Female Sex Hormones, Salt, and Blood Pressure Regulation

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There are gender-associated differences in blood pressure (BP) in humans, with men having higher BP than age-matched pre-menopausal women and being at greater risk for cardiovascular and renal diseases. The mechanisms responsible for the gender differences in BP control and regulation are not clear, although there is some evidence that interactions between sex hormones and the kidneys could play a role. However, the response to salt in pre- and post-menopausal women, and in particular the influence of exogenous and endogenous female sex hormones on renal hemodynamics and tubular segmental sodium handling, have been poorly investigated. Recently we have shown that both endogenous and exogenous female sex hormones markedly influence the systemic and renal hemodynamic response to salt. We have found that BP in young normotensive women, regardless of oral contraceptive use, is rather insensitive to salt. However, the renal hemodynamic and the tubular responses to salt vary significantly during the normal menstrual cycle and with the administration of oral contraceptives. Furthermore, after the menopause, BP tends to become salt sensitive, a pattern that could be due to aging as well as to the modification of the sex hormone profile. These observations provide new insights pertaining to potential mechanisms explaining the lower incidence of cardiovascular disease and progression of renal disease in pre-menopausal women (which tend to disappear with the menopause); these observations also emphasize the importance of considering more carefully the phase of the menstrual cycle whenever conducting physiologic studies in women and enrolling women in clinical studies. Finally, increased salt sensitivity in menopausal women strongly encourages the use of diuretics.

Key Words: Female hormones, blood pressure, sodium, endogenous lithium, renal hemodynamics.

Gender-associated differences in blood pressure (BP) have been observed in animals as well as in humans. Thus, in humans, men have higher BP levels than women until the age of 60 to 70 years, when BP becomes progressively more comparable in both men and women. Hence, men are also at greater risk for developing cardiovascular and renal complications. The mechanisms responsible for these gender differences in BP are not well understood, but several hypotheses have been proposed suggesting a role of androgens and female sex hormones.

The kidneys play a major role in the regulation of BP. According to the hypothesis of Guyton et al, a decrease in renal sodium excretion or a rightward shift of the pressure–natriuresis relationship can lead to a long-term increase in BP and the development of hypertension. In accordance with this hypothesis, Reckelhoff et al have reported that the pressure–natriuresis curve is blunted in male spontaneously hypertensive rats (SHR) and that castration of male SHR restores the pressure–natriuresis relationship, suggesting that androgens do contribute to the higher BP measured in males. In addition, androgen receptor blockade lowers BP in male SHR to the level of female SHR and appears to protect against hypertension and end-organ damage. Reckelhoff et al also reported that the administration of testosterone to ovariectomized female SHR increases BP and modifies the pressure–natriuresis relationship. This latter finding would indicate that androgens could also play a role in the rise in BP observed in menopausal women. Yet, the role of androgens in mediating the increase in BP in post-menopausal women remains a topic of discussion. Several studies have also suggested that sex steroid hormones have direct vascular effects that may contribute to the gender differences in BP regulation.
Whether female sex hormones also modulate the renal handling of sodium and thereby contribute to the gender-associated differences observed in animal models and in humans is also a subject of controversy. In this review, we discuss the potential links among female sex hormone status, salt balance, and renal function and their possible influence on BP regulation. We also present recent results indicating that both endogenous and exogenous female sex hormones have important effects on the systemic and renal responses to changes in sodium intake in young, healthy, normotensive women, regardless of whether they are using oral contraceptives (OC), and in menopausal women who are not receiving hormonal replacement therapy.

Gender Differences in the Activity of the Renin-Angiotensin System

The renin-angiotensin system is one of the key hormonal systems regulating BP and modulating the pressure–natriuresis relationship. Several studies have reported gender differences in various components of the renin-angiotensin cascade that could partially explain the gender differences in BP. 17 Thus, in a normotensive population, plasma renin activity (PRA) has been reported to be higher in men than in women regardless of age and ethnic heritage. 18 Exogenous female sex hormones administered for oral contraception have also been shown to stimulate angiotensinogen production, which may lead to a increase in BP in some women. 19 Other studies have found that PRA is higher in post-menopausal than in pre-menopausal women, although PRA remains higher in men than in women of the same age. 17 In animals significant differences have also been observed between males and females. The administration of testosterone to ovariectomized female rats increases PRA, and PRA is lower in males after castration. 20,21 Finally, in Sprague-Dawley rats, a linear correlation between the levels of testosterone and plasma renin activity levels has been reported, 3,17 suggesting that testosterone stimulates the renin-angiotensin system. In accordance with this observation, several studies have found that androgens like oestrogens enhance renal angiotensinogen mRNA. 20,22

