Kidney International, Vol. 61 (2002), pp. 425–431

Renal segmental tubular response to salt during the normal menstrual cycle

Antoinette Pechère-Bertschi, Marc Maillard, Hans Stalder, Hans R. Brunner, and Michel Burnier

Policlinique de Médecine and Division of Endocrinology, University Hospital, Geneva, and Division of Hypertension and Vascular Medicine, University Hospital, Lausanne, Switzerland

Renal segmental tubular response to salt during the normal menstrual cycle.

Background. It has been suggested that women gain weight and develop peripheral edema during the luteal phase of the menstrual cycle because they tend to retain sodium and water. However, there is actually no clear evidence for physiological, cyclic variations in renal sodium handling during the menstrual cycle. We prospectively assessed the changes in segmental renal sodium handling occurring during the menstrual cycle in response to changes in salt intake.

Methods. Thirty-five normotensive women were enrolled. Seventeen women were randomized and studied in the follicular and 18 in the luteal phases of their menstrual cycle. All women were assigned at random to receive a low (40 mmol/day) or a high (250 mmol/day) sodium diet for seven days on two consecutive menstrual cycles. Renal sodium handling and hemodynamics were measured at the end of each diet period.

Results. The changes in sodium intake induced comparable variations in sodium excretion in both phases of the menstrual cycle. In the follicular phase, the increase in salt intake was associated with no change in renal hemodynamics, an increased fractional excretion of lithium (FE_{Li}) and a decreased fractional distal reabsorption of sodium (FDR_{Na}), suggesting that sodium reabsorption is reduced both in the proximal and the distal tubules. In contrast, in the luteal phase, the renal response to salt was characterized by a significant renal vasodilation and a marked salt escape from the distal nephron, compared to the women investigated in the follicular phase ($P < 0.01$). Sodium reabsorption by the proximal nephron was not reduced as indicated by the unchanged FE_{Li}.

Conclusions. These results show that the segmental renal handling of sodium differs markedly in the two phases of the menstrual cycle. They suggest that the female hormones modulate the renal handling of sodium at the proximal and distal segments of the nephron in young normotensive women.

Key words: sodium, endogenous lithium, renal hemodynamics, female sex hormones, luteal phase, follicular phase.

Received for publication April 6, 2001
and in revised form August 16, 2001
Accepted for publication September 19, 2001

The luteal phase of the normal menstrual cycle is associated with several hormonal changes such as increases in plasma progesterone, estrogens, aldosterone and plasma renin activity, which at least theoretically could promote an increased reabsorption or modulation of sodium handling by the kidneys [1–6]. However, despite the common belief that women gain weight premenstrually due to sodium retention, there is little convincing evidence that sodium and water retention indeed occurs during the luteal phase of a normal menstrual cycle. Some studies have found a cyclic change in body weight in some women, but it was not consistently observed during the luteal phase and the observation was not always reproduced in subsequent hormonal cycles [7–9]. In addition, several other studies actually failed to demonstrate any significant cyclic variations in body weight during normal menstrual cycles [10–14].

Today, the effects of estrogens and progesterone on the renal tubular function remain poorly understood. In fact, very few studies have examined the influence of the female sex hormones on renal sodium excretion carefully and prospectively [13–17], and the salt-induced variations in proximal and distal sodium reabsorption have never been examined carefully during the two phases of the normal menstrual cycle. Thus, it is still not clear if there are physiological, cyclic variations of sodium handling during the normal menstrual cycle, or rather a redistribution of fluid volume from the intravascular to the extravascular space related to an increased permeability in limb vessels and peripheral vasodilation [18, 19]. We have reported recently that young normotensive women evaluated on a low and high sodium diet have a blood pressure response to salt that is comparable in the follicular and the luteal phases of the normal menstrual cycle and is characterized by a salt-resistant pattern. However, we have found that salt loading induces significantly different renal hemodynamic responses during the menstrual cycle [20]. In the luteal phase an increase in salt intake induces a renal vasodilation and a decrease in

filtration fraction, whereas in the follicular phase sodium loading had no renal hemodynamic effect.

Our study describes the changes in tubular responses to sodium occurring during the two phases of the menstrual cycle in healthy, normotensive women. Using a protocol in which the sequence of administration of low and high sodium diets was randomized, we show that the follicular and the luteal phases of the normal menstrual cycle are characterized by marked differences in proximal and distal tubular responses to sodium.

METHODS

Subjects

Thirty-five normotensive female volunteers recruited mostly among the medical students and the hospital staff of the University Hospital of Geneva were enrolled in this study. All women were healthy, not pregnant, and had regular menstruations not varying by more than three days between cycles. None was taking oral contraceptives or any medication known to affect renal function. At the initial visit, a full medical history and a clinical examination were undertaken. The subjects were asked on which date their last cycle began, and on the usual length of their menstrual cycle over the last 12 months. Women with irregular cycles or with cycles longer than 32 days were not included. The volunteers were randomly assigned into two groups to study their follicular or luteal phase of their cycle. A total of 17 women were allocated to the follicular phase and 18 to the luteal phase. The study protocol was reviewed and approved by the institutional ethics committee (University Hospital, Geneva), and all subjects gave their written informed consent.

