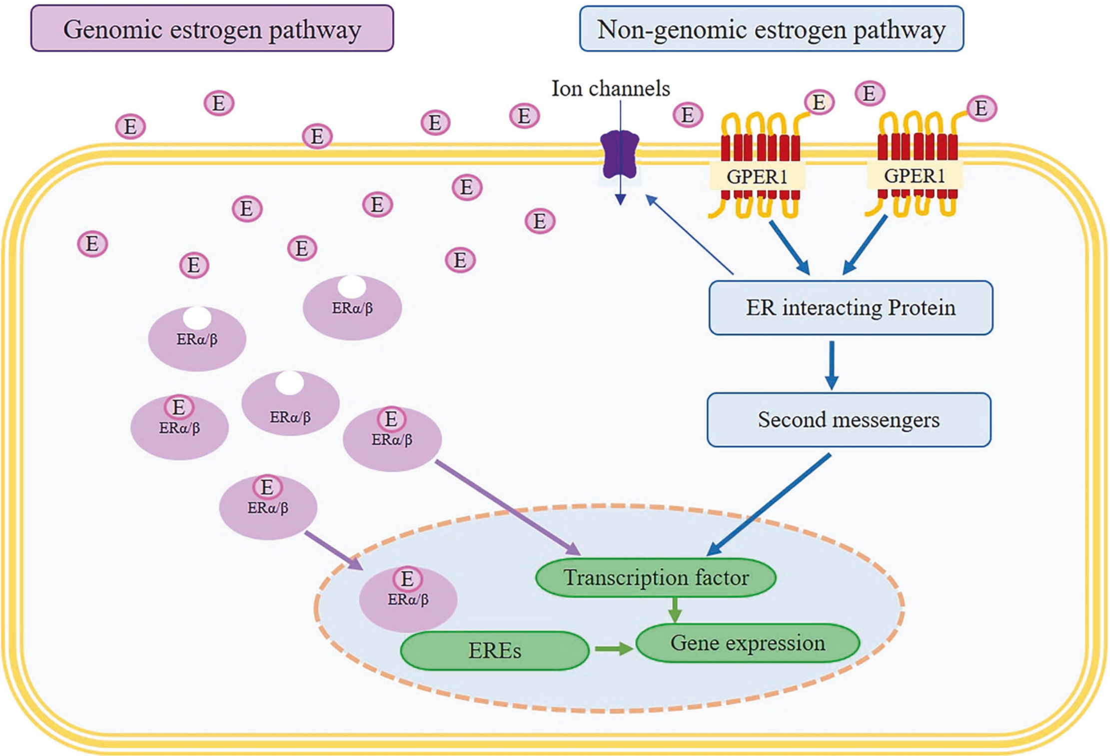


Fig. 2 Genomic and non-genomic estrogen signaling pathways. There are different estrogen-mediated signaling mechanisms. 1) Genomic signaling: estrogen binds to ERs. The complex dimerizes and translocate to the nucleus inducing transcriptional changes in estrogen-responsive genes with or without EREs. 2) Non- genomic signaling: the membrane bound receptor induces cytoplasmic events such as modulation of membrane-based ion channels, second-messenger cascades and transcription factors. E estrogen, ERα estrogen receptor alpha, ERβ estrogen receptor beta, GPER1 G protein-coupled estrogen receptor 1, EREs estrogen response elements

Nevertheless, these functions can be impaired when pathological conditions arise. Due to the intracellular location of ERα and ERβ, their activation generally requires several hours or more, resulting in a gradual “genomic effect” (Fig. 2) [70].

In the non-nuclear signaling pathway, E2 interacts with GPER1, rapidly triggering nuclear transcription factors by regulating ion channel openings or activating associated enzymes such as $Ca2^+$ mobilization, phosphatidylinositol 3-kinase, and mitogen-activated protein kinase. This mechanism functions independently of gene regulation and occurs almost immediately, within seconds to minutes, thus, it is referred to as a rapid “non-genomic effect” (Fig. 2) [70].

