Review
Renin angiotensin system and gender differences in the cardiovascular system

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Abstract
In the effort to explain gender-related differences of the cardiovascular system, the renin–angiotensin system experienced intensive exploration. Indeed, the development of hypertension as well as the progression of coronary artery disease and heart failure have two factors in common: (1) display distinct gender specific characteristics and (2) are enhanced by the renin–angiotensin system. It is therefore interesting to note that data from experimental animals, epidemiological surveys, and clinical investigations suggest that the components of the circulating as well as tissue-based renin–angiotensin system are markedly affected by gender. However, the issue is complicated by counter-regulatory effects of estrogen on the system with the substrate, on one hand, and the processing enzymes as well as the chief receptor, on the other hand. In fact, angiotensinogen is up-regulated particularly by oral administration of estrogen, whereas renin, angiotensin-converting enzyme (ACE), and AT-1 receptor are down-regulated by the hormone. While under well-defined experimental conditions the net effect of estrogen appears to result in suppression of the renin–angiotensin system, the clinical situation may be more complex. The judgment is further complicated by the difficulty in precisely measuring the activity of the system at the tissue level. Moreover, clinically relevant read-outs for the activity of the renin–angiotensin system may be regulated multifactorially or only indirectly affected by the system. Nevertheless, the undisputable, profound biochemical changes in the renin–angiotensin system related to the estrogen status allow speculation that such interaction explains some of the differences in the cardiovascular system of men and women. © 2002 Elsevier Science B.V. All rights reserved.

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1. Regulation of RAS components by estrogen

Gender and sex hormones affect the components of the renin–angiotensin system (RAS) by a number of mechanisms (Fig. 1). Unfortunately, counter-regulatory actions as well as some difficulties in studying components of the renin–angiotensin system biochemically or functionally at the tissue level have blured our knowledge. In fact, it was only 15 years ago that the consensus in the scientific community favoured the notion that estrogen activates the renin–angiotensin system [1–7]. Nowadays, more precise measurements of plasma renin as well as a better appreciation of the roles of ACE and the AT-1 receptor allow to judge the situation differently. Indeed, experimental animals with a stimulated renin–angiotensin system and hypertension may experience a significant inhibition of angiotensin II generation and blood pressure reduction with estrogen replacement [8–15]. In humans, the net effect of physiological estrogen concentrations on the overall activity of the system and, as a consequence, blood pressure appears to be similar. However, the data vary to some extent and have to be evaluated on an individual basis. In fact, a recent meta-analysis suggested overall a mild increase in blood pressure of women using contraceptive medications and a mild decrease in those using estrogen replacement therapy [16].

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Fig. 1. The figure displays the cascade leading to angiotensin II formation and subsequent receptor activation and the influence of estrogen and testosterone on various components.

1.1. Angiotensinogen

Angiotensinogen or renin substrate is predominantly synthesized in the liver. An estrogen response element in its gene promoter markedly stimulates angiotensinogen synthesis and explains higher circulating levels in women as compared to men [17, 18]. Moreover, premenopausal women have slightly higher angiotensinogen levels than postmenopausal women and estrogen replacement therapy or contraceptive medication both increase angiotensinogen in the circulation [5, 19, 20]. Interestingly, high concentrations of estrogen in the portal vein, i.e. the liver’s exposure to unphysiological concentrations after oral administration of estrogen, cause most of the well-documented angiotensinogen stimulation [21]. In fact, studies employing transdermal estrogen replacement therapy that avoided the first pass effect demonstrated only mild if any stimulation of angiotensinogen production [19, 20, 22]. Thus, pharmacological rather than physiological concentrations of estrogen account for much of the angiotensinogen stimulation (and LDL lowering), and can, therefore be prevented by transdermal or intramuscular estrogen replacement [19, 20, 22–24].

1.2. Renin

For decades, studies on renin relied on measurement of plasma renin activity. In this assay the cumulative generation of angiotensin I rather than renin itself is being quantified (Fig. 2). Measurements of plasma renin activity are partially dependent on the concentration of angiotensinogen (or renin substrate) in the assay system. Indeed, plasma renin activity is, in part, reflecting renin substrate levels which, as outlined above, are markedly higher in
women using contraceptives or oral estrogen replacement medication. It is not surprising therefore that plasma renin activity, i.e. angiotensin I levels measured in the assay, are increased or rather variable in women using oral estrogen replacement [1,2,25]. This ex vivo interaction can be neutralized by either addition of excess amounts of angiotensinogen (the assay is then named plasma renin concentration) or, nowadays, by direct immunometric measurements of renin. In other words, these modifications of the assay allow to measure renin rather than a combined effect of angiotensinogen and renin.