Clinical investigation

After being characterized on their regular sodium intake, the volunteers were randomized to receive a low (40 mmol sodium per day) or a high (250 mmol sodium per day, by adding 6 g of salt in their usual diet) sodium diet for a seven-day period during two consecutive menstrual cycles. The diets were conducted at home and all women received detailed recommendations on how to follow a low salt diet. After each seven-day diet period, 24-hour urines were collected separately during the day (8 a.m. to 10 p.m.) and during the night (10 p.m. to 8 a.m.) in order to measure sodium excretion. Concomitantly, 24-hour blood pressure values were recorded using ambulatory blood pressure monitoring (Profilomat; Disetronic, Burgdorf, Switzerland). This device has been validated by the British Hypertension Society and was rated B/A.

On the next day, the volunteers were admitted to the hospital at 8.30 a.m. after an overnight fast to measure their renal function. Renal hemodynamics were measured using sinistrin (an analog of inulin) and paraaminohippuric acid (PAH) clearances as described previously [21]. After lying quietly in a supine position for a 90 minute period of equilibration and the administration of an oral water load of 5 mL/kg to ensure a stable urine output, the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF) were measured twice, in two 90-minute clearance intervals.

Analytic procedures

Sodium excretion was expressed as $U_{Na}V$ in mmol/day or μmol/min, where U_{Na} is the urinary sodium concentration and V is the urinary volume expressed either in mL/24 h or in mL/min. Proximal renal sodium handling was assessed by the determination of endogenous lithium in plasma and urine using graphite furnace atomic absorption spectrophotometry [22, 23] and by the fractional excretion of lithium and sodium using the standard formula (FE_X = clearance of x divided by the GFR). In addition, the fractional distal reabsorption of sodium, i.e., the percentage of the distally delivered sodium reabsorbed in the post-proximal nephron segments, was calculated as $[(FE_{Li} - FE_{Na})/FE_{Li}] * 100$. Plasma catecholamines were determined by high performance liquid chromatography (HPLC) [24], and plasma renin activity (PRA) and aldosterone by radioimmunoassay [25, 26]; atrial natriuretic peptide (ANP) and arginine vasopressin (AVP) also were measured after one hour of the subject in a supine position [27, 28]. Plasma progesterone levels were measured using an enzyme immunoassay (Kryptor, CIS bio, Saclay, France) in all patients to characterize the phase of the cycle. Sinistrin (Inutest®) was purchased from Laevosan Gesellschaft (Zürich, Switzerland) and PAH from SERB, Laboratoires pharmaceutiques (Paris, France).

Statistics

All results are expressed as mean ± standard error (SEM). Data were then analyzed using the paired or unpaired Student *t* test for independent samples when appropriate.

RESULTS

The baseline characteristics of the women included in this study and evaluated on a free sodium diet are presented in Table 1. Briefly, the volunteers investigated in the follicular and the luteal phases were comparable in age, body mass index, average cycle length, and serum creatinine. The two groups had a comparable usual daily sodium intake as reflected by their urinary sodium excretion on a free diet. More than half of the subjects in each group suffered from mild premenstrual symptoms of swelling and bloating. As expected plasma progesterone levels were significantly higher in the luteal than in

Table 1. Characteristics of the patients on a free sodium diet[a]

	Follicular phase $N=17$	Luteal phase $N=18$
Age *years*	27.6	30.1
range	21–40	20–39
Systolic/diastolic BP *mm Hg*		
day time	109 ± 1/75 ± 1	110 ± 2/76 ± 2
night time	98 ± 2/64 ± 3[b]	99 ± 2/65 ± 2[b]
Heart rate *bpm*	77 ± 3	76 ± 2
Weight *kg*	60 ± 2.1	60 ± 3
BMI kg/m^2	21 ± 0.7	22 ± 0.9
Cycle's length *days*	28 ± 0.5	29 ± 0.6
Premenstrual symptoms	8/17	12/18
Cycle's study day	9.4 ± 0.6	26 ± 0.7
range	5–14	20–30
Serum creatinine *μmol/L*	83 ± 2	83 ± 2
$U_{Na}V$ *μmol/min*	197 ± 16	182 ± 11

Abbreviations are: BP, blood pressure; BMI, body mass index; $U_{Na}V$, urinary sodium excretion. Values are mean ± SE.

