Role of RIHP and Renal Tubular Sodium Transporters in Volume Retention of Pregnant Rats

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Background: Normal pregnancy is characterized by sodium and water conservation and an increase in plasma volume that is required for an uncomplicated pregnancy. Renal interstitial hydrostatic pressure (RIHP) is significantly decreased in pregnant rats. This decrease in RIHP may play an important role in the sodium and water retention that characterizes normal pregnancy. Paradoxically this enhanced renal sodium and water reabsorption appear to conflict with the consistent findings of a general decrease in abundance of renal tubular sodium transporters during normal pregnancy. The objective of this review is to examine the apparent discrepancy between the increases in renal tubular sodium and water reabsorption, facilitated by decreases in RIHP, and the seemingly discordant decreases in abundance of renal tubular transporters during normal pregnancy in rats.

Methods: Western blots and immunohistochemistry were used to evaluate abundance and localization of renal tubular transporters. RIHP was measured directly and continuously via a polyethylene (PE) matrix that was implanted in the left kidney of rats at the age of 11 to 16 weeks.

Results: Average basal RIHP and fractional excretion of sodium (FENa) were found to be significantly lower (P < .05) in midterm pregnant (MP; n = 18) and late-term pregnant (LP; n = 20) rats compared with nonpregnant (NP; n = 16) rats (3.5 ± 0.3 mm Hg and 1.46 ± 0.24% for MP; 3.3 ± 0.1 mm Hg and 1.41 ± 0.21% for LP; and 7.6 ± 0.6 mm Hg and 3.67 ± 0.24% for NP). Cortical Na⁺-K⁺-ATPase and Na-Pi2a cotransporter (Na-Pi) protein expression tend to decline with pregnancy. Also cortical Na⁺-H⁺ exchanger–1 (NHE-1) protein expression declines steadily during the course of pregnancy from MP to LP compared with that in NP rats, and cortical Na⁺-H⁺ exchanger–3 (NHE-3) protein expression is significantly lower in MP and LP compared with NP rats.


Key Words: Pregnant rats, volume retention, renal interstitial hydrostatic pressure, renal tubular transporters, proximal tubule reabsorption.

Normal pregnancy is characterized by a significant decrease in renal interstitial hydrostatic pressure (RIHP),¹ conservation of sodium and water and by a significant increase in extracellular fluid volume and plasma volume.²,³ Pressure natriuresis and diuresis responses are decreased in pregnant rats,¹,³ and these attenuated responses are associated with blunted increases in RIHP with increases in renal perfusion pressure (RPP) during pregnancy.¹ Paradoxically the enhanced sodium and water reabsorption that has been demonstrated during pregnancy is associated with a tendency for a reduction in net activity and abundance of renal tubular sodium transporters.⁴ In the absence of any other renal function adaptations during pregnancy, a generalized reduction in net activity of renal sodium tubular transporters per se would result in a decrease in net sodium and water retention. Therefore it is reasonable to assume that during normal pregnancy, other renal function adaptations that promote sodium and water retention counterbalance and exceed the natriuretic effects of a generalized reduction in net activity.
of renal sodium tubular transporters. Mahaney et al. showed a reduction in renal Na\(^+/\)K\(^+/\)ATPase activity in midterm and late-term pregnant SD rats compared with virgin rats. The authors noted that the observed reduction in Na\(^+/\)K\(^+/\)ATPase activity and abundance in the renal cortex of pregnant rats, especially in late pregnancy, was unexpected, as this might cause natriuresis that would not promote the massive volume retention that is observed in late-term pregnant rats. It was concluded that whatever promotes net sodium and water retention during pregnancy must be capable of overwhelming the natriuresis that can result from a reduction in Na\(^+/\)K\(^+/\)ATPase activity that is observed during pregnancy. Whether a relationship exists between RIHP and Na\(^+/\)K\(^+/\)ATPase activity under basal conditions or during pregnancy has not yet been determined. Therefore the objective of this review is to develop a proposal, with special emphasis on the decrease in RIHP, that might explain the apparent discrepancy between the net increases in renal tubular sodium and water reabsorption and the net decreases in abundance and activity of renal tubular transporters during normal pregnancy. The previously published and unpublished data presented in this review are focused on changes in RIHP and on localization, protein expression, and activity of renal tubular sodium transporters Na\(^+/\)K\(^+/\)ATPase, Na\(^+/\)H\(^+/\)exchangers 1 and 3 (NHE-1 and NHE-3) and Na\(^+/\)Pi\(^+/\)co-transporter (Na-Pi) in midterm pregnant (MP), late-term pregnant (LP), and nonpregnant (NP) rats.