There is also some evidence that the response to a stimulation of the renin-angiotensin system differs in men and women. Thus, Miller et al have compared the renal hemodynamic response to the infusion of exogenous angiotensin II in young normotensive pre-menopausal women and in age-matched men and found striking differences. 23 Both groups exhibited an increase in BP and a decrease in effective renal plasma flow (ERPF) with angiotensin II, but only men maintained their glomerular filtration rate (GFR) resulting in an increased filtration fraction. In women, the administration of angiotensin II decreased GFR, leading to a reduction in filtration fraction. This has been interpreted as a lesser increase in intraglomerular pressure in women, an observation which may play a role in renal disease progression. The incidence of end-stage renal disease is indeed lower in women than in men even after adjustment for age and race. 24 Furthermore, the rate of progression to end-stage renal disease is often slower in women than in men, independently of BP or serum cholesterol levels. 25
Premenstrual symptoms 8/17 12/18

FIG. 1. Pressure–natriuresis relationship in normotensive women during the normal menstrual cycle, during use of oral contraceptives, and after menopause. All women received randomly a diet low in sodium (40 mmol Na/day) and high in sodium (250 mmol Na/day) for 7 days. Blood pressure was measured over 24 h using ambulatory blood pressure monitoring.

Characteristics of these subjects are presented in Table 1. All subjects were randomized to receive a diet low in sodium (40 mmol Na/day) and a diet high in sodium (250 mmol Na/day) for 7 days during 2 consecutive months. At the end of each 7-day diet period, 24-h ambulatory BP as well as renal hemodynamics and renal sodium handling and an hormonal profile were measured.35–39

As shown in Fig. 1, we found that the BP and heart rate response to salt is comparable in the luteal and in the follicular phases of the normal menstrual cycle. In both phases of the cycle, the pressure–natriuresis relationship is steep, suggesting that these women are essentially insensitive to salt. The administration of OC does not modify the pressure–natriuresis relationship, suggesting little if any effect of exogenous female sex hormones on the BP response to salt. In contrast, the pressure–natriuresis curve of menopausal women is significantly shifted to the right, indicating that BP becomes salt sensitive after the menopause as suggested previously by Weinberger et al.40

Unfortunately, our study does not allow any conclusion

Table 1. Characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Follicular (n = 17)</th>
<th>Luteal (n = 18)</th>
<th>Contraceptive (n = 27)</th>
<th>Menopause (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>27.6</td>
<td>29.1</td>
<td>26</td>
<td>49*</td>
</tr>
<tr>
<td>Range</td>
<td>21–40</td>
<td>20–39</td>
<td>20–40</td>
<td>43–50</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>7/17</td>
<td>9/18</td>
<td>14/27</td>
<td>9/12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21 ± 0.6</td>
<td>21.4 ± 0.9</td>
<td>20.8 ± 0.5</td>
<td>25.3* ± 1.2</td>
</tr>
<tr>
<td>Premenstrual symptoms</td>
<td>8/17</td>
<td>12/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>27.6 ± 0.5</td>
<td>28.6 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>108.8/74.9</td>
<td>110.3/76.1</td>
<td>108/72</td>
<td>117.8* /80.5*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77.3 ± 3</td>
<td>76.1 ± 3</td>
<td>82 ± 2</td>
<td>80.9 ± 2.5</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>83.1 ± 2</td>
<td>83.2 ± 2</td>
<td>76 ± 2</td>
<td>87 ± 2</td>
</tr>
<tr>
<td>UₙaV (μmol/min)</td>
<td>197 ± 16</td>
<td>182 ± 11</td>
<td>168 ± 12</td>
<td>194 ± 18</td>
</tr>
</tbody>
</table>

