Role of nitric oxide in the natriuretic and diuretic responses in pregnant rats

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Khraibi, Ali A., Tianzheng Yu, and Daiyi Tang. Role of nitric oxide in the natriuretic and diuretic responses in pregnant rats. Am J Physiol Renal Physiol 285: F938–F944, 2003.—Normal pregnancy is characterized by sodium conservation and increase in plasma volume, yet the natriuretic response to acute saline volume expansion (VE) is intact in pregnant rats. Nitric oxide (NO) has been suggested to play a role in renal and cardiovascular adaptations to normal pregnancy. The objective of this study was to determine the role of NO in the natriuretic and diuretic responses to VE during pregnancy. Infusion of N\textsuperscript{\textsubscript{G}}-monomethyl-L-arginine (L-NMMA) was used to inhibit NO synthesis. Nine groups of Sprague-Dawley (SD) rats were studied: nonpregnant (NP-VE, n = 7), midterm pregnant (MP-VE, n = 8), and late-term pregnant (LP-VE, n = 8) SD groups that underwent VE alone after a control period; NP-L-NMMA (n = 7), MP-L-NMMA (n = 8), and LP-L-NMMA (n = 7) SD groups that were infused with L-NMMA after a control period; and another three groups of SD rats (NP-VE-L-NMMA, n = 8; MP-VE-L-NMMA, n = 8; and LP-VE-L-NMMA, n = 12) that underwent simultaneous VE and L-NMMA infusion after a control period. The change in fractional excretion of sodium was 7.22 ± 1.03% for NP-VE, 8.99 ± 1.85% for NP-L-NMMA, and 17.66 ± 1.85% for NP-VE-L-NMMA (P < 0.05 vs. NP-VE and NP-L-NMMA); 6.61 ± 1.07% for MP-VE, 7.99 ± 1.92% for MP-L-NMMA, and 10.24 ± 1.91% for MP-VE-L-NMMA (not significant [NS] vs. MP-VE and MP-L-NMMA); 8.20 ± 1.92% for LP-VE, 8.09 ± 0.70% for LP-L-NMMA, and 7.57 ± 1.11% for LP-VE-L-NMMA (both NS vs. LP-VE and LP-L-NMMA). The increase in renal interstitial hydrostatic pressure was significantly greater in all NP compared with pregnant groups with similar experimental intervention (i.e., VE, L-NMMA, or VE-L-NMMA). In conclusion, the natriuretic and diuretic responses to VE and L-NMMA infusion were additive in NP but not in pregnant rats, indicating a possible lower ability of pregnant rats to respond to combined significant natriuretic and diuretic stimuli.

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Because it appears that there is an interaction between NO and renal sodium and water handling during pregnancy, the objective of this study was to determine the effect of inhibition of NO with \(L\)-NMMA infusion on the natriuretic and diuretic responses to VE during pregnancy. Furthermore, the effects of \(L\)-NMMA infusion on MAP, RIHP, natriuresis, and diuresis were determined in pregnant rats. Also, fractional excretion of phosphate (\(FE_\text{P}\)) and fractional excretion of lithium (\(FE_\text{Li}\)) were used as indexes for proximal tubule reabsorption (5, 12, 24, 25) in the present studies to determine any potential changes in reabsorption in this segment of the nephron in response to VE and \(L\)-NMMA infusion.

**METHODS**

All rats in these studies were female Sprague-Dawley rats purchased from Harlan Sprague Dawley (Indianapolis, IN). All rats were fed a normal Purina Rat Chow containing 0.1 meq sodium/g and had free access to water. All protocols in this study 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.

**Polyethylene matrix implantation.** The implantation procedure of the polyethylene (PE) matrix has been previously described (19). RIHP was measured directly and continuously via a PE matrix that was implanted in the left kidney of rats when they were 11–14 wk old.

**Monitoring of the estrous cycle and induction of pregnancy in rats.** Monitoring of the estrous cycle and induction of pregnancy in rats has been described previously (19). Approximately 1 wk after PE matrix implantation, vaginal swabs were taken daily in all rats to monitor their estrous cycle. As previously described, swabs were inserted in a slide. As previously described, the slide was immediately fixed with 1% toluidine blue solution (with a few drops of 1 N potassium hydroxide) and observed under the microscope for cells that characterize each stage of the estrous cycle. A male breeder and a female Sprague-Dawley 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 −24 h of being in the same cage with the male breeder Sprague-Dawley rat. The presence of sperm on the fixed slide of the vaginal smear indicated day 1 of pregnancy.