### Methods

All rats in the studies that are illustrated in Figs. 1 to 4 and Table 1 were female SD rats purchased from Harlan Sprague Dawley (Indianapolis, IN). All rats were fed Teklad Global 18% Protein Rodent Diet (Harlan, Madison, WI) and had free access to water. All protocols in these studies were in accordance with the National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committee at Eastern Virginia Medical School.
All data reported in Table 1 and in Fig. 1 were pooled from two separate studies that have been conducted in our laboratory.1,5 The experimental conditions for both of the control periods in both of these studies were similar, and therefore the rats were pooled. The reported values in Table 1 and Fig. 1 represent measurements during a control period in anesthetized NP rats (n = 16), MP (12 to 14 days after conception; n = 18), and LP (18 to 21 days after conception; n = 20). It should be noted that fractional excretion of lithium (FELi) was determined in only one of the two studies5 from which these data were pooled; therefore, and as indicated in Table 1, the n value for the FELi are n = 7 for NP, n = 8 for MP, and n = 8 for LP groups of rats.

**Polyethylene Matrix Implantation**

The implantation procedure for the polyethylene (PE) matrix has been described.1,5 For data reported in Table 1 and in Fig. 1, RIHP was measured directly and continuously via a PE matrix that was implanted in the left kidney of rats at 11 to 16 weeks of age. For the renal interstitial compliance data reported in Fig. 2, two PE matrices were implanted in the left kidney when the rats were 12 to 13 weeks of age. One of the two matrices was used to measure RIHP directly and continuously, and the second was used for direct renal interstitial volume expansion (DRIVE) 4 to 6 weeks after matrix implantation.

**Monitoring of Estrous Cycle and Induction of Pregnancy in Rats**

Monitoring of the estrous cycle and induction of pregnancy in rats has been described.1,5 Approximately 1 week after PE matrix implantation, vaginal swabs were taken daily in all rats to monitor their estrous cycle. To determine the stage in the estrous cycle, female rats were
restrained manually and a wet swab was inserted into the vagina and smeared on a slide. As previously described the slide was immediately fixed with 1% toluidine blue solution (with a few drops of 1N potassium hydroxide) and observed under the microscope for cells that characterize each stage of the estrous cycle. A male breeder and a female SD rat were housed together for 1 day when the female was found to be in the estrous stage. The female was tested for the presence of sperm in the vagina the next day after approximately 24 h of being in the same cage with the male breeder SD rat. The presence of sperm on the fixed slide of the vaginal smear indicated day 1 of pregnancy.

For data reported in Table 1 and in Fig. 1, on the day of the acute experiment, rats were anesthetized with Inactin (100 mg/kg; Sigma-Aldrich Co., St. Louis, MO) and catheters were placed in the trachea (PE-240) and left jugular vein (PE-50) for intravenous infusion of 1.5 mL/100 g body wt/h of saline with 6 mmol/L LiCl (in the group of rats in which FEK was determined) and 1.5 mL/100 g body wt/h of a solution of 3% inulin and 6.25% bovine serum albumin in saline (with 6 mmol/L LiCl in the group of rats in which FEK was determined). A PE-50 catheter was implanted in the left carotid artery for mean arterial pressure (MAP) measurement and blood withdrawal. A PE-90 catheter with a flared tip was placed in the bladder for urine collection. The rats were allowed to stabilize for 1 h after completion of the surgical procedures. A 30-min control clearance period was started during which MAP and RIHP were measured and recorded on a continuous basis. At the end of this period approximately 1 mL of blood was withdrawn from the left carotid artery for plasma electrolytes, lithium, and inulin measurements. All rats were killed by air embolism while still under deep anesthesia, and both kidneys were excised and weighed. This method of euthanasia is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association.

The glomerular filtration rate was calculated from the clearance of inulin, and inulin concentrations were measured by the anthrone method. Sodium and lithium concentrations in plasma and urine were measured using flame photometry (model 943, Instrumentation Laboratory, Lexington, MA). Phosphate concentrations in plasma and urine were measured according to the method of Chen et al.