[a] These data were obtained one month before the dietary intervention was started in the same corresponding phase of the cycle; the same day of the cycle was studied on low and high salt

[b] $P < 0.01$ vs. daytime

Table 2. Systemic and renal hemodynamic response to salt in the normal menstrual cycle

	Follicular ($N=17$)		Luteal ($N=18$)	
Na diet *mmol/day*	low 40	high 250	low 40	high 250
Systolic BP *mm Hg*				
daytime	108 ± 1	110 ± 3	108 ± 2	110 ± 2
nighttime	96 ± 2[a]	100 ± 3[a]	94 ± 2[a]	97 ± 2[a]
Diastolic BP *mm Hg*				
daytime	75 ± 2	74 ± 1	72 ± 1	74 ± 2
nighttime	65 ± 2[a]	65 ± 2[a]	63 ± 2[a]	65 ± 2[a]
Heart rate *beats/min*				
daytime	81 ± 4	80 ± 2	80 ± 2	79 ± 2
nighttime	65 ± 3[a]	66 ± 2[a]	62 ± 2[a]	65 ± 2[a]
GFR $mL/min/1.73\ m^2$	91 ± 4	95 ± 2.8	96 ± 5	95 ± 6
ERPF $mL/min/1.73\ m^2$	463 ± 24	447 ± 20	464 ± 26	532 ± 36[b,c]
FF *%*	19.8 ± 1	22 ± 1	20.6 ± 1	17.8 ± 1[b,d]
Body weight *kg*	59.9 ± 2.3	60.5 ± 2.2	59.4 ± 3.1	60.6 ± 3.0

Abbreviations are: BP, blood pressure; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction. Values are mean ± SE.

[a] $P < 0.01$ daytime vs. nighttime

[b] $P < 0.05$ high vs. low salt diet

[c] $P < 0.05$ and [d] $P < 0.01$ vs. follicular

Table 3. Segmental renal sodium handling response to salt loading in the normal menstrual cycle

	Follicular ($N=17$)		Luteal ($N=18$)	
Na diet *mmol/d*	low 40	high 250	low 40	high 250
Plasma Na *mmol/L*	139 ± 0.4	140 ± 0.5	139 ± 0.5	140 ± 0.5
Plasma K *mmol/L*	3.8 ± 0.06	3.8 ± 0.04	3.9 ± 0.05	3.9 ± 0.05
$U_{Na}V$ *μmol/min*				
daytime	30 ± 3	183 ± 17[f]	39 ± 5	178 ± 16[f]
nighttime	25 ± 4	125 ± 18[af]	34 ± 7	118 ± 13[af]
U_KV *μmol/min*				
daytime	45 ± 5.1	41 ± 5.3	51 ± 5.2	55 ± 8.0
nighttime	33 ± 3.2[b]	27 ± 5.2[a]	43 ± 5.2[a]	46 ± 6.2[d]
Urinary volume *L*				
daytime	1.50 ± 0.2	1.52 ± 0.2	1.41 ± 0.16	1.34 ± 0.6
nighttime	0.48 ± 0.7[b]	0.66 ± 0.13[b]	0.45 ± 0.06[b]	0.47 ± 0.10[b]
FE_{Na} *%*				
daytime	0.24 ± 0.02	1.37 ± 0.13[f]	0.31 ± 0.04	1.26 ± 0.08[f]
nighttime	0.20 ± 0.03	0.95 ± 0.11[f]	0.25 ± 0.04[a]	0.97 ± 0.08[bf]
FE_{Li} *%*				
daytime	19.4 ± 2.2	30.4 ± 7[e]	15.6 ± 1.8	14.2 ± 1.3[d]
nighttime	18 ± 3	29.5 ± 7.5[e]	16.1 ± 1.9	18.2 ± 2.4[ac]
FDR_{Na} *%*				
daytime	98.6 ± 0.2	93.7 ± 1[f]	98 ± 0.3	90 ± 1.3[df]
nighttime	98.6 ± 0.2	94.9 ± 0.8[f]	98.3 ± 0.3[b]	93 ± 1.2[af]

Abbreviations are: FE_{Na}, fractional excretion of sodium; FE_{Li}, fractional excretion of lithium; FDR_{Na}, fractional distal reabsorption of sodium.

[a] $P < 0.05$ and [b] $P < 0.01$ vs. day

[c] $P < 0.05$ and [d] $P < 0.01$ vs. follicular

[e] $P < 0.05$ and [f] $P < 0.01$ high vs. low

the follicular phase and were not affected by the sodium diets (see later in Table 4).

Systemic and renal hemodynamic responses to salt

The salt-induced changes in day- and nighttime ambulatory blood pressure, heart rate and renal hemodynamics published previously [20] are summarized in Table 2. A significant nocturnal decrease in systolic and diastolic blood pressure was found in both phases of the cycle whatever the diet. However, no significant difference in daytime and nighttime ambulatory blood pressure and heart rate was observed on a high and low sodium intake, when the follicular phase is compared with the luteal phase. Changes in salt intake had no significant effect on the GFR whatever the phase of the cycle. However, a marked increase in the ERPF was observed on a high salt diet in the luteal phase compared to the follicular phase and compared to the low salt diet. Thus, on high salt, filtration fraction was significantly lower in the luteal phase.