Nine groups of female Sprague-Dawley rats were studied in these experiments. Three groups were nonpregnant (NP). These were rats that were individually housed together for −24 h with a male breeder when they were in the estrous stage but found to be nonpregnant during the acute experiments. Three groups were midterm pregnant (MP; 12–14 days after conception). These rats were pregnant for 12–14 days when the VE and/or \(L\)-NMMA studies were performed. Three groups were late-term pregnant (LP; 18–20 days after conception). These rats were pregnant for 18–20 days when the VE and/or \(L\)-NMMA studies were performed.

**Acute saline VE groups.** Nonpregnant (NP-VE; \(n = 7\)), midterm pregnant (MP-VE; \(n = 8\)), and late-term pregnant (LP-VE; \(n = 7\)) Sprague-Dawley groups underwent VE (5% body wt/30 min saline with 6 mM LiCl) after a control period. On the day of the acute experiment, the average body weight was 284 ± 9 g for NP, 301 ± 10 g for MP, and 367 ± 11 g for LP groups of rats.

**L-NMMA infusion groups.** Nonpregnant (NP-\(L\)-NMMA; \(n = 7\)), midterm pregnant (MP-\(L\)-NMMA; \(n = 8\)), and late-term pregnant (LP-\(L\)-NMMA; \(n = 7\)) Sprague-Dawley groups were infused intravenously with \(L\)-NMMA (15 mg/kg bolus injection followed by an infusion of 500 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)) after a control period. On the day of the acute experiment, the average body weight was 272 ± 2 g for NP, 325 ± 5 g for MP, and 352 ± 17 g for LP groups of rats.

**Acute saline VE and \(L\)-NMMA infusion groups.** Nonpregnant (NP-VE-\(L\)-NMMA; \(n = 7\)), midterm pregnant (MP-VE-\(L\)-NMMA; \(n = 7\)), and late-term pregnant (LP-VE-\(L\)-NMMA; \(n = 12\)) rats underwent both VE and \(L\)-NMMA infusion (VE-\(L\)-NMMA) after a control period. On the day of the acute experiment, the average body weight was 272 ± 2 g for NP, 302 ± 11 g for MP, and 370 ± 9 g for LP groups of rats.

**Surgical procedure for VE and/or \(L\)-NMMA infusion experiments.** On the day of the acute experiment, rats were anesthetized with Inactin (100 mg/kg), 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\(^{-1}\)·h\(^{-1}\) saline with 6 mM LiCl and 1.5 ml·100 g body wt\(^{-1}\)·h\(^{-1}\) of a solution of 3% inulin and 6.25% bovine albumin in saline (with 6 mM LiCl). A PE-50 catheter was implanted in the left carotid artery for 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 1 h to recover after completion of the surgical procedures. Next, a control period of 30 min was started. During the 30-min clearance period, MAP and RIHP were measured and recorded continuously. At the end of this period, −1 ml of blood was withdrawn from the left carotid artery for plasma electrolytes, lithium, and inulin measurements. At this time, VE (5% body wt/30 min of saline with 6 mM LiCl), \(L\)-NMMA infusion (15 mg/kg bolus injection followed by an infusion of 500 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)), or VE and \(L\)-NMMA infusion (5% body wt/30 min and \(L\)-NMMA, 15 mg/kg bolus injection followed by an infusion of 500 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)) was started. Urine was collected for 20 min starting immediately in the groups of rats that received only \(L\)-NMMA infusion. Urine was also collected for 20 min starting 10 min after the initiation of VE in all groups that were volume expanded. Again, during the second clearance period, MAP and RIHP were measured and recorded continuously. At the end of this period, −1 ml blood was withdrawn from the left carotid artery for plasma electrolytes, lithium, and inulin measurements. All rats were killed by air embolism at the end of the experiment 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.

Glomerular filtration rate was calculated from the clearance of inulin, and inulin concentrations were measured by the anthrone method (11). 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. (7).