Calculation of Renal Interstitial Compliance

For the renal interstitial compliance data reported in Fig. 2, the surgical procedures were primarily similar to those

### Table 1. Renal hemodynamic characteristics in nonpregnant female, midterm pregnant (12 to 14 days after conception), and late-term pregnant (18 to 21 days after conception) groups of Sprague-Dawley rats

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonpregnant rats (NP) (n = 16)</th>
<th>Midterm pregnant rats (MP) (n = 18)</th>
<th>Late-term pregnant rats (LP) (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>119 ± 2</td>
<td>122 ± 2</td>
<td>121 ± 2</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>2.82 ± 0.22</td>
<td>3.16 ± 0.30</td>
<td>3.15 ± 0.23</td>
</tr>
<tr>
<td>UNaV (µEq/min)</td>
<td>14.69 ± 1.16</td>
<td>5.61 ± 0.75*</td>
<td>5.79 ± 0.83*</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>31.94 ± 2.63</td>
<td>23.38 ± 2.71*</td>
<td>24.10 ± 3.07*</td>
</tr>
<tr>
<td>FEK (%)†</td>
<td>26.62 ± 4.20</td>
<td>23.93 ± 5.02</td>
<td>16.67 ± 3.10</td>
</tr>
</tbody>
</table>

FEK = fractional excretion of potassium; FEK = fractional excretion of lithium; GFR = glomerular filtration rate; MAP = mean arterial pressure; UNaV = urinary sodium excretion.

Values are mean ± standard error.

* Significant difference (P < .05) between nonpregnant group and midterm pregnant or late-term pregnant group of rats compared with Student unpaired t test.

† n = 7 for nonpregnant group, n = 8 for midterm pregnant group, and n = 8 for late-term pregnant group. Data in Table 1 have been compiled from two previous studies.
described above for data reported in Table 1 and in Fig. 1. However, for these groups of NP (n = 8), MP (n = 8), and LP (n = 8) (data in Fig. 2), the rats were allowed to stabilize 1 h after completion of the surgical procedures. A control period of 20 min was then started. At this time a bolus infusion of 100 μL of saline was given through the infusion matrix directly into the renal interstitium and an additional 50 μL bolus infusion of saline was given in the middle of the control period (10 min after the initial saline infusion). During the 20-min control clearance period, MAP and RIHP were measured and recorded on a continuous basis. At the start of the second 20-min experimental period, a bolus infusion of 100 μL of a solution of 2.5% bovine serum albumin in saline was given through the infusion matrix directly in the renal interstitium and an additional 50 μL bolus infusion of the same solution was given in the middle of the experimental period (10 min after the initial DRIVE) to maintain the increase in RIHP. Renal interstitial compliance, which is defined as change in renal interstitial volume divided by the change in RIHP, was determined by the dividing of the volume of the solution of 2.5% bovine serum albumin in saline that was infused during the DRIVE period (150 μL for all rats) by ΔRIHP that resulted from this direct infusion in the renal interstitium.

Tissue Preparation and Western Blotting

Cortical renal tissue was collected from three groups of female SD rats (NP, n = 5; MP, n = 5; and LP, n = 5). The rats were anesthetized with Inactin (100 mg/kg) and kidneys were removed. Kidneys were immediately placed in ice-cold phosphate buffered saline, and the cortex and medulla were separated. One kidney from each rat was placed in 10% phosphate buffered formalin (Sigma Chemical Co., St. Louis, MO) and later used for immunohistochemistry, and renal cortex from the other kidney was stabilized 1 h after completion of the surgical procedures. A control period of 20 min was then started. At this time a bolus infusion of 100 μL of saline was given through the infusion matrix directly into the renal interstitium and an additional 50 μL bolus infusion of saline was given in the middle of the control period (10 min after the initial saline infusion). During the 20-min control clearance period, MAP and RIHP were measured and recorded on a continuous basis. At the start of the second 20-min experimental period, a bolus infusion of 100 μL of a solution of 2.5% bovine serum albumin in saline was given through the infusion matrix directly in the renal interstitium and an additional 50 μL bolus infusion of the same solution was given in the middle of the experimental period (10 min after the initial DRIVE) to maintain the increase in RIHP. Renal interstitial compliance, which is defined as change in renal interstitial volume divided by the change in RIHP, was determined by the dividing of the volume of the solution of 2.5% bovine serum albumin in saline that was infused during the DRIVE period (150 μL for all rats) by ΔRIHP that resulted from this direct infusion in the renal interstitium.