BMI = body mass index; UₙaV = urinary sodium excretion.
Data are mean ± SEM.
* P < .05 v other phases.
about the main mechanism of this increase in salt sensitivity that develops after the menopause and, particularly, whether it is due to aging only or to the modification of the hormonal profile. In humans, some studies have suggested that the BP increase after the onset of menopause is linked to a reduced synthesis of estradiol or to an imbalance between androgens and female sex hormones, but this remains to be demonstrated. Nevertheless, our results may provide new clues to explain why the incidence of hypertension clearly increases in post-menopausal females, exceeding that in age-matched men. Indeed, if sodium intake is not reduced, the increased responsiveness to sodium at the menopause may contribute to increase BP and to favour the development of hypertension. Of note, the menopause is often associated with a weight gain, and the prevalence of obesity is higher in post-menopausal women than in age-matched men. This would indicate that sodium intake is certainly not reduced in menopausal men. We have also reported previously that the increase in body weight occurring at the time of the menopause is actually associated with a significant increase in ambulatory BP.

**Female Sex Hormones and the Renal Hemodynamic Response to Salt**

The literature is also conflicting concerning the possible changes in renal hemodynamics occurring during the normal menstrual cycle. Indeed, using either endogenous creatinine clearance or [51Cr] EDTA clearance, some investigators have reported small increases in GFR together with either no change or an increase in renal plasma flow during the luteal phase, whereas others found no change in body weight occurring at the time of the menopause is actually associated with a significant increase in ambulatory BP.

In our normotensive subjects studied either during the follicular or during the luteal phase of their menstrual cycle, GFR and renal plasma flow were similar in the two phases of the cycle when subjects were studied while receiving a low sodium diet. However, whereas salt loading had no effect on renal hemodynamics in the follicular phase, the administration of salt during the luteal phase induced a marked renal vasodilation with no change in GFR (Fig. 2). Hence, a significant decrease in filtration fraction was observed while receiving high salt during the luteal but not during the follicular phase. Plasma renin activity (PRA) and aldosterone levels decrease significantly after sodium loading in the two phases of the menstrual cycle. Yet, the salt-induced suppression of PRA is partly blunted in the luteal compared with the follicular phase.

Thus, our data suggest that in contrast to arterial pressure, the control of the renal circulation is salt sensitive during the luteal phase of the menstrual cycle and that endogenous female sex hormones act in a direct or indirect way on glomerular hemodynamics with a possible effect on the efferent arteriole, inasmuch as the filtration fraction decreases upon salt loading. By comparison, the renal hemodynamic response to salt in young normotensive male subjects is characterized by an increase in renal plasma flow and a concomitant rise in GFR, which was not observed in women studied in the luteal phase. To explain the salt-induced renal vasodilatation and fall in filtration fraction in women studied during the luteal phase, we propose the hypothesis that estrogens modulate the renal hemodynamics indirectly via the nitric oxide (NO) pathway and perhaps prostaglandin formation, thereby inhibiting the effects of angiotensin II on glomerular hemodynamics. Indeed, estrogen levels are high in the luteal phase, and estradiol has been shown to increase local prostaglandin E2 (PGE2) and I2 (PGI2) production and to activate NO synthase. Because NO has been proposed as a physiologic antagonist of angiotensin II and because blockade of endothelium-derived NO synthesis has been shown to increase intraglomerular pressure and perhaps prostaglandin synthesis, the effect of angiotensin II on glomerular hemodynamics and particularly on efferent arteriolar tone. Through this mechanism, estrogens could cause renal vasodilation and a decrease in filtration fraction.

There are few data on the renal hemodynamic effects of OC. An early study by Hollenberg et al has shown that OC in healthy young women reduces the effective
renal plasma flow, an effect that appears to be due to an activation of the renin-angiotensin system by OC. The administration of OC has also been found to increase creatinine clearance in young women studied while receiving a free sodium intake. Kang et al reported significant increases in systolic BP, renal vascular resistance, and filtration fraction in OC users compared with nonusers and showed that these differences were at least partially abolished by angiotensin II blockade. Based on their data, the authors have suggested that despite humoral evidence of renin angiotensin system activation by OC, the tissue response may actually be down-regulated, perhaps at a receptor level. In a more recent study, Ribstein et al failed to confirm that the renin-angiotensin system plays a prominent role in maintaining a high BP in women with OC-associated hypertension.