Activation of ERα has been demonstrated to alleviate endothelial dysfunction. ERβ activation leads to a decrease in BP, vasoconstriction, and mitigation of cardiac hypertrophy. Additionally, GPER1 contributes to reducing BP, promoting vasodilation, and decreases vascular smooth muscle cells (VSMCs) proliferation and migration [74]. The reduction in E2 levels associated with the onset of menopause disrupts mitochondrial activity and exacerbates inflammatory responses, abnormal blood vessel formation, and microvascular disorders [75]. E2 may further impact BP by modulating the RAS, attenuating sympathetic-driven vasoconstriction, modulating salt sensitivity, influencing body mass, and diminishing oxidative stress. Collectively, these mechanisms play a role in vascular inflammation and the development of cardiovascular and renal dysfunction, including hypertension [76, 77].

Estrogen and RAS

Sex disparities in the expression of RAS components have also been identified [78, 79]. As age progresses, E2 declines in female rats, leading to increased intrarenal RAS activation [80]. E2 down-regulates ACE2 and AT1R while significantly up-regulating AT2R; these effects are diminished or lost in ER-α knockout mice [81]. In female Sprague Dawley rats, the kidneys show a notable concentration of ER-α and GPER mRNA [82]. Studies have determined the role of ER-β in protecting against hypertension through both vascular [77] and central [83] mechanisms. In vascular mechanism, E2 reduces vasoconstriction by enhancing the expression of inducible nitric oxide synthase via ER-β [77]. In the central mechanism, the paraventricular nucleus and rostral ventrolateral medulla

ERβ are involved in the protective effects against aldosterone-induced hypertension [83].

Estradiol and renal RAS receptor expression

In rodents, the levels of renal Ang II receptor types are affected by E2 showing notable variations across species, strains, and regions [84]. Males typically exhibit increased AT1R expression at both the RNA and protein levels [39]. According to Rogers and colleagues study, the density of AT1R in glomeruli and specific binding is lower in female Sprague-Dawley rats compared to male rats [85]. E2 prevents the increase in AT1R density observed in the renal medulla and cortex following ovariectomy (OVX) [86], and may reduce the activation of the ACE/AT1R pathway [39, 87], whereas OVX itself increases AT1R expression and binding in the kidney [84]. E2 enhances the expression of AT2R [88, 89] and reduces the AT1R/AT2R ratio [90]. Female Sprague-Dawley rats undergo an estrogen-mediated increase in AT2R expression within cardiac and renal tissues [91, 92]. Sampson et al. revealed higher expression of the AT2R, ACE2, and Ang 1-7 genes in the renal tissue of adult females than in that of males [93]. One study demonstrated that sex chromosomes influence the gene expression of AT1R, AT2R, and MasR in the renal cortex [94]. Renal MasR expression varies between males and females. Adult female rats exhibit higher MasR mRNA levels in their kidneys compared to males [88, 93].

Estradiol and RAS in renal function

The influence of E2 on the expression of components within the RAS may alter renal function. There is a significance of sex differences in MasR expression and functions in the renal system under both physiological and pathological conditions [95]. For example, MasR has been shown to differentially regulate renal blood flow (RBF) responses to Ang 1-7 between male and female rats. Ang 1-7 infusion resulted in a dose-dependent increase in RBF in both sexes. Notably, MasR blockade significantly diminished this response only in female rats [96]. Mansoori et al. provided evidence documenting the sex-dependent vasodilatory effect of Ang 1-7 in the renal vascular bed [97]. In male rats, blocking both AT1R and AT2R resulted in an increase in RBF when MasR was inhibited, but this effect was not seen in female rats [97]. E2-treated OVX rats exhibited a reduced in RBF response to Ang 1-7 following MasR blockade [98]. Blocking MasR restricts the opportunities for E2 to exert its protective effects. A779, an antagonist of MasR, significantly improved the RBF in male rats, in response to Ang 1-7 infusion when the Ang II receptors were blocked, and this observation did not occur in female animals [99]. The study suggested that Ang1-7 administration may not involve MasR in mediating renal vascular responses in male rats, and these responses are not associated with Ang II receptors [99].

In summary, renal Ang II receptor expression and renal function is influenced by E2, which reduces the activation of the ACE/AT1R pathway, decreases the AT1R/AT2R ratio, and increases AT2R activation. The AT2R, ACE2, and Ang 1-7 genes and MasR were more highly expressed in the renal tissue of adult females than in that of males. This causes different renal hemodynamic responses in males and females.