Statistical Analyses

Statistical analyses were performed using SPSS version 10.0 statistical software (SPSS Inc., Chicago, IL). The data were analyzed with one-way or two-way analysis of variance (ANOVA) followed by a post hoc Bonferroni correction for multigroup comparisons (Fig. 2). All data are reported as means ± SEM. Values of P < .05 were accepted as indicating statistically significant differences.

Results

The study results are shown in Table 1 and Figs. 1 to 4. As shown from data that have been compiled from two pre-
reported studies from our laboratory, RIHP, FE_{Na}, urinary sodium excretion (U_{Na}V), and V were significantly decreased in MP and LP compared with NP groups of rats (Fig. 1 and Table 1). Furthermore FE_{Pi} and FE_{K} had a consistent tendency to decrease in MP and LP compared with NP groups of rats (Fig. 1 and Table 1), suggesting an increase in proximal tubular sodium reabsorption during pregnancy. Also as shown in Table 1, fractional excretion of potassium (FE_{K}) was significantly lower in MP and LP compared with NP. Coupled with the significant reductions in renal sodium and water excretions, this significant decrease in FE_{K} indicates a generalized reduction in renal excretion of electrolytes during pregnancy. The results of the current study showed that cortical Na^{+}-K^{+}-ATPase and Na-Pi protein expression tended to decline with pregnancy (Fig. 3). In addition cortical NHE-1 protein expression declined steadily during the course of pregnancy from MP to LP compared with NP rats, and cortical NHE-3 protein expression was significantly lower in MP and LP compared with NP rats (Fig. 3). Taken together, previous studies as well as the results of this study suggest a reduction in the overall activity of renal tubular sodium transporters during pregnancy. Furthermore immunohistochemical localization studies were performed in the present study. Figure 4 provides representative photomicrographs of immunohistochemical localization of Na^{+}-K^{+}-ATPase (basolateral), NHE-1 (basolateral), and NHE-3 (luminal) in kidney from NP, MP, and LP rat (magnification ×400). It is interesting to note that the cortical NHE-3 protein expression was significantly lower in pregnant compared with nonpregnant SD rats (Fig. 3); however it appears that the localization of NHE-3 protein expression was more pronounced in the apical side of the proximal tubule in midterm pregnant rats compared with a more diffuse appearance in the apical side and in the cytoplasm in nonpregnant and late-term pregnant rats (Fig. 4). All negative controls showed absence of a positive signal, as illustrated in Fig. 4 (bottom micrographs).

Discussion

The broad objective of this review is to develop an integrated proposal that might explain the apparent discrepancy between the net increases in renal tubular sodium and water reabsorption and the net decreases in abundance and activity of renal tubular transporters during normal pregnancy. The different components of this proposal, which are based on previously published and unpublished data, are illustrated in Fig. 5. The roles that each of these components play in the volume retention of normal pregnancy are presented.

Pressure Natriuresis and RIHP Responses during Pregnancy

Pressure natriuresis and diuresis responses have been shown by Masilamani et al and by others to be significantly attenuated during normal pregnancy in rats. We have shown that normal pregnancy is characterized by a significant decrease in basal RIHP (Fig. 1). Furthermore the attenuated pressure natriuresis and diuresis responses are associated with blunted increases in RIHP during pregnancy. The attenuated pressure natriuresis and diuresis responses may contribute to the conservation of sodium and water to the significant increase in extracellular fluid volume and plasma volume that are observed during normal pregnancy, as decreases in RIHP have been consistently shown to have antinatriuretic effects and to cause significant decreases in sodium and water reabsorption under various experimental conditions. The possible roles of the decreased basal RIHP and the attenuated increases in RIHP in response to factors such as increases in RPP and volume expansion, in increasing extracellular fluid and plasma volumes during normal pregnancy are schematically illustrated in Fig. 5.

