Effect of interactions between nitric oxide and angiotensin II on pressure diuresis and natriuresis

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NITRIC OXIDE (NO) is a humoral factor produced within the kidney, and increasing evidence indicates that NO is one of the most important systems controlling renal function. Administration of Nω-nitro-L-arginine methyl ester (L-NAME, 37 nmol·kg−1·min−1) lowered renal blood flow and reduced the slopes of the pressure diuresis and natriuresis responses by 44 and 40%, respectively. Blockade of AT1 receptors with valsartan increased slightly sodium and water excretion at low renal perfusion pressure (RPP). Blockade of AT2 receptors with PD-123319 had no effect on renal function. The administration of valsartan or PD-123319 to rats given L-NAME had no effect on the renal vasoconstriction induced by NO synthesis blockade. In addition, in rats given L-NAME, valsartan elevated baseline excretory values at all RPP studied, but it had no effect on the sensitivity of the pressure diuresis and natriuresis response. However, the administration of PD-123319 to L-NAME-pretreated rats shifted the slopes of the pressure diuresis and natriuresis responses toward control values, indicating that the impairment produced by NO synthesis blockade on pressure diuresis is dependent on the activation of AT2 angiotensin receptors.

The pressure diuresis and natriuresis response is an important renal mechanism of regulation of sodium excretion that is thought to be nonadaptable and responsible for the long-term control of arterial pressure (2). According to this hypothesis, arterial pressure is dependent on the mechanisms regulating pressure diuresis, many of which are not completely understood. A variety of studies have shown that NO synthesis blockade resets the pressure natriuretic response toward higher pressures (5, 6, 18, 19, 26). This is consistent with the observation that chronic administration of L-NAME produces sustained sodium-dependent arterial hypertension (3, 13, 20, 27). Because the preglo-merular autoregulatory vasoconstriction should increase endothelial shear stress and NO secretion as arterial pressure rises, it has been hypothesized that the vascular endothelium may be the sensor and NO may be the mediator coupling elevations in arterial pressure with reductions in tubular sodium and water reabsorption through intrarenal hemodynamic changes (5) or direct tubular actions (17, 31). This point of view is compatible with the fact that pressure diuresis is associated with elevations in nitrate and/or nitrite excretion (16, 32). Thus NO appears to play a central role in the control of renal function and arterial pressure.

The renin-angiotensin system is also an important controller of sodium and water excretion and arterial pressure (9). Whether NO inhibits or stimulates renin release remains controversial, but increasing evidence indicates that NO synthesis blockade increases renin secretion (28) and renal tissue angiotensin II content (33) when renal perfusion pressure (RPP) is not allowed to rise. In addition, the changes observed in renal function after NO synthesis blockade seem to be due, at least in part, to the fact that physiologically, NO buffers the influence of endogenous vasoconstrictor systems within the kidney. In this regard, it has been reported that short-term angiotensin II infusions elevate the renal excretion of nitrate and/or nitrite and that the increase in renal vascular resistance observed during angiotensin II infusions is greater after NO synthesis inhibition (4). These data suggest that vasoconstriction may augment shear stress and NO production, which in turn acts as a regulatory system by restraining the constrictor action of a variety of hormones, such as angiotensin II. Also, several studies performed in rats have shown that angiotensin AT1 receptor blockade prevents most of the acute renal effects of L-NAME (29, 33).

Chronic blockade of NO synthesis produces arterial hypertension (3, 13, 20, 27) resulting from the fact that L-NAME shifts pressure natriuresis toward higher pressures. This form of hypertension resulting from NO deficiency appears to be dependent on the renin-angiotensin system, because it can be prevented by administration of enalapril or the angiotensin receptor antagonists losartan and A-81988 (10, 22). These studies suggest that at least part of the action of L-NAME on pressure diuresis and natriuresis may be mediated through potentiation of the renin-angiotensin system. This is in apparent contradiction with a previous study by Majid et al. (19), which reported that pretreatment with losartan had no effect on the impairment of pressure diuresis produced by NO synthesis blockade.
However, losartan has recently been shown to be ineffective in increasing the pressure diuresis response in angiotensin II-infused rats, whereas AT₂ receptor blockade with PD-123319 shifts pressure diuresis toward lower pressures, indicating that angiotensin II blunts the pressure diuresis response through activation of the AT₂ receptor subtype (14). Nevertheless, at present, little is known about the interactions between NO and AT₂ angiotensin receptors in the control of pressure diuresis. Therefore, the purpose of the present study was to evaluate the effect of AT₁ and AT₂ angiotensin receptor blockade on L-NAME-induced changes in pressure diuresis and natriuresis.