**Statistical analyses.** Statistical analyses were performed using SPSS 10.0 statistical software (SPSS, Chicago, IL). The data were analyzed with standard paired Student’s \(t\)-tests for comparisons between the first and second clearance periods in the same group. For comparisons among groups at equivalent periods, a one-way ANOVA followed by a post hoc Bonferroni correction was used for comparisons of NP and MD or LP groups. All data are means ± SE, and \(P < 0.05\) was accepted as a statistically significant difference.
† Significantly greater compared with NP rats.
‡ Significant difference compared with MP rats.
§ Significant difference compared with LP rats.

Table 1. Changes in renal responses to acute saline VE, l-NMMA infusion, and VE plus l-NMMA infusion in NP Sprague-Dawley rats

<table>
<thead>
<tr>
<th></th>
<th>NP-VE (n = 7)</th>
<th>NP-L-NMMA (n = 7)</th>
<th>NP-VE-L-NMMA (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>VE</td>
<td>Control</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>126.6 ± 1.5</td>
<td>114.0 ± 3.1*</td>
<td>136.6 ± 4.2</td>
</tr>
<tr>
<td>RHP, mmHg</td>
<td>6.8 ± 0.3</td>
<td>10.0 ± 0.4*</td>
<td>6.9 ± 0.6</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>2.9 ± 0.6</td>
<td>3.2 ± 0.4</td>
<td>2.6 ± 0.1</td>
</tr>
<tr>
<td>UNaV, μeq/min</td>
<td>11.6 ± 1.5</td>
<td>45.5 ± 4.2*</td>
<td>9.5 ± 1.4</td>
</tr>
<tr>
<td>FEna, %</td>
<td>3.4 ± 0.7</td>
<td>10.7 ± 1.4*</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>FELi, %</td>
<td>28.9 ± 3.7</td>
<td>49.6 ± 6.2*</td>
<td>26.2 ± 3.1</td>
</tr>
<tr>
<td>FEPi, %</td>
<td>6.7 ± 1.9</td>
<td>23.8 ± 3.6*</td>
<td>12.2 ± 4.4</td>
</tr>
<tr>
<td>V, μl/min</td>
<td>57.6 ± 9.8</td>
<td>351.4 ± 30.8b</td>
<td>59.1 ± 7.1†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. NP, nonpregnant; l-NMMA, Nω-monomethyl-l-arginine; VE, volume expansion (5% body wt/30 min); MAP, mean arterial pressure; RHP, renal interstitial hydrostatic pressure; GFR, glomerular filtration rate; UNaV, urinary sodium excretion; FEna, fractional excretion of sodium; FELi, fractional excretion of lithium; FEPi, fractional excretion of phosphate; V, urine flow rate.

† Significant difference (P < 0.05) between control and experimental periods in the same group of rats compared with Student’s paired t-test. ‡ Significant difference compared with NP-L-NMMA group at equivalent periods using a one-way ANOVA followed by a post hoc Bonferroni correction.

DISCUSSION

The results of the present study show that basal RIHP and the increase in RIHP during VE and l-NMMA infusion were attenuated during pregnancy. However, VE and l-NMMA infusion resulted in a similar increase in sodium and water excretions in NP and pregnant groups of rats, indicating intact excretory responses to VE and to l-NMMA infusion during pregnancy. In the groups that received simultaneous VE and l-NMMA infusion, basal RHP and the increase in RIHP were attenuated in pregnant rats; however, this combined experimental intervention resulted in a significantly greater increase in sodium and water excretions in NP compared with pregnant groups of rats. RHP, FEna, and V increased significantly in all groups of pregnant and NP rats, in response to VE, l-NMMA infusion, or simultaneous VE and l-NMMA infusion; however, the natriuretic and diuretic responses to simultaneous VE and l-NMMA infusion were additive in NP but not in pregnant rats. Also, FEPi and FELi, which were used as indexes for proximal tubule reabsorption, increased significantly in all groups of pregnant and NP rats in response to VE, l-NMMA infusion, or simultaneous VE and l-NMMA infusion, suggesting...