The investigations on the interaction between the estrogen status and renin largely reflect these technological aspects. While traditionally the overall consensus suggested that renin activity is stimulated by estrogen, current studies using direct assays document that the enzyme levels are actually suppressed [6,7,19,26–28]. Indeed, some studies that used both technological approaches report opposite responses of plasma renin activity and concentration in individual patients receiving estrogen replacement therapy (Fig. 2) [24]. Direct measurements of renin by the radioimmunometric assay clearly document lower levels in women as compared to men [19]. Moreover, premenopausal women and postmenopausal women using estrogen replacement therapy display lower renin levels as compared to men or postmenopausal women without substitution [19,29]. The precise mechanism of renin down-regulation by estrogen is not entirely clear. A molecular interaction may be mediated by modulation of sympathetic activity which is known to be lowered by estrogen replacement therapy [30]. Suppression of the sympathetic nervous system, on the other hand, is known to suppress the renin production at the macula densa for example via a CREB element in the renin promotor [31,32], and other mechanisms [33].

1.3. Angiotensin-converting enzyme

The implications of estrogen status for plasma and tissue ACE activity were only recently explored. In fact, both the conversion rate of angiotensin I to angiotensin II as well as the biochemical activity of the enzyme appear to be affected by estrogens in experimental animals [6,13,34]. In addition, the majority of human studies documents a mild to moderate suppression of ACE activity with estrogen replacement therapy [19,27].

1.4. AT-1 receptor

Most of the traditionally observed effects of the renin–angiotensin system are mediated by the AT-1 receptor. Like renin and ACE, the AT-1 receptor appears to be down regulated by estrogen replacement therapy [12,35]. Both, studies in humans as well as experimental animals observed consistently such interaction at the level of receptor density as well as down-stream activation steps [12,35,36].

1.5. Other components

Further interaction between estrogen status and the renin–angiotensin system may be related to plasma levels of the vasodilatory heptapeptide ANG1-7 [13,36,37], kininogene [38], renin binding protein [39], and the AT-1 receptor [40,41]. However at present time, only scattered data are available to illustrate such potential effects.

Moreover, the central role of the renin–angiotensin system within the neurohormonal network raises the option for indirect modulation of its components. For example, the estradiol metabolites 2-hydroxyestradiol and 2-methoxyestradiol inhibit endothelin-1 synthesis by means of an estrogen receptor-independent mechanism [42]. Lower endothelin levels on the other hand may lead to lower RAS activity [43]. Likewise, estrogen levels have profound implications for NO synthesis which, in turn, is known to play a central role in regulation of renin synthesis [7,44,45].

1.6. RAS and testosterone

In addition to the effects of estrogen, gender-related differences of the renin–angiotensin system may be amplified by testosterone. Testosterone treatment in ovariec-tomized female rats increases plasma renin activity [46]. On the other hand, plasma renin activity decreases with castration in male rats [46]. Furthermore, it was found that there is a linear correlation between the level of testosterone and plasma renin activity in castrated rats treated with increasing doses of testosterone. Moreover, molecular studies have shown that angiotensinogen mRNA is higher in male rats than in female and that castration reduces whereas testosterone treatment increases angiotensinogen mRNA [26,46]. An increase in angiotensinogen substrate may in part explain the increase in renin activity mentioned above.

2. Estrogen-mediated modulation of the RAS in pathophysiological conditions

The implications of the estrogen status in modulating the renin–angiotensin system may differ (1) depending on the mode of estrogen administration and (2) on the experimental or clinical context. Most notably, physiological levels of estrogen or those achieved with estrogen replacement therapy are largely different from the effects seen with synthetic preparations or high doses used for contraceptive utilization of the hormone. Moreover, equine and human estrogen metabolites or different dosages may differ in their effects. Perhaps even more importantly, the route of application, i.e. transdermal vs. oral, may affect the integrated activity of the system.

In addition, disease conditions that are largely dependent on the activated renin–angiotensin system may visualize
estrogen effects more prominently. For example, transgenic rats with renin-related hypertension display a profound sexual dimorphism in blood pressure regulation, that is largely dependent on the interaction between estrogen and components of the renin–angiotensin system [13,47]. Likewise, in two-kidney-one-clip rats (2K1C) plasma renin activity appears to increase less in female as compared to male rats [9]. Ovariectomy, on the other hand, can enhance the rise of renin in 2K1C rats [9]. Consequently, renal hypertension develops more frequently in male or ovariectomized rats as compared to female 2K1C animals.

Hypercholesterolemia and estrogen deficit may also affect the level of AT-1 receptor expression. Indeed, both conditions up-regulate synergistically, AT-1-mRNA levels in vascular smooth muscle cells and, thus, may amplify the risks of menopause for the cardiovascular system [35,48,49].