MATERIALS AND METHODS

Experiments were performed on 51 Munich-Wistar rats (200–250 g body wt) purchased from Harlan Laboratories (Madison, WI) and bred in our animal care facility. All procedures followed were in accordance with the “Recommendations from the Declaration of Helsinki” and the “Guiding principles in the care and use of animals” approved by the Council of the American Physiological Society. The rats were anesthetized with an intramuscular injection of ketamine (30 mg/kg) and an intraperitoneal injection of Inactin (thiobutabarbital, 50 mg/kg) and were placed on a heated table to maintain body temperature at 36.5°C. Cannulas were placed in the femoral vein for infusions and in the femoral artery for measurements of arterial pressure. An aortic clamp was placed above the left renal artery, and ties were loosely placed around the mesenteric and celiac arteries so that RPP could be manipulated by adjusting peripheral resistance, as described previously. The left kidney was denervated by stripping all visible nerves from the renal artery and coating the hilar region of the kidney with a 10% solution of phenol in ethanol. Plasma levels of norepinephrine, aldosterone, cortisol, and vasopressin were maintained at fixed levels throughout the experiment by continuous intravenous infusion at the following doses: norepinephrine, 333 ng·kg⁻¹·min⁻¹; aldosterone, 66 ng·kg⁻¹·min⁻¹; cortisol, 33 mg·kg⁻¹·min⁻¹; and vasopressin, 0.17 ng·kg⁻¹·min⁻¹ (23). The rats received an intravenous injection of a 0.9% sodium chloride solution containing all hormones indicated above and 1% bovine serum albumin, at a rate of 2 ml·100 g⁻¹·h⁻¹ throughout the experiment.

A cannula was placed in the left ureter for collection of urine. [³H]Inulin (1 μCi/ml) was included in the infusion solution to allow for measurement of GFR. An electromagnetic flow probe (Skalar, Copenhagen, Denmark) was placed around the renal artery to allow for measurement of RBF.

Experimental protocols. Urine flow, sodium excretion, RBF, GFR, and arterial pressure were measured during a 30-min control period. Then, either saline (group 1, control, n = 13 rats), L-NAME (groups 2, 4, and 6; 37 nmol·kg⁻¹·min⁻¹; n = 10, 8, and 6 rats, respectively), valsartan (an AT₁ angiotensin II receptor antagonist, 92 μmol/kg, group 3, n = 8 rats), or PD-123319 (an AT₂ angiotensin II receptor antagonist, 98 nmol·kg⁻¹·min⁻¹, group 5, n = 6 rats) was administered intravenously, and, after a 30-min equilibration period, urine and plasma samples were collected again in a 15-min experimental clearance period. Then, either valseartan (92 μmol/kg, group 4) or PD-123319 (98 nmol·kg⁻¹·min⁻¹, group 6) was administered intravenously, and, after a 30-min equilibration period, urine and plasma samples were collected in a third 15-min clearance period. After that, RPP was lowered to 100 mmHg by aortic occlusion; 10 min later, urine flow, sodium excretion, GFR, and RBF were measured during a 30-min period. RPP was then elevated by 20 mmHg by release of the clamp on the abdominal aorta, and, after a 10-min equilibration period, urine and plasma samples were collected during a 20-min experimental period. Finally, we increased RPP to 20 mmHg above control by tying off the mesenteric and celiac arteries, and urine and plasma samples were again collected during a 15-min experimental period.

The dose of valsartan used was enough to abolish the arterial pressure and RBF responses to a 100-ng bolus of angiotensin II (+44 ± 3 vs. 0 mmHg and −4.6 ± 0.5 vs. 0 ml/min, respectively). The dose of PD-123319 used in the present study has been reported to yield adequate plasma concentrations to block AT₁ receptors (14, 15).

Analytic methods. Urine volume was measured gravimetrically and factored by grams of kidney weight. [³H]Inulin concentrations in urine and plasma samples were determined with the use of liquid scintillation spectrophotometry. GFR was calculated as the urine-to-plasma inulin concentration ratio times urine flow rate. The sodium concentration of urine and plasma samples was determined by flame photometry.

Statistical methods. Data are presented as means ± SE. The significance of differences in the measured values within groups was analyzed using a one-way analysis of variance for repeated measures followed by a Fisher’s least significant differences (LSD) test. The significance of differences in the measured values between groups was analyzed using a two-way analysis of variance for repeated measures followed by a Fisher’s LSD test (8). P < 0.05 (2-tailed test) was considered statistically significant.