Estrogen and RAS components in hypertension

Several models of hypertension have shown alterations in the intrarenal RAS [100–103]. Disparities in hypertension between the sexes have been observed in the SHR strain [104] and the Dahl salt-sensitive strain [105], as well as in deoxycorticosterone salt [106, 107] and renal-wrap hypertension [108]. In a study conducted by Xue et al., it was shown that male mice experienced a significantly greater increase in BP compared to female mice, with castration attenuating and OVX augmenting Ang II-induced hypertension. The animal models have revealed some inconsistencies regarding the roles of sex differences in Ang II-induced hypertension [109–113]. The variations include complete reversal, reduced responses, or no effect at all in female rats or mice, depending on the Ang II infusion doses (either low or high pressor), the animal models used (rat or mouse, global AT1a or AT2 receptor knockout), or the administration methods (subcutaneous or intraperitoneal infusion). Below, we highlight several studies that have reported interactions between E2 and renal RAS components and renal function in hypertension.

Estrogen and renal RAS components in HTN

In humans, the correlation between hypertension and renal injury with an elevated RAS activation is stronger in males than in females [114]. Hinojosa-Laborde et al. reported that in aged female Dahl salt-sensitive rats, the binding of AT1R to renal glomeruli increased, accompanied by an increase in BP [115]. This increase was further exacerbated by OVX but was abolished by chronic E2 treatment [115]. Another study demonstrated that in Dahl salt-sensitive rats following OVX, E2 counteracted the increase in AT1R protein expression in the kidneys and subsequently increased their systolic blood pressure. Furthermore, chronic blockade of AT1R normalized BP in these rats. The results imply that AT1R is might be related to heightened salt sensitivity [116]. Male spontaneously hypertensive rats (SHRs) exhibits increased levels of AT1R mRNA and protein expression in both the vasculature and kidney, while females display increased AT2R expression [117, 118]. Female SHRs exhibit greater expression of Mas protein in the kidney cortex than male SHRs [93, 117]. In aging SHRs, AT1R expression is the same in both sexes [119]. ARBs leads to a greater reduction in ABP in aged male SHRs than in aged female SHRs, despite no difference in the intrarenal mRNA expression of ACE or AT1R between the sexes [119]. Chronic low-dose Ang II infusion has been reported to lower the mean arterial pressure in intact female and estrogen-replaced OVX rats. This is attributed to an increase in renal and cardiac AT2R and MasR, however, this effect was not observed in OVX rats [91]. Additionally, research has shown that renal vasoconstriction was lessened in women than in men when AT1R blockade was given, which implies that this was a result related to AT2R [120–122]. In AT2R knock-out mice, female mice exhibited a weaker response to Ang II infusion than male wild-type and female AT2R knock-out mice [109]. ACE2 has been demonstrated to protect females, but not males, from the pressor effects of Ang II infusion in studies utilizing ACE2-knockout mice [123]. In animal models of hypertension, Ang 1-7 levels are consistently greater in female than in male, and blocking MasR eliminates the protective effect that is unique to females against vascular damage [117, 124, 125]. Similarly, Brosnihan et al. found that E2 can stimulate the production of Ang 1-7 in transgenic hypertensive rats [126]. Ji et al. revealed that administering E2 supplementation following renal wrapping in OVX rats led to an increase in renal ACE2 expression, which was previously reduced due to wrapping [127]. In two-kidney, one clip (2K1C) hypertensive model, MasR expression decreased [101]. Lee et al. investigated to compare the intratubular RAS between male and female 2K1C rats. Five weeks post-surgery, it was observed that the levels of ACE and Ang II were significantly lower in female than in male [128]. Moreover, higher levels of ACE2, Ang 1-7, and MasR have been detected in female [128]. A summary of the effects of estrogen on renal RAS components in various hypertension models is shown in Fig. 3.