Segmental renal sodium handling during the menstrual cycle and the effect of salt

In the two phases of the menstrual cycle, significant increases in body weight were observed when the women were switched from a low to a high sodium intake. However, the weight gain was comparable in both phases of the cycle (Table 2). Table 3 shows the diet-induced changes in overall sodium excretion and proximal and distal renal sodium handling. As expected, the daytime and nighttime urinary sodium excretion increased significantly from a low to a high sodium intake in the two phases of the menstrual cycle ($P < 0.01$), indicating that compliance to the regimen was excellent in these groups of women. On a high salt diet, nighttime sodium excretion was always lower than daytime sodium excretion whatever the phase of the menstrual cycle. The diet-induced variations in fractional excretion of sodium (FE_{Na}), which corrects sodium excretion for GFR, were of the same magnitude in the follicular and in the luteal phases of the menstrual cycle. However, marked differences in proximal and distal sodium handling were found when women studied in the follicular phase were compared to

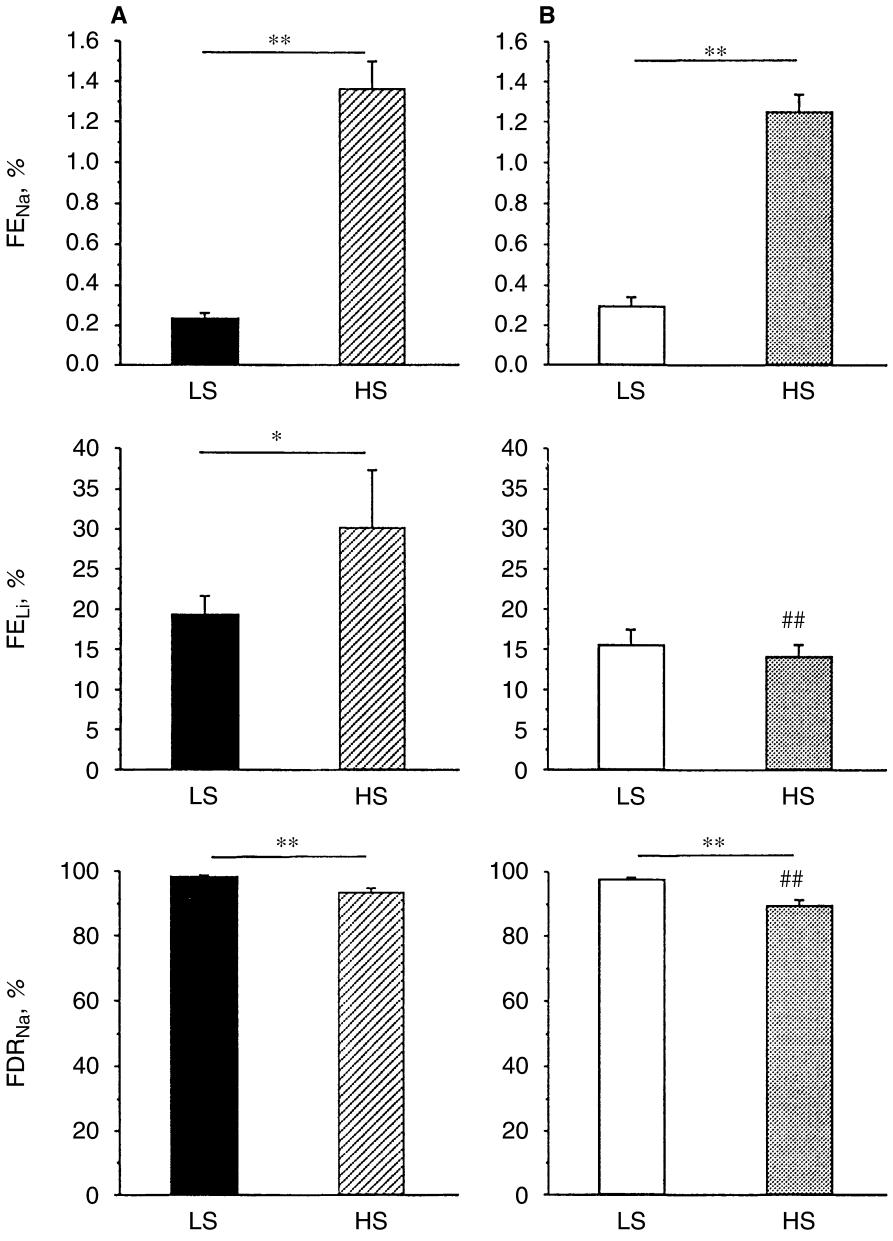

Fig. 1. Salt-induced variations in daytime fractional excretions of sodium (FE_{Na}) and endogenous lithium (FE_{Li}) and fractional distal reabsorption of sodium (FDR_{Na}) in normotensive women studied during the follicular and the luteal phases of the menstrual cycle. Abbreviations are: LS, low salt diet defined as 40 mmol/day Na; HS, high salt diet at 250 mmol/day Na. $^{**}P < 0.01$ high vs. low salt diet; $\#\#P <$ 0.01 high salt luteal vs. high salt follicular.