Renal Interstitial Compliance and Cardiovascular Compliance during Pregnancy

Compliance is defined as an increase in volume divided by increase in pressure. Because the determination of the compliance depends mainly on the structural composition of a particular compartment, instantaneous (acute) changes in the compliance are not likely to occur. In a recent study we determined the renal interstitial compliance in pregnant and nonpregnant rats by DRIVE, which selectively increases RIHP. Bolus infusions of 150 μL of a solution of 2.5% bovine serum albumin in saline were given through the infusion matrix directly in the renal interstitium and the increase in RIHP was then recorded. The results showed that renal interstitial compliance (change in renal interstitial volume / change in RIHP) is greater in pregnant compared with nonpregnant rats (Fig. 5).
2). When factored by the kidney weight, the relationship remained similar to the relationships that are shown in Fig. 2, with renal interstitial compliance being greater in pregnant compared with nonpregnant rats. It is likely that changes in renal interstitial compliance could occur during pregnancy, as the renal interstitium is composed of a gel of glycosaminoglycans, and hormonal changes that occur during pregnancy might modify the viscosity of this gel. An increase in the viscosity of the renal interstitial gel would result in an increase in renal interstitial compliance, and might significantly reduce the transmission of RPP to the renal interstitium and further decrease transmission of increased pressure in the renal interstitium to the renal tubules. As shown in Fig. 5, we propose that because the greater the renal interstitial compliance the less will be the rise in RIHP for a given increase in renal interstitial volume, it is likely that the increase in renal interstitial compliance is playing a significant role in the increase in renal tubular sodium and water reabsorption and the volume retention that occur during pregnancy.

The exact mechanism that leads to increased renal interstitial compliance during pregnancy is not yet known. The renal interstitium is composed of a gel of glycosaminoglycans. It is reasonable to assume that the level of hydration of this gel might be modified by hormonal changes, such as increases in relaxin, that occur during pregnancy. In a recent study by Conrad et al in which chronic administration of relaxin was used in conscious nonpregnant rats, data collected indicated that relaxin contributes to the increase in global arterial compliance (one measure of pulsatile arterial load, typically derived from cardiac output and the diastolic decay of the aortic pressure waveform) and modification of the vascular structure including the extracellular matrix. In addition to its vasodilatory action, relaxin promotes growth and softening of the cervix, which facilitates rapid delivery of live young. Relaxin reduces fibrosis in the kidney, heart, and lung, and significantly decreases the total collagen content without altering the proportions of collagen types in the pubic symphysial tissues in nonpregnant female SD rats. Based on these established effects of relaxin, it is reasonable to suggest that relaxin may play an important role in the increase in renal interstitial compliance during pregnancy. It should be noted that other factors that are increased or activated during pregnancy may also play important roles in the increase in renal interstitial compliance. These factors may include nitric oxide, sex hormones, the renin-angiotensin system, atrial natriuretic peptide, and the renal nerves, all of which are increased or activated during pregnancy.

Natriuretic and Diuretic Sensitivity to Increases in RIHP during Normal Pregnancy

The natriuretic and diuretic sensitivities to increases in RIHP (ΔFE_{Na}/ΔRIHP and ΔV/ΔRIHP) increase gradually with pregnancy and reach a maximum during late term. The gradual increase in natriuretic and diuretic sensitivity might provide an adaptive mechanism to protect against excessive volume expansion, especially close to term. As shown schematically in Fig. 5, we propose that renal adaptive mechanisms that include increases in natriuretic and diuretic sensitivities to increases in RIHP occur during normal pregnancy and can lead to volume retention and maintenance of the volume expansion of pregnancy. According to this hypothesis, during normal pregnancy RIHP decreases, probably as a result of increased renal interstitial compliance, which can result in significant increases in proximal tubular reabsorption. If more volume is retained than is needed for a normal pregnancy, then RIHP will increase from the low levels that are observed during pregnancy. The increase in RIHP will trigger the increased natriuretic and diuretic sensitivity mechanism to excrete the extra sodium and water and to bring back the volume expansion to the normal level that is needed for an uncomplicated normal pregnancy. It should be noted that the ability of pregnant rats to respond by increasing sodium and water excretion to a significant natriuretic stimulus such as systemic saline volume expansion remains intact.