Table 2. Changes in renal responses to acute saline VE, l-NMMA infusion, and VE plus l-NMMA infusion in MP Sprague-Dawley rats

<table>
<thead>
<tr>
<th></th>
<th>MP-VE (n = 7)</th>
<th>MP-L-NMMA (n = 7)</th>
<th>MP-VE-L-NMMA (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>VE</td>
<td>Control</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>119.4 ± 3.9</td>
<td>101.3 ± 3.1*</td>
<td>132.0 ± 3.6†</td>
</tr>
<tr>
<td>RHP, mmHg</td>
<td>4.0 ± 0.3†</td>
<td>5.5 ± 0.3*</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>2.3 ± 0.2</td>
<td>2.5 ± 0.3</td>
<td>2.7 ± 0.2</td>
</tr>
<tr>
<td>UNaV, μeq/min</td>
<td>7.9 ± 1.1</td>
<td>29.6 ± 2.8*</td>
<td>6.1 ± 0.9</td>
</tr>
<tr>
<td>FEna, %</td>
<td>2.4 ± 0.3</td>
<td>9.1 ± 1.0*</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>FELi, %</td>
<td>30.9 ± 2.2</td>
<td>56.8 ± 5.8*</td>
<td>29.5 ± 2.8</td>
</tr>
<tr>
<td>FEPi, %</td>
<td>10.1 ± 3.0</td>
<td>29.1 ± 3.7*</td>
<td>1.8 ± 0.9†</td>
</tr>
<tr>
<td>V, μl/min</td>
<td>58.8 ± 7.8</td>
<td>203.8 ± 24.6*</td>
<td>46.9 ± 4.7</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. MP, midterm pregnant. * Significant difference (P < 0.05) between control and experimental periods in the same group of rats compared with Student’s paired t-test. † Significant difference compared with NP-VE group. ‡ Significant difference compared with MP-L-NMMA group at equivalent periods using a one-way ANOVA followed by a post hoc Bonferroni correction.

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Changes in renal responses to acute saline VE, L-NMMA infusion, and VE plus L-NMMA infusion in LP Sprague-Dawley rats

Table 3. Changes in renal responses to acute saline VE, L-NMMA infusion, and VE plus L-NMMA infusion in LP Sprague-Dawley rats

<table>
<thead>
<tr>
<th></th>
<th>LP-VE (n = 7)</th>
<th>LP-L-NMMA (n = 7)</th>
<th>LP-VE-L-NMMA (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>VE</td>
<td>Control</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>129.6 ± 2.8</td>
<td>118.0 ± 4.1*</td>
<td>134.9 ± 4.3</td>
</tr>
<tr>
<td>RIIIP, mmHg</td>
<td>3.4 ± 0.4</td>
<td>4.9 ± 0.5*</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>2.1 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>UNaV, µeq/min</td>
<td>8.5 ± 1.3</td>
<td>38.6 ± 3.8*</td>
<td>7.6 ± 1.6</td>
</tr>
<tr>
<td>FENa,%</td>
<td>3.2 ± 0.7</td>
<td>11.4 ± 2.0*</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>FEPi,%</td>
<td>31.8 ± 5.8</td>
<td>51.4 ± 6.9*</td>
<td>29.1 ± 5.6</td>
</tr>
<tr>
<td>V, µl/min</td>
<td>69.1 ± 12.5</td>
<td>289.3 ± 33.1*</td>
<td>58.1 ± 9.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. LP, late-term pregnant. *Significant difference (P < 0.05) between control and experimental periods in the same group of rats compared with Student’s paired t-test. †Significant difference compared with LP-VE group. ‡Significant difference compared with LP-L-NMMA group at equivalent experimental periods using a one-way ANOVA followed by a post hoc Bonferroni correction.

Significantly in all groups of rats, pregnant and NP, in response to L-NMMA infusion (Table 2); however, the increase in MAP (ΔMAP) was significantly greater in pregnant compared with NP rats (Fig. 3).