those evaluated in the luteal phase (Fig. 1). During the follicular phase, the fractional excretion of endogenous lithium (FE_{Li}) increased significantly on a high sodium diet and the fractional distal reabsorption of sodium (FDR_{Na}) decreased slightly but significantly, indicating that sodium balance is maintained by a decrease in both proximal and distal sodium reabsorption. In contrast, during the luteal phase of the menstrual cycle, the FE_{Li} did not increase and a very marked fall in FDR_{Na} was observed on a high sodium intake. This latter finding suggests that in the luteal phase, sodium balance is controlled almost exclusively by the distal segments of the nephron. As shown in Table 3, the FE_{Li} of women studied in the luteal phase was significantly lower when they were on a high salt diet than that of women studied in the follicular phase ($P < 0.01$ vs. follicular).

Response of vasoactive hormones to sodium intake

The effects of changing sodium intake on the vasoactive hormones profile in the follicular and luteal phases are presented in Table 4. As expected, plasma progesterone levels were significantly higher ($P < 0.01$) in the luteal phase of the cycle and the sodium intake had no effect on this parameter. Plasma renin activity and aldosterone levels decreased significantly ($P < 0.01$) after sodium loading in the two phases of the menstrual cycle. Yet, the suppression of PRA and aldosterone induced by the sodium load was partly blunted in the luteal

Table 4. Hormonal response to salt in the normal menstrual cycle

	Follicular ($N = 17$)		Luteal ($N = 18$)	
Na diet *mmol/day*	low 40	high 250	low 40	high 250
Progesterone *ng/mL*	0.7 ± 0.2	0.7 ± 0.2	6.8 ± 1.5[d]	7.1 ± 1.7[d]
PRA *ng/mL/h*	0.86 ± 0.15	0.13 ± 0.03[b]	1.01 ± 0.24	0.28 ± 0.07[bd]
Aldosterone *nmol/L*	0.38 ± 0.04	0.11 ± 0.02[b]	0.49 ± 0.07	0.16 ± 0.02[bd]
AVP *pg/mL*	0.47 ± 0.08	0.50 ± 0.09	0.39 ± 0.05	0.61 ± 0.13
ANP *pg/mL*	45.6 ± 5.1	61.6 ± 8.2	45.2 ± 6.1	66.8 ± 9.2[a]
Norepinephrine *nmol/L*	2.18 ± 0.36	2.15 ± 0.22	3.34 ± 0.47[c]	2.38 ± 0.3

Abbreviations are: PRA, plasma renin activity; AVP, arginine-vasopressin; ANP, atrial natriuretic peptide.
[a] $P < 0.05$ and [b] $P < 0.01$ vs. low
[c] $P < 0.05$ and [d] $P < 0.01$ vs. follicular

compared with the follicular phase ($P < 0.05$). Plasma norepinephrine levels were significantly higher in sodium-depleted women studied in the luteal than in those evaluated in the follicular phase ($P = 0.03$). Plasma atrial natriuretic peptide (ANP) levels increased significantly ($P < 0.05$) after sodium loading in women studied in the luteal phase.

DISCUSSION

The results of this study demonstrate that the renal response to salt differs markedly in women investigated in the luteal and the follicular phases of the normal menstrual cycle. In the follicular phase, the renal response to a sustained increase in sodium intake is characterized by no change in renal hemodynamics and decreases in both proximal and distal sodium reabsorption. In contrast, during the luteal phase, increasing sodium intake leads to a renal vasodilation, a marked sodium escape from the distal nephron, and no change in proximal sodium reabsorption. These observations suggest that the female sex hormones, in particular progesterone, modulate the renal tubular response to sodium in normal women.

The cyclic changes in urinary sodium excretion and body weight occurring during the normal menstrual cycle have been the topic of many investigations that to date have provided relatively contradictory results [7–16]. Most studies were performed on subjects ingesting an unrestricted and uncontrolled sodium diet, and they often were given large amounts of water to investigate renal function. We have recently demonstrated that acute water loading may be an important confounding factor interacting with renal sodium handling [29, 30]. This prospective study is the first, to our knowledge, to use a randomized design to investigate rigorously the effect of controlled changes in sodium intake on renal sodium handling during the normal menstrual cycle. Since the main changes occurred in segmental rather than overall Na handling, these could not be observed without specific investigation of proximal tubular sodium reabsorption using techniques, such as the endogenous lithium clearance, which enabled a separate analysis of the sodium handling by the proximal nephron and indirectly sodium reabsorption by the segments beyond the proximal tubule (combining the loop of Henle, the convoluted distal tubule and the collecting duct). This method is considered currently to be the most reliable technique to investigate segmental renal sodium handling in humans. There have been some concerns about lithium being reabsorbed in the distal nephron in rats on a low sodium diet [31]. In humans, however, there is no strong evidence that lithium is reabsorbed in the distal nephron, particularly when subjects were on a regular or high sodium diet [31]. Whether lithium is reabsorbed distally in subjects on a low salt diet is still debated. However, even in salt-depleted subjects, amiloride has been shown to increase sodium excretion without affecting the fractional excretion of lithium [31]. One limit of this method in the present study is that inter-individual variations may be large enough to mask true differences between phases of the menstrual cycle. This was perhaps the case on low salt diets where the differences were small and did not reach statistical significance.