Estrogen, RAS, and renal function in HTN

Animal studies have also illustrated the effects of E2 through RAS receptors on renal function in hypertension. For instance, in our previous study, we showed that in the 2K1C model, administrating E2 to female OVX rats reduced the impact of losartan on the RBF to Ang II infusion [129]. This attenuation may occur via a decrease in AT1R expression in 2K1C model [101, 130, 131] or due to an unknown mechanism that promotes the vasoconstrictor actions of AT2R in groups that received supraphysiological levels of E2 [132]. In female OVX, 2K1C model showed that the effects of A779 and E2 on RBF responses to Ang II infusion decreased [133], possibly due to a decrease in MasR expression in the nonclipped kidney [128]. Pezeshki et al. reported that blocking AT1R (with losartan) increased

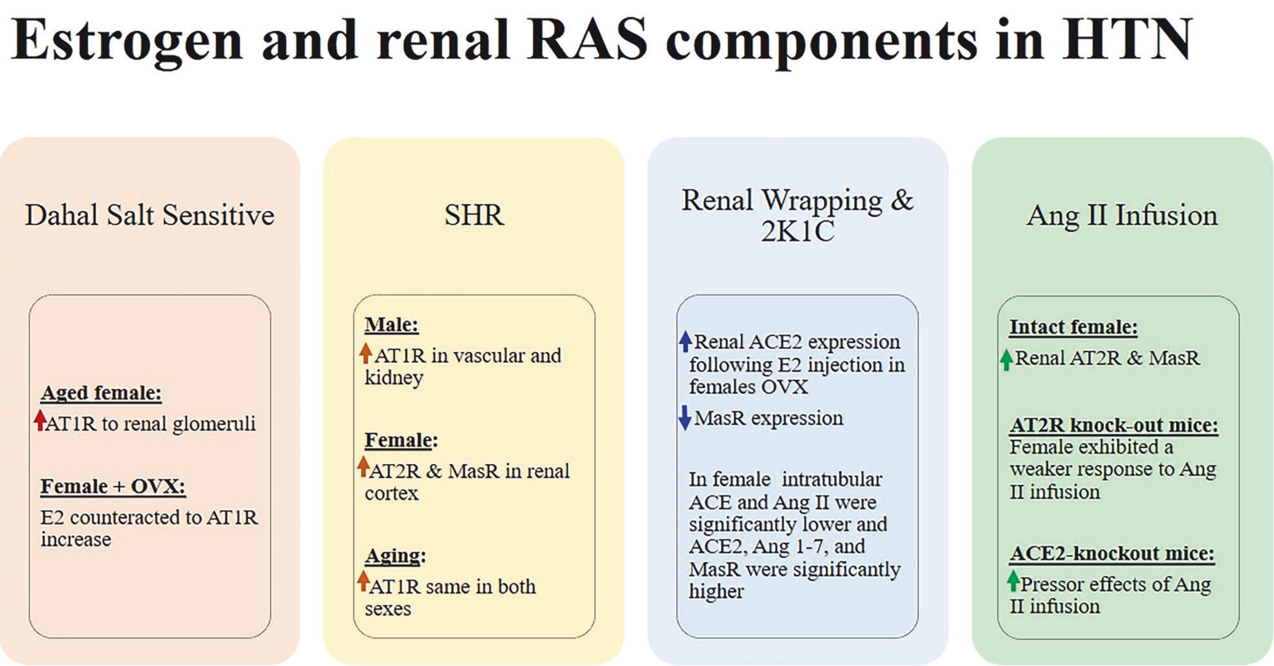


Fig. 3 Effects of estrogen on renal RAS components in various hypertension models. SHR Spontaneously hypertensive rats, 2K1C Two-kidney, one-clip renal hypertension, Ang II Angiotensin II, ACE2 Angiotensin-converting enzyme 2, AT1R Angiotensin II type 1 receptor, AT2R Angiotensin II type 2 receptor, MasR Angiotensin 1-7 receptor, OVX Ovariectomy, E2 Estradiol

RBF in response to Ang II, but no differences were detected between the sexes. However, co-blockade of AT1R and MasR significantly increased the response of RBFs to Ang II in males but not in females [134]. This finding suggested that there may be different interactions between receptors within the RAS in male and female rats. A study conducted by Safari et al. indicated that in normotensive OVX rats high-dose E2 pretreatment increased the renal vasoconstrictor response to Ang II. Nonetheless, this enhanced response was not evident when AT2R was acutely blocked with PD123319 [132]. So they concluded high levels of E2 result in renal vasoconstriction through AT2R-mediated mechanisms. Also, they examined how Ang II infusion affected RBF in normal male and female Wistar rats with AT2R and masR blocked [135]. The results showed that MasR blockade led to a reduction in basal RBF in female rats, while no such effect was observed in male rats. Interestingly, co-administration of MasR and AT2R antagonists did not show a synergistic impact on basal RBF. The result of this study indicated that the activation of both AT2Rs and MasRs unexpectedly enhanced the constriction of renal blood vessels by Ang II. However, this response in normotensive female rats is greater than in male rats [135]. MasR blockade [117] or ACE2 knock-out [123] also eliminated the disparities in the Ang II-induced response between the sexes. According to Bürgelová et al. study, intrarenal MasR blockade did not affect renal function in normotensive rats. However, it resulted in a significant decrease in renal hemodynamics in 2K1C rats [136].