In the present study, NP rats were used as controls for pregnant rats. NP rats are rats that were individually housed together for ~24 h with a male breeder when they were in the estrous stage but found to be nonpregnant during the acute experiments. The use of NP rats compared with virgin rats as controls for

Fig. 1. Changes in fractional excretion of sodium (ΔFENa, A) and changes in urine flow (ΔV; B) in response to acute saline volume expansion (VE), infusion of Nω-monethyl-L-arginine (L-NMMA; 15 mg/kg bolus followed by 500 μg·kg⁻¹·min⁻¹ continuous infusion), or simultaneous VE and L-NMMA infusion (VE-L-NMMA) in nonpregnant (NP; n = 7, 7, and 8, respectively), midterm pregnant (MP; n = 8, 8, and 7, respectively), and late-term pregnant (LP; n = 7, 7, and 12, respectively) groups of Sprague-Dawley rats. †Significant difference compared with NP groups of rats at equivalent experimental periods using a one-way ANOVA followed by a post hoc Bonferroni correction.

Fig. 2. Changes in fractional excretion of phosphate (ΔFEPi; A) and changes renal interstitial hydrostatic pressure (ΔRIHP; B) in response to VE, infusion of L-NMMA (15 mg/kg bolus followed by 500 μg·kg⁻¹·min⁻¹ continuous infusion), or VE-L-NMMA infusion in NP (n = 7, 7, and 8, respectively), MP (n = 8, 8, and 7, respectively), and LP (n = 7, 7, and 12, respectively) groups of Sprague-Dawley rats. †Significant difference compared with NP groups of rats at equivalent experimental periods using a one-way ANOVA followed by a post hoc Bonferroni correction.
potential pseudopregnancy as controls for pregnant rats. The advantages of using NP females after 2 wk of a potential pseudopregnancy is substantial in that it avoids the possible complications of pregnancy, similarities in hormonal profiles, and renal function have been reported in pregnant and pseudopregnant Sprague-Dawley rats (2). In the present study, the total number of NP rats used was 22 (Table 1). In the overwhelming majority of NP rats (20 out of 22 rats), the acute experiments were performed 15 or more days after these rats were individually housed with a male breeder. Furthermore, the results of two previous studies show that basal renal function of virgin (18) and NP females (15) is similar under the same experimental conditions as those of the present study, and at a similar MAP of 118 mmHg. The use of virgin females as controls for pregnant rats is advantageous in that it avoids the possible complications of pseudopregnancy that might occur in NP females, especially if experiments are performed in these rats within 2 wk of a potential pseudopregnancy. Some of the advantages of using NP females after 2 wk of a potential pseudopregnancy as controls for pregnant rats are that both groups would have been identically housed with a male breeder and that the rats that have been found to be nonpregnant during the acute terminal experiment could still be utilized for the study.

The results of this study confirm those of previous studies that RIHP is significantly lower in pregnant rats (15, 16, 19) and that acute VE results in an increase in RIHP that is attenuated in pregnant compared with NP Sprague-Dawley rats (19). However, the natriuretic and diuretic responses to acute saline VE remain intact during pregnancy (19). The lower basal RIHP and the attenuated increase in RIHP with VE in pregnant rats suggest an increase in renal interstitial compliance during pregnancy (19). As shown in Table 1, acute saline VE resulted in similar natriuretic and diuretic responses in NP, MP, and LP rats.

Pressure natriuresis and diuresis responses are decreased in pregnant rats (15, 20), and these attenuated responses are associated with blunted increases in RIHP with increases in renal perfusion pressure (RPP) during pregnancy (15). In normotensive rats, infusion of L-NMMA has been shown to cause significant increases in blood pressure and natriuretic and diuretic responses that resemble pressure natriuresis (13). The natriuretic and diuretic responses of L-NMMA infusion are mediated by the significant increases in RPP, since preventing RPP from increasing almost abolishes these responses in normotensive rats (13). Because pressure natriuresis has been shown to be attenuated in pregnant rats and because NO has been suggested to play an important role in determining blood pressure responses in normotensive rats (13), the lower basal RIHP and that L-NMMA infusion caused similar natriuretic and diuretic responses in pregnant compared with NP rats (Fig. 1 and Table 2) and that L-NMMA infusion caused similar natriuretic and diuretic responses in pregnant compared with NP groups of rats (Figs. 2 and Table 2). MAP increased by ~17 mmHg in NP, ~31 mmHg in MP (P < 0.05 vs. NP), and ~28 mmHg in LP (P < 0.05 vs. NP) groups of rats (Fig. 3), whereas ΔFENa and ΔV were similar for NP and pregnant groups of rats (Figs. 1 and 2) in response to L-NMMA infusion. These results may be explained by the previous reported finding showing that pressure natriuretic and diuretic responses were attenuated in pregnant rats (15, 20). Taken together, it appears that the greater increase in MAP (ΔMAP) with L-NMMA infusion in pregnant (MP and LP) compared with NP rats compensated for the attenuated pressure natriuretic and diuretic responses resulting in similar ΔFENa and ΔV in response to L-NMMA infusion in all three groups of rats (Figs. 1 and 3). Also, the greater increase in ΔMAP with L-NMMA infusion in pregnant