Our earlier study in the same young normotensive women found that the blood pressure response to salt was comparable during the two phases of the menstrual cycle and was characterized by a salt-resistant pattern [20]. We also reported that the renal hemodynamic response to salt differed throughout the menstrual cycle, a high sodium intake leading to a renal vasodilation in the luteal phase but no change during the follicular phase. Since the glomerular filtration rate was not affected by the sodium intake, the filtration fraction was decreased in the luteal but not in the follicular phase with salt loading. This observation suggested that the control of renal plasma flow becomes salt-sensitive during the luteal phase. Since estrogen levels are high in the luteal phase and oestradiol has been shown to increase prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2) production and to activate nitric oxide synthase [32, 33], and sodium intake has been found to increase nitric oxide production in salt-resistant rats [34], we have proposed that estrogens may modulate the renal hemodynamics indirectly via the nitric oxide pathway and perhaps prostaglandin formation. Whether progesterone also plays a role in modulating this renal vasodilation remains a matter of debate [35–37].

In normotensive men, the administration of a high salt diet for one week leads to a significant increase in FE_{Li} and a decrease in FDR_{Na}, indicating that both the proximal and the distal reabsorptions are reduced to maintain sodium balance [30]. Identical changes were found in women studied during the follicular phase of the menstrual cycle. Interestingly, however, a different pattern was obtained in the luteal phase. In this period, a compa-

rable increase in sodium intake was associated with no increase in FE_{Li} and a marked decrease in the distal reabsorption of sodium. The precise effects of female sex hormones on renal tubular function so far are poorly understood. However, progesterone is known to be a natriuretic hormone possibly acting as a competitive mineralocorticoid receptor antagonist [38]. Thus, an increase in serum progesterone theoretically could lead to a relative escape of sodium from the distal nephron. Since progesterone has a lower affinity for mineralocorticoid receptors than aldosterone itself, the interference of progesterone with distal renal sodium handling should be more prominent when aldosterone levels are low and progesterone levels very high. This hormonal profile was actually found in women studied in the luteal phase who were on a high sodium diet. Thus, in our patients, the finding of a markedly reduced sodium reabsorption in the distal nephron 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 luteal phase of the menstrual cycle. The ability of progesterone to act as an anti-aldosterone compound during the luteal phase and to lead to a sodium loss, and a compensatory rise in plasma renin activity, has been proposed previously, but this effect has never been demonstrated at the tubular level in normal women as it is presented in this study [10, 38, 39]. The changes in proximal and distal renal sodium handling also may be a direct consequence of the renal vasodilation that is a primary event in the post-ovulatory period, as also found in this study. The renal vasodilation may result in an inappropriate increased proximal sodium reabsorption during high sodium intake through the tubuloglomerular feedback mechanism, which is then compensated by a decrease distal reabsorption of sodium. This mechanism is similar to that involved with regard to sodium handling during pregnancy [5, 40].

The unchanged fractional excretion of lithium when going from a low to a high salt diet in the luteal phase is somewhat surprising, and indicates that sodium reabsorption in the proximal tubule remains high despite the greater sodium intake. Based on the present findings one cannot exclude a direct tubular effect of progesterone to stimulate proximal sodium reabsorption. Two potential mechanisms could explain this phenomenon. The first is linked to the renal vasodilation as discussed above. However, the persistent proximal sodium reabsorption on a high sodium diet also may represent a compensatory mechanism of the proximal tubule to avoid an excessive loss of sodium by the distal nephron. Since the distal nephron is responsible for the fine-tuning of sodium excretion, a progesterone-induced interference with the distal sodium reabsorption should lead to sodium wasting. As a consequence, sodium reabsorption by the proximal tubule should be maintained to preserve sodium balance. The increase in proximal sodium reabsorption also may provide a clue for the blunted salt-induced decrease in plasma renin activity observed in the luteal phase compared to the follicular phase. 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 will stimulate renin secretion. In turn, the increased plasma renin activity and angiotensin II further enhance the sodium reabsorption by the proximal nephron.

The present study has some limitations. The first is that different women were studied in the follicular and in the luteal phases. Because of the amount of blood taken in each study phase, it was technically impossible to study both phases in all of the women. The second limitation is that neither the potassium nor the protein intake was controlled. Thus, the 24-hour urinary potassium excretion was significantly greater in women studied in the luteal phase than in those of the follicular phase. Yet, potassium intake was very stable in both groups when the diet was changed from a low to a high sodium intake. Thus, the difference in potassium intake could have accounted for some of the differences in renal hemodynamics and tubular parameters observed in the follicular and luteal phases, but not for the various responses to salt observed within each phase.