RESULTS

The effects of L-NAME (37 nmol·kg⁻¹·min⁻¹, group 2) on renal function are presented in Table 1. L-NAME (37 nmol·kg⁻¹·min⁻¹) increased mean arterial pressure by 8 mmHg, decreased RBF (−2.3 ml·min⁻¹·g⁻¹), and lowered absolute sodium and water excretion (−22 and −27%, respectively).

The effects of AT₁ and AT₂ angiotensin receptor blockade on arterial pressure and renal function are presented in Table 1. Valsartan (group 3) reduced mean arterial pressure by 7 mmHg and increased RBF by 1.2 ml/min, but it had no significant effects on renal excretion. PD-123319 (group 5) had no effects on arterial pressure or renal function.

The interactions between angiotensin II and NO on renal function are also presented in Table 1. The administration of valseartan to L-NAME-pretreated rats (group 4) restored MAP, GFR, and sodium and water excretion to near control levels, but it had no effect on the renal vasoconstriction produced by previous NO synthesis blockade. Similarly, PD-123319 abolished the increase in arterial pressure and the reductions in sodium and water excretion produced by the administration of L-NAME, but the fall in RBF resulting from L-NAME was unaffected by the AT₂ antagonist.

The effects of AT₁ or AT₂ angiotensin receptor blockade on pressure diuresis and natriuresis are depicted in Figs. 1–4. Valsartan tended to increase sodium and water excretion at low RPP, although this effect was only significant at 120 mmHg of RPP (Fig. 1). The administration of PD-123319 had no effect on pressure diuresis (Fig. 3).
Table 1. Effects of valsartan or PD-123319 on L-NAME-induced changes in MAP, RBF, GFR, V, UNaV, and FENa in rats with denervated kidney

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP, mmHg</th>
<th>RBF, ml·min⁻¹·g⁻¹</th>
<th>GFR, µl·min⁻¹·g⁻¹</th>
<th>V, µl·min⁻¹·g⁻¹</th>
<th>UNaV, µeq·min⁻¹·g⁻¹</th>
<th>FENa, %</th>
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<td>Contr</td>
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<td>E xpt 1</td>
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<td>135 ± 4</td>
<td>8.6 ± 0.6</td>
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<td>E xpt 2</td>
<td>±3</td>
<td>134 ± 3</td>
<td>8.0 ± 0.5*</td>
<td>1.076 ± 0.49</td>
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<td>1.134 ± 0.49</td>
<td>48.1</td>
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Values are means ± SE. Experimental period (Expt 1), administration of either N-nitro-L-arginine methyl ester (L-NAME, 37 nmol·kg⁻¹·min⁻¹, groups 1, 2, and 3), valsartan (92 µmol/kg, group 4), L-NAME + valsartan (group 5), or PD-123319 (98 nmol·kg⁻¹·min⁻¹, group 6) in rats treated with L-NAME. MAP, mean arterial pressure; RBF, renal blood flow; GFR, glomerular filtration rate; V, urine flow; UNaV, sodium excretion; FENa, fractional sodium excretion; Contr, control. *Significant difference from control value of same group; †significant difference from previous value of same group.

The interactions between angiotensin II and NO on pressure diuresis are presented in Figs. 1–4. L-NAME + valsartan (98 nmol·kg⁻¹·min⁻¹, group 6) reduced the slopes of the pressure diuresis (0.611 vs. 0.230 µl·min⁻¹ of control rats) and rats treated with L-NAME + valsartan. Means ± SE are presented. Significantly different from same value of control group.
0.8, 6.7 ± 0.9, and 6.6 ± 0.7% at 100, 120, and 140 mmHg of RPP, respectively, and in control rats was 1.5 ± 0.3, 3.0 ± 0.4, and 5.1 ± 0.4% (Fig. 1). Despite the fact that the administration of valsartan after L-NAME restored GFR to control levels at all RPP studied, the vasoconstrictor effect of this high dose of L-NAME was unaffected by the AT1 antagonist (Fig. 2). However, the administration of the AT2 antagonist PD-123319 abolished the excretory effects of L-NAME (group 6, Fig. 3), increasing the slopes of the pressure diuresis (0.822 ± 0.184 µl·min⁻¹·mmHg⁻¹) and natriuresis responses (0.146 ± 0.028 µeq·min⁻¹·mmHg⁻¹) to values that were not significantly different from responses of control rats (group 1). However, PD-123319 had no effect on RBF and GFR when administered after L-NAME (Fig. 4).