In our normotensive women, OC had a marked influence on the renal hemodynamic response to salt, although systemic BP was not affected (Fig. 2). Indeed, upon salt loading, GFR increased significantly in women taking OC, whereas renal plasma flow was unchanged; consequently, filtration fraction was significantly increased, suggesting an increased intraglomerular pressure. Importantly, plasma renin activity in our OC users was several-fold higher than the activity measured in OC nonusers studied at comparable levels of salt intake. Therefore, the mechanism resulting in the salt-induced increase in GFR in OC users may actually be the same as the one that we hypothesized to occur during the luteal phase of the menstrual cycle but with one important difference: namely, the baseline activity of the renin-angiotensin system. Thus, in OC users, the vasodilatory effect of estrogens may be more prominent at the level of the afferent arteriole, thereby leading to an increase in GFR and filtration fraction. An alternative explanation for the apparent difference between endogenous and exogenous female sex hormones, as reflected by the more pronounced effect of salt loading on renal hemodynamic in OC users than in nonusers, is perhaps a difference in potency between endogenous and exogenous female sex hormones. Indeed, combined OC agents deliver pharmacologic levels of estrogens that exhibit six to 10 times the estrogenic activity provided by endogenous estrogens.

Several investigators have found that sodium induces a renal vasoconstriction in salt-sensitive patients. We found a similar pattern, with a salt-induced reduction in renal plasma flow and an increase filtration fraction, in our group of salt-sensitive normotensive menopausal women. This maladaptive response to a sodium load may be attributed to a lack of estrogens leading again to a reduced capacity of the renal circulation to vasodilate. An endothelial dysfunction has frequently been observed after the menopause, with an impaired systemic endothelium-dependent relaxation. In addition, it is also known that PRA is higher in post-menopausal than in pre-menopausal women. In our evaluation of normotensive menopausal women, suppression of PRA is blunted after salt loading. At the time of menopause, in addition to aging and together with the loss of estradiol (which is known to decrease renin release), this poor suppression of renin by salt could contribute to the development of salt-sensitive hypertension in elderly women and may reflect an interaction between the renin system and menopausal status.

Altogether, our results demonstrate that endogenous as well as exogenous female sex hormones strongly affect the renal hemodynamic response to salt in young normotensive women, although these hormones do not affect the BP response to sodium.

**Female Sex Hormones and Renal Sodium Handling**

The menstrual cycle as well as the menopause are characterized by great variations in plasma progesterone, estrogen, aldosterone, and plasma renin activity—hormonal systems that are known to modulate the renal tubular handling of sodium either in the proximal or in the distal nephrons. In addition, androgen receptors have been localized in the proximal tubule segment of the nephron, suggesting that testosterone could also affect renal sodium reabsorption. So far, several studies have examined the effects of female sex hormones on the overall 24-h sodium excretion. The results of these studies are often contradictory, perhaps because most studies were conducted in subjects ingesting uncontrolled amounts of sodium or because subjects were receiving large amounts of water to measure renal function, which is an important confounding factor interacting with renal sodium handling. None of these studies have really attempted to analyze in more detail the respective changes in proximal and distal sodium reabsorption occurring either during the normal menstrual cycle or with the administration of OC.

In the past few years, we have used the endogenous lithium clearance technique to investigate the respective changes in proximal and post-proximal tubular sodium reabsorption to investigate the tubular adaptation occurring with large changes in sodium intake in normotensive as well as hypertensive individuals. This technique is currently considered to be the most reliable approach to investigate proximal segmental renal sodium handling in humans. When young normotensive men are shifted from a low-salt to a high-salt diet, the lithium clearance increases significantly and the fractional distal reabsorption of sodium decreases, indicating that both the proximal and the distal reabsorptions of sodium are reduced to maintain sodium balance.