Finally, it is traditionally assumed that normal women gain weight premenstrually due to sodium retention, but there is very little scientific evidence to support this viewpoint. Some studies have reported a cyclical change in weight, not consistently premenstrual, and in contrast, studies reporting on a total of 199 subjects have shown no cyclic weight change during normal menstrual cycles [8, 11–15]. Here we demonstrate that carefully controlled sodium loading induces a weight gain of the same magnitude in the follicular and the luteal phases of the menstrual cycle. Thus, our results confirm that no systematic sodium retention occurs in the luteal phase of the normal menstrual cycle, based on weight determination, which 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 actually may result from a redistribution of fluid from the intravascular into the interstitial compartment rather than to sodium retention [18]. Yet, in some predisposed women suffering from marked pre-menstrual syndrome, an exaggerated and critical response with sodium retention cannot be ruled out.

In summary, this study demonstrates that the female sex hormones strongly affect the renal hemodynamic and the segmental tubular response to salt in young normotensive women. These results further emphasize the importance of considering the phase of the menstrual cycle whenever conducting physiological studies in pre-menopausal women. These initial observations also should establish the need for further investigations on the role of

female sex hormones on renal function in menopausal women, women receiving contraceptives or a hormonal replacement therapy.

ACKNOWLEDGMENTS

This work was supported by the Fonds National Suisse de la Recherche Scientifique (MB: Nr 32-42543.94). Dr. Pechère-Bertschi was supported by a Marie-Heim Vögtlin grant of the Fonds National Suisse de la Recherche Scientifique (Nr 3234-45005.95).

Reprint requests to Michel Burnier, M.D., Division of Hypertension and Vascular Medicine, CHUV, 1011 Lausanne, Switzerland.
E-mail: Michel.Burnier@chuv.hospvd.ch