Renal Sodium Tubular Transporters during Normal Pregnancy

The results of Western blot analysis show that cortical Na^{+}-K^{+}-ATPase protein expression tended to decrease with pregnancy, reaching significance (P < .05) in late-term (LP) compared with NP rats (Fig. 3). Also cortical NHE-1 protein expression declines steadily during the course of pregnancy from midterm (MP) to late-term (LP) compared with NP rats (Fig. 3). As shown in Fig. 3, cortical NHE-3 protein expression was significantly lower in MP and LP rats compared with NP rats. Also cortical Na-Pi cotransporter protein expression had a tendency to be lower in pregnant (MP and LP) compared with NP rats. Figure 4 shows representative photomicrographs of renal immunohistochemical localization of Na^{+}-K^{+}-ATPase, NHE-1, and NHE-3 in NP, MP, and LP rats. Taken together, results of previous studies as well as the present study suggest a decrease in the overall activity of renal tubular sodium transporters during pregnancy. Figure 5 introduces a proposal that has been developed, with special emphasis on the decrease in RIHP that has been established during pregnancy, that might explain the apparent discrepancy between the increases in renal tubular sodium and water reabsorption and the paradoxical decreases in abundance and activity of renal tubular transporters during normal pregnancy. In this proposal we are introducing a hypothesis that would provide an explanation for the volume retention and the overall decrease in renal tubular sodium transporter activity and abundance.
in pregnant rats (Fig. 5). According to this proposal, during normal uncomplicated pregnancy, a simultaneous decrease in RIHP and net activity of renal tubular transporters (Na\(^{+}\)-K\(^{+}\)-ATPase, NHE-1, NHE-3, and Na-Pi) occurs. The more pronounced increase in sodium and water reabsorption that results from the decreased RIHP exceeds the reduction in net abundance and presumably activity of renal tubular transporters resulting in a net sodium and water reabsorption during pregnancy. It can be speculated that if the net activity of renal transporters (assuming that activity is directly proportional to protein expression) were not decreased during pregnancy, then the decrease in RIHP would result in greater sodium and water reabsorption and therefore in more volume expansion than is required for an uncomplicated normal pregnancy. Further studies are needed to determine whether there is a causal relationship between RIHP and renal tubular transporter protein expression under basal conditions and during normal pregnancy.

About two thirds of the glomerular ultrafiltrate is reabsorbed by the proximal tubule, and the majority of luminal sodium reabsorption is coupled to Na\(^{+}\)-H\(^{+}\) exchanger activity, with NHE-3 being the primary isoform responsible for proximal apical sodium entry.\(^{20}\) There is strong evidence for a dynamic and rapid bidirectional regulation of NHE-3 in the proximal tubule mediated by redistribution of the exchanger out of and into the apical microvilli.\(^{20}\) This rapid bidirectional regulation and redistribution of the exchanger can affect sodium reabsorption in the proximal tubule. Redistribution and abundance of NHE-3 can be affected by hypertension, renal injury, renal nerve activity, and insulin.\(^{20–22}\) Therefore it is likely that the abundance and localization of NHE-3 as well as other renal tubular transporters including NHE-1, Na\(^{+}\)-K\(^{+}\)-ATPase, and Na-Pi are altered during pregnancy. It is interesting to note that the cortical NHE-3 protein expression was significantly lower in pregnant compared with non-pregnant SD rats (Fig. 3); however it appears that the localization of NHE-3 protein expression was more pronounced in the apical side of the proximal tubule in midterm pregnant rats (Fig. 4) compared with a more diffuse appearance in the apical side and in the cytoplasm in nonpregnant and late-term pregnant rats.

Conclusion: Hypothesis That Might Explain Volume Retention during Pregnancy

We propose (Fig. 5) that renal adaptive mechanisms that include decreases in RIHP, changes in protein expression of renal tubular transporters, and increases in natriuretic and diuretic sensitivities to increases in RIHP occur during normal pregnancy and can lead to volume retention and maintenance of the volume expansion of pregnancy. First, during normal pregnancy RIHP decreases, probably as a result of increased renal interstitial compliance.\(^{1,5,11,13}\) Decreases in RIHP have been shown to result in significant increases in proximal tubular reabsorption. Second, changes in protein expression of renal tubular transporters result in a net decrease in the activity of these renal tubular sodium transporters specifically in the proximal tubule where most of the sodium reabsorption occurs. These changes in the activity of renal tubular sodium transporters prevent the decrease in RIHP from causing more sodium retention than is required for a normal uncomplicated pregnancy. Third, the natriuretic and diuretic sensitivities to increases in RIHP increase gradually with pregnancy and reach a maximum during late term.\(^{5,13}\) This gradual increase in natriuretic and diuretic sensitivities might provide a renal adaptive mechanism to protect against excessive volume expansion, especially close to term, and might involve changes in the activity of the renal tubular sodium transporters during pregnancy. If more volume is retained than is needed for a normal pregnancy, then RIHP will increase from the low levels that are observed during pregnancy, as is the case with experimental acute systemic saline volume expansion\(^{5}\) or direct renal interstitial volume expansion.\(^{13}\) The increase in RIHP will trigger the increased natriuretic and diuretic sensitivity mechanism to excrete the extra sodium and water and to bring back the volume expansion to the normal level that is needed for an uncomplicated normal pregnancy.

References