In summary, compared with female animals, male animals exhibit augmented renal constrictor responses to exogenous Ang II, while E2 changes the expression of the receptor and other components of the RAS under conditions of hypertension. Substantial evidence supports a more significnt role for the RAS depressor arm in women than men which can ultimately cause different renal hemodynamic responses in both sexes.

The complexities of estrogen effects on blood pressure

Research shows that E2, progesterone, and testosterone significantly affect endothelial cells, VSMCs, extracellular matrix, and various proteases. Moreover, menopausal hormone therapy (MHT) alleviates vasomotor symptoms associated with menopause in Post-MW [137]. This led to trials examining MHT's effects on CVD, but results were inconclusive [138]. E2 is used in contraception and MHT to ease menopause symptoms due to its vasodilatory effects [137]. Initial observational data from the Nurses' Health Study suggested a reduced risk of cardiovascular incidents and mortality related to CVD in Post-MW who were administered oral E2 [139, 140]. However, major randomized trials like Women's Health Initiative (WHI) and Heart and Estrogen/progestin Replacement Study (HERS) found no cardiovascular benefits and reported increased cerebrovascular risks with MHT [141, 142]. Although a transient reduction in coronary artery disease events was noted in the MHT group during the later phases of HERS, this advantage did not persist during long-term follow-up. Thus, MHT is not recommended to reduce CVD risk in Post-MW with existing coronary artery disease [143]. As noted in laboratory models, supraphysiological doses of estrogen elicited different responses in renal blood flow, as noted in Section "Estrogen, RAS, and renal function in HTN" [132, 135]. The lack of cardiovascular benefit may relate to MHT factors (type, dose, administration), differences in E2 receptors, timing and duration of therapy, hormone levels, and preexisting cardiovascular health or medical conditions [144].

Gender differences in the effects of RAS inhibitors

About 43% of hypertension trials analyze data by sex, revealing that ACEIs and ARBs may work better in men [145], while women, being more sensitive, often need lower ARB doses and experience more ACEI side effects but may benefit more from ARBs [120, 146]. Current guidelines, except for pregnancy-related cases, do not specify sex-based treatment differences. A meta-analysis found these drugs equally effective for major cardiovascular event prevention in both sexes [147], though women on losartan had higher angina hospitalizations than men [148]. Several extensive clinical studies show that RAS inhibitors reduce mortality and heart failure risks similarly in both sexes, but women and older adults are often underrepresented and may receive suboptimal guideline-based therapy [145, 149]. More research is needed to understand how sex hormones and hormonal therapies influence RAS activity and treatment response [80, 146], including the non-classical vasodilatory RAS pathway [80, 146]. Developing sex-specific clinical guidelines for RAS inhibitor use, depends on collecting detailed, sex-disaggregated data from both clinical trials and real-world practice [145, 146].

Conclusion

Hypertension is a major contributor to cardiovascular and renal diseases. Two key factors influencing BP regulation in both males and females are RAS and sex hormones. The interplay between estrogen, BP, and RAS is notably complex. Research has indicated alterations in the components of the RAS across various hypertension models. The effect of E2 on the expression of receptors and components of the RAS leads to varying sex-related hemodynamic responses in different models of hypertension. Although E2 is protective, MHT has minimal or no clinically meaningful effect on BP in most women and may even increase risk depending on dose, route, individual factors, physiological state, and E2 formulation. This mechanistic complexity should be acknowledged in the manuscript, along with the variability in individual responses and the inconsistent cardioprotection from MHT. However, the administration of ACEI and ARBs for hypertension did not show any significant differences in endpoint outcomes between the two genders in clinical trial studies. Future treatments and research should focus on these differences by ensuring equal participation of men and women, designing sex-specific treatment protocols, and exploring alternative RAS pathways to enhance heart and kidney health outcomes for all.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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