REFERENCES

1. Katz FH, Romfh P: Plasma aldosterone and renin activity during the menstrual cycle. *J Clin Endocrinol Metab* 34:819–821, 1972
2. Munday MR, Brush MG, Taylor RW: Correlations between progesterone, Oestradiol and aldosterone levels in premenstrual syndrome. *Clin Endocrinol* 14:1–9, 1981
3. Brown JJ, Davies DL, Lever AF, Robertson JIS: Variations in plasma renin during the menstrual cycle. *Br Med J* 2:1114–1115, 1964
4. Michelakis AM, Yoshida H, Dormois JC: Plasma renin activity and plasma aldosterone during the normal menstrual cycle. *Am J Obstet Gynecol* 123:724–726, 1975
5. Chapman AB, Zamudio S, Woodmansee W, *et al*: Systemic and renal hemodynamic changes in the luteal phase of the menstrual cyclic mimic early pregnancy. *Am J Physiol* 273:F777–F782, 1997
6. Spaanderman MEA, van Beck E, Ekhart THA, *et al*: Changes in hemodynamic parameters and volume homeostasis with the menstrual cycle among women with a history of preeclampsia. *Am J Obstet Gynecol* 182:1127–1134, 2000
7. Thorn GW, Nelson KR, Thorn DW: A study of the mechanism of edema associated with menstruation. *Endocrinology* 22:155–163, 1938
8. Watson PE, Robinson MF: Variations in body-weight of young women during the menstrual cycle. *Br J Nutr* 19:237–248, 1965
9. Hassan Ahmad AK, Carter G, Tooke JE: Postural vasoconstriction in women during the normal menstrual cycle. *Clin Sci* 78:39–47, 1990
10. Michelakis AM, Stant EG, Brill AB: Sodium space and electrolyte excretion during the menstrual cycle. *Amer J Obstet Gynec* 109:150–154, 1971
11. Andersch B, Hahn L, Anderson M, Isaksson B: Body water and weight in patients with premenstrual tension. *Br J Obstet Gynaecol* 85:546–550, 1978
12. Edwards OM: Bayliss. Postural fluid retention with idiopathic oedema: Lack of relationship to the phase of the menstrual cycle. *Clin Sci Molec Med* 48:331–333, 1975
13. Bisson DL, Dunster GD, O'Hare JP, *et al*: Renal sodium retention does not occur during the luteal phase of the menstrual cycle in normal women. *Br J Obstet Gynaecol* 99:247–252, 1992
14. Olson BR, Forman MR, Lanza E, *et al*: Relation between sodium balance and menstrual cycle symptoms in normal women. *Ann Intern Med* 125:564–567, 1996
15. Edwards OM, Bayliss RIS: Urinary excretion of water and electrolytes in normal females during the follicular and luteal phases of the menstrual cycle: The effect of posture. *Clin Sci Molec Med* 45:495–504, 1973
16. Parboosingh J, Doig A, Michie EA: Renal excretion of water and solute during the normal menstrual cycle. *J Obst Gynaecol Br Comm* 80:978–983, 1973
17. Atherton JC, Bielinska A, Davison JM, *et al*: Sodium and water reabsorption in the proximal and distal nephron in conscious pregnant rats and third trimester women. *J Physiol* 396:457–470, 1988
18. Jones EM, Fox RH, Verow PW: Variations in capillary permeability to plasma proteins during the menstrual cycle. *J Obstet Gynaecol Brit Common* 73:666–669, 1966
19. Van Beek E, Houben AJHM, van Es PN, *et al*: Peripheral haemodynamics and renal function in relation to the menstrual cycle. *Clin Sci* 91:163–168, 1996
20. Pechère-Bertschi A, Maillard M, Stalder H, *et al*: Blood pressure and renal hemodynamic response to salt during the normal menstrual cycle. *Clin Sci* 98:697–702, 2000
21. Pechère-Bertschi A, Nussberger J, Decosterd L, *et al*: Renal response to the angiotensin II receptor subtype 1 antagonist irbesartan versus enalapril in hypertensive patients. *J Hypertens* 16: 385–393, 1998
22. Magnin JL, Decosterd LA, Centeno C, *et al*: Determination of trace lithium in biological fluids using graphite furnace atomic absorption spectophotometry. Variability of urine matrices circumvented by cation exchange solid phase extraction. *Pharmaceutica Acta Helv* 71:237–246, 1996
23. Steinhauslin F, Burnier M, Magnin JL, *et al*: Fractional excretion of trace lithium and uric acid in acute renal failure. *J Am Soc Nephrol* 4:1429–1437, 1994
24. Bauersfeld W, Ratge D, Knoll E, Wisser H: Determination of catecholamines in plasma by HPLC and amperometric detection. Comparison with a radioenzymatic method. *J Clin Chem Clin Biochem* 24:185–188, 1986
25. Bakiri F, Benmiloud M, Vallotton MB: The renin-angiotensin system in panhypopituitarism: Dynamic studies and therapeutic effects in Sheehan's syndrome. *J Clin Endocrinol Metab* 56:1042–1047, 1983
26. Kubasik NP, Warren K, Sine HE: Evaluation of a new commercial radioassay kit for aldosterone using an iodinated tracer. *Clin Biochem* 12:59–61, 1979
27. Nussberger J, Mooser V, Maridor G, *et al*: Caffeine-induced diuresis and atrial natriuretic peptides. *J Cardiovasc Pharmacol* 15:685–691, 1990
28. Brunner DB, Burnier M, Brunner HR: Plasma vasopressin in rats: Effect of sodium, angiotensin, and catecholamines. *Am J Physiol* 244:H259–H265, 1983
29. Burnier M, Pechère-Bertschi A, Nussberger J, *et al*: Studies of the renal effects of angiotensin II receptor blockade: The confounding factor of acute water loading on the action of vasoactive systems. *Am J Kid Dis* 26:108–115, 1995
30. Burnier M, Monod ML, Chiolero A, *et al*: Renal sodium handling in acute and chronic salt loading/depletion protocols: The confounding influence of water loading. *J Hypertens* 18:1657–1664, 2000
31. Koomans HA, Boer WH, Dorhout Mees EJ: Evaluation of lithium clearance as a marker of proximal tubule sodium handling. *Kidney Int* 36:2–12, 1989
32. Terragno NA, Terragno DA, Pacholczy D: Prostaglandins and the regulation of uterine blood flow in pregnancy. *Nature* 249:57–58, 1974
33. Weiner CP, Soain IL, Baykis SA, *et al*: Induction of calcium-dependent nitric oxide synthase by sex hormones. *Proc Natl Acad Sci USA* 91:5212–5216, 1994
34. Chen PY, Sanders PW: L-Arginine abrogates salt-sensitive hypertension in Dahl/Rapp rats. *J Clin Invest* 88:1559–1567, 1991
35. Miller VM, Vanhoute PM: Progesterone and modulation of endothelium-dependent response in canine coronary arteries. *Am J Physiol* 261:R1022–R1027, 1991
36. Hashimoto M, Akishita M, Eto M, *et al*: Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation* 92:3431–3435, 1995
37. Barbagallo L, Dominguez LJ, Licata G, *et al*: Vascular effects of progesterone. Role of cellular calcium regulation. *Hypertension* 37:142–147, 2001
38. Landau RL, Lugibihl K: Inhibition of the sodium retaining influence of aldosterone by progesterone. *Clin Endocrinol* 18:1237–1245, 1958
39. Sundsfjord JA, Aakvaag A: Plasma angiotensin II and aldosterone excretion during the menstrual cycle. *Acta Endocrinol* 64:452–458, 1970
40. Brochner-Mortensen J, Paaby P, Fjeldborg P, *et al*: Renal haemodynamics and extracellular homeostasis during the menstrual cycle. *Scand J Clin Lab Invest* 47:829–835, 1987