Similar investigations were conducted in our normotensive women, and significant differences in tubular responses were observed between the follicular and the luteal phases. In the follicular phase, the renal tubular response to a sustained increase in sodium intake is comparable to that in men. In contrast, during the luteal phase, increasing sodium intake leads to a marked sodium escape from the distal nephron and no change in proximal sodium reabsorption, suggesting that while maintaining a diet high
in sodium, the sodium balance is controlled mainly by the distal segments of the nephron with a paradoxical increase in sodium reabsorption in the proximal nephron. Thus, the relationship between the proximal reabsorption of sodium as measured by the fractional excretion of lithium (FELi) and the overall fractional excretion of sodium (FE Na) is flat and significantly different from that in women studied in the follicular phase (Fig. 3). The finding of significantly reduced sodium reabsorption in the distal nephron in the luteal phase when consuming a high-salt diet may reflect the pivotal role of progesterone to act as an anti-aldosterone compound and to participate in the maintenance of sodium balance during the premenstrual phase. This effect of progesterone is particularly demonstrable with a high-salt diet when circulating aldosterone levels are low. The increased reabsorption of sodium in the proximal tubule with a high-salt diet is more surprising. Although one cannot exclude a direct tubular effect of progesterone to stimulate proximal sodium reabsorption, possibly in relation with the renal vasodilation, we believe that the low lithium clearance represents a compensatory mechanism of the proximal tubule to avoid an excessive loss of sodium by the distal nephron, thereby preventing sodium wasting and maintaining sodium balance. The increase in proximal sodium reabsorption may actually provide a clue for the blunted salt-induced decrease in plasma renin activity observed in the luteal phase compared with the follicular phase as discussed earlier here. Indeed, as sodium reabsorption is enhanced in the proximal segments of the nephron, the delivery of sodium to the macula densa is reduced. A decreased sodium delivery at the juxta-glomerular apparatus will stimulate renin secretion. In turn, the increased PRA and angiotensin II further enhance the sodium reabsorption by the proximal nephron.

Endogenous progesterone is known to be natriuretic, but synthetic derivatives of progesterone may lack natriuretic properties, for they have decreased affinity for renal mineralocorticoid receptors. In our young patients using OC, the renal tubular handling of sodium was similar to that observed in normal women in the follicular phase. However, the FELi /FE Na relationship is shifted to lower levels of FELi (Fig. 3). This shift may be attributed to the activation of the renin-angiotensin system by OC, leading to an increased proximal reabsorption of sodium. A high reabsorption of sodium was also found to occur in the distal tubule as reflected by the very high distal reabsorption of sodium. Thus, combined OC do not appear to affect the balance between the proximal and the distal nephron segments. However, because of the activation of the renin-angiotensin system, women using OC may have a greater tubular responsiveness.

**Effect of Sodium Loading on Body Weight in Women**

Despite the common belief that women gain weight premenstrually because of sodium retention, there is little convincing evidence that sodium and water retention indeed occur during the luteal phase of a normal menstrual cycle. We found that under carefully controlled sodium diets, a high sodium intake induces a weight gain of the same magnitude in the follicular and the luteal phase of the cycle (≈1.0 kg), showing that no systematic sodium retention occurs in the luteal phase of the normal menstrual cycle (Fig. 4). This observation was based on weight determination, which of course provides no information on water redistribution within the body. The results suggest that the symptoms of edema and bloating reported by some women in the second phase of the cycle may be due to either a redistribution of fluid from the intravascular into the interstitial compartment rather than to sodium retention or to increased sodium appetite during the luteal phase of the menstrual cycle. When the diet is changed from a low-salt to a high-salt diet, the weight gain is comparable in women using OC. However, the weight gain is significantly more marked in menopausal women (+2.5 kg for comparable changes in sodium intake).
tivariate analysis of the four groups disclosed that salt-induced change in body weight was a strong determinant of the change in BP (\( P < .03; 95\% \) confidence interval 0.10 to 2.28).

**Conclusion**

In conclusion, endogenous and exogenous sex female hormones profoundly influence systemic and renal response to salt in women. Our data show that the BP of young normotensive women, regardless of whether they are using contraceptives, is rather insensitive to salt, with a normal pattern of adaptation of renal proximal and distal reabsorption to changing salt intake. In contrast, women become salt sensitive after menopause. In contrast to the systemic pressure, the renal hemodynamic response to salt is modulated by female sex hormones. These hormones also affect the regulation of sodium excretion. These recent observations provide new insights into potential mechanisms explaining the lower incidence of cardiovascular disease and the lower rate of progression of renal disease in pre-menopausal women, which tend to disappear with menopause. They also emphasize the importance of considering more carefully the phase of the menstrual cycle whenever conducting physiologic and pharmacologic studies in pre-menopausal women and when enrolling women in clinical studies, to prevent the strong influence of progesterone and high levels of estrogens on renal and systemic parameters. The increased salt sensitivity in menopausal women strongly encourages the use of diuretics in hypertensive women, which is in agreement with recent hypertension guidelines.

**References**