Estrogen may also affect vascular tone and the activity of the RAS by indirect mechanisms. For example, estrogen reverses acetylcholine-induced vasoconstriction via possible facilitation of endothelium-dependent relaxation [50,51]. This may be mediated by an enhancement of NO production via stimulation of NO-synthase [52–54], mediated in part by an estrogen α-receptor-dependent action [55].

3. Modulation of angiotensin II effects by estrogen

In addition to the bidirectional regulation of plasma and tissue components, estrogen may affect the down-stream signaling of the AT-1 receptor [35]. In this respect, experimental studies demonstrated that estrogen may shift the vasoconstrictor–vasodilator balance of the renin–angiotensin system [9,13,56]. For example, transgenic animals with high renin hypertension displayed an attenuated pressure response to intravenous angiotensin after estrogen replacement [13]. Interestingly, angiotensin II actions in the central nervous system may also largely differ by gender. For example, the pressure and dipsogenic response to centrally administrated angiotensin II in anesthetized dogs was substantially augmented in male animals [57].

Similarly, studies in healthy humans suggest that the half time of the pressure response after discontinuation of angiotensin may be greater in men than in women [58]. A vascular bed that is particularly sensitive to angiotensin II is the renal circulation. In response to angiotensin II both men and women display a reduction in effective renal plasma flow [58,59]. However, under this condition, only men maintain their glomerular filtration rate (GFR) suggesting a significant augmentation of filtration fraction [59]. In addition, angiotensin-related aldosterone secretion appears to be effected by the estrogen status. While some but not all studies observed lower aldosterone concentrations in women, experimental studies in rats clearly document that angiotensin II increases peak plasma aldosterone levels in dependence of the estrogen status with highest levels observed in male or ovariectomised rats [12].

Finally, Nickenig et al. [48] demonstrated that the generation of free radicals by vascular smooth muscle cells can be enhanced by angiotensin II but largely suppressed by estrogen. In fact, these data offer a potential mechanism that explains the shift of complications from atherosclerotic disease into the postmenopausal age-group [48,60].

4. Modification of genotype–phenotype interaction by estrogen

In addition to numerous exogenous factors, genotypic variation determines the activity of the renin–angiotensin system. In this respect, numerous studies demonstrated that genetic polymorphisms of the ACE, angiotensinogen, or AT-1 receptor genes display more profound effects in men than in women [61–66]. Indeed, most of such association studies were only positive when the subgroup of men was considered. Likewise, the correlations of plasma ACE activity with blood pressure or left ventricular hypertrophy were predominantly observed in men [63,67].

A rather distinct phenotype related to the renin–angiotensin system is non-modulation essential hypertension [61]. Herewith, abnormal responses of renal blood flow or aldosterone secretion to angiotensin II on high or low salt diet are characterized. Interestingly, in women, the expression of the non-modulation phenotype is observed less frequently than in men and almost absent in the premenopausal state [61]. Taken together, the modulatory role of the estrogen status with respect to the renin–angiotensin system may relate to the genetically determined activity of the system in a given individual.

5. Clinical outlook

The progression of renal or cardiac failure as well as the rate of cardiovascular mortality differ largely in premenopausal women as compared to men of the same age group. Even more dramatic is the difference in prevalence of atherosclerotic disease between men and women. The mechanisms explaining the protective effects of female gender for the heart, vessels and kidneys are incompletely understood. Interestingly, recent evidence suggests that the estrogen-related organ protection may be more profound in the setting of primary prevention, as a large, prospective trial in the setting of secondary prevention has failed to document such benefit (HERS, [68]). The distinction between primary and secondary prevention may not apply to the renin–angiotensin system since its inhibition is unequivocally beneficial for patients with or without vascular, cardiac or renal disease.
In this context, the complex interaction between the renin–angiotensin system and estrogen status is of utmost clinical relevance. As outlined before, the estrogen status affects the renin–angiotensin system in a bidirectional mode. Particularly, oral equine estrogen substitution, as conducted in the HERS trial [68], implies a profound stimulation of angiotensinogen, such that a down-regulation of renin and ACE as well as the AT-1 receptor may be insufficient to show functional relevance. Transdermal estrogen replacement lacks angiotensinogen stimulation but may still suppress renin and ACE [19]. Thus, the mode of estrogen replacement therapy may be of particular clinical relevance with respect to the renin–angiotensin system and the success of primary and secondary prevention. Moreover, future research may develop selective estrogen receptor modulators (SERMs) that provide a better defined response of the renin–angiotensin system.

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