![Graph A](image1)

**Fig. 3.** Mean arterial pressure (MAP; A) during a control period and a period of infusion of L-NMMA (15 mg/kg bolus followed by 500 μg·kg⁻¹·min⁻¹ infusion) in NP (n = 7), MP (n = 8), and LP (n = 7) groups of Sprague-Dawley rats and changes in MAP (ΔMAP; B) from control to L-NMMA infusion period in NP, MP, and LP groups of Sprague-Dawley rats. *Significant difference between control and L-NMMA infusion period in the same group of rats compared with paired Student’s t-test. †Significant difference compared with NP groups of rats at equivalent experimental periods using a one-way ANOVA followed by a post hoc Bonferroni correction.
compared with NP rats suggests that NO may play an important role in causing vasodilation and thus lower blood pressure during pregnancy.

Simultaneous VE and L-NMMA infusion resulted in natriuretic and diuretic responses that were similar to either VE or L-NMMA infusion in pregnant (both MP and LP) rats (Fig. 2). In addition, the increases in FEP, and FE*Li were similar with simultaneous VE and L-NMMA infusion to those that resulted from either VE or L-NMMA infusion in pregnant rats (Table 3 and Fig. 2). These findings suggest that the simultaneous effects of VE and L-NMMA infusion on sodium and water excretions, as well as on the ability to reduce reabsorption in the proximal tubule, are similar to those that result from either VE or L-NMMA infusion in pregnant rats. In contrast, simultaneous VE and L-NMMA infusion resulted in natriuretic, diuretic, and phosphaturic responses that were additive in NP rats (Figs. 1 and 2). These data suggest that, when NP rats are subjected simultaneously to VE and L-NMMA infusion, the increase in sodium and water excretions and the decrease in proximal tubule reabsorption are similar to those that result from the combined effect of VE and L-NMMA infusion when performed separately. NO biosynthesis, which is increased during pregnancy, appears to blunt the reflex renal response to atrial distention (23). In a recent study by Tam and Kaufman (23), inhibition of NO biosynthesis with L-NAME treatment restored the attenuated urine and sodium output in pregnant rats to simulated increases in circulating blood volume that was achieved experimentally by atrial distention of an implanted intracardiac balloon (23).

In summary, the results of the present studies show that the natriuretic, diuretic, and phosphaturic responses to simultaneous VE and L-NMMA infusion were additive in NP but not in pregnant rats. Also, FEP, and FE*Li, which were used as indexes for proximal tubule reabsorption, increased significantly in all groups of pregnant and NP rats in response to VE, L-NMMA infusion, or simultaneous VE and L-NMMA infusion, suggesting a reduction in proximal tubule reabsorption as a result of these experimental interventions (Tables 1–3); however, the phosphaturic responses to simultaneous VE and L-NMMA infusion were significantly greater in NP compared with pregnant groups of rats. The data in the present study suggest that the ability of pregnant rats to increase sodium and water excretion beyond a certain point is limited. This limited renal excretory response to combined natriuretic and diuretic stimuli (VE and L-NMMA infusion in this case) during pregnancy may be mediated by a failure to reduce proximal tubule reabsorption beyond a certain level in these rats. In contrast, when NP rats were challenged experimentally with a combination of VE and L-NMMA infusion, the natriuretic, diuretic, and phosphaturic responses were additive in these rats.

In conclusion, the natriuretic, diuretic, and phosphaturic responses to VE and L-NMMA infusion were additive in NP but not in pregnant rats, indicating a reduced ability of pregnant rats to respond to combined significant natriuretic and diuretic stimuli.

DISCLOSURES

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REFERENCES