**DISCUSSION**

Previous studies have shown that blockade of NO reduces RBF and sodium and water excretion (12, 18, 19, 26) and also blunts pressure diuresis (5, 6, 18, 19). The effects of L-NAME seem to result at least in part from potentiation of the renin-angiotensin system (29, 33). In addition, this potentiation of the actions of angiotensin II appears to be an important factor in the pathogenesis of hypertension induced by chronic NO synthesis blockade (10, 22). The kidney plays an important role in the long-term control of arterial pressure; arterial hypertension may only occur when the pressure diuresis response is reset toward higher pressures (2). Thus it seems reasonable to postulate that part of the effect of NO synthesis blockade on pressure diuresis may be mediated through the renin-angiotensin system. However, at present, little is known about the interactions between NO and the renal vasoconstrictor systems in the control of pressure diuresis and natriuresis.

In the present study, NO synthesis blockade raised arterial pressure by ~10 mmHg and also reduced RBF...
and sodium and water excretion. In addition, the administration of L-NAME shifted pressure diuresis and natriuresis toward higher pressures, in agreement with previous reports (5, 6, 18, 19). This effect seems to result from an increased tubular sodium reabsorption at 140 mmHg of RPP, as indicated by the fall in the fractional excretion of sodium produced in rats given L-NAME. However, NO synthesis blockade also reduced RBF and GFR, and those hemodynamic effects could have contributed to reduce the slope of the pressure diuresis and natriuresis response.

It is well established that the renin-angiotensin system is an important modulator of sodium excretion and arterial pressure. Chronic administration of angiotensin II shifts the relationship between sodium intake and arterial pressure toward higher pressures, whereas blockade of the renin-angiotensin system resets the chronic renal function curve toward lower pressures (9). Also, it has been previously demonstrated that the acute administration of angiotensin II blunts pressure diuresis in volume-expanded rats (21). On the other hand, the blockade of the renin-angiotensin system with captopril in volume-expanded rats (21) or with losartan in dogs (19) failed to affect the acute pressure diuresis response. This apparent contradiction is consistent with the observation that losartan (10 mg/kg) did not affect pressure diuresis in angiotensin II-infused rats (14), indicating that the impairment produced by angiotensin II on pressure diuresis is not mediated through activation of AT1 receptors. In contrast, the AT2 agonist CGP-42112B blunted pressure diuresis, whereas AT2 receptor blockade with PD-123319 shifted the pressure diuresis curve to the left in angiotensin II-infused rats (14). It seems that, although AT2 receptors are sparse within the adult rat kidney, the effects of angiotensin II on pressure diuresis and natriuresis are mediated through the AT2 receptor subtype (7, 14).

In the present study, it was observed that valsartan reduced arterial pressure slightly and increased RBF, indicating that renin secretion is not abolished in this volume-expanded preparation. Valsartan also slightly increased sodium and water excretion at low RPP, although this effect was only significant at 120 mmHg of RPP. These results are compatible with the idea that the increased renin secretion produced as arterial pressure falls contributes to reduce sodium and water excretion, as previously postulated by Romero et al. (25). In the present study, AT1 receptor blockade had no systemic or renal effects, in agreement with a previous report (15). This indicates that, in control conditions in this preparation, most of the actions of endogenous angiotensin are mediated through the AT1 receptor subtype (which represents 90–95% of angiotensin receptors in adult rat kidneys), and only when intrarenal levels of angiotensin are elevated (i.e., in angiotensin-infused rats) is PD-123319 able to shift pressure diuresis to the left (14).

In the present study, the administration of valsartan after L-NAME lowered arterial pressure to control levels, but it had no effect on the renal vasoconstriction induced by NO synthesis blockade, in agreement with previous studies showing that L-NAME produced an important fall in RBF in rats (33) and dogs pretreated with losartan (19). This contradicts the work of Sigmon et al. (29), who found that pretreatment with losartan abolished the renal hemodynamic effects of L-NAME in rats. The reasons for those discrepancies are unknown. Nevertheless, in the present study, AT1 receptor blockade abolished the effects of L-NAME on glomerular filtration and sodium and water excretion. Those results are in accord with Takenaka et al. (33), who observed that losartan prevented the effects of L-NAME on GFR and sodium and water excretion in rats. In addition, in the present study, the administration of valsartan after L-NAME elevated sodium and water excretion at all RPP studied, but it did not affect the slope of the pressure diuresis and natriuresis relationship, indicating that the effect of L-NAME reducing the sensitivity of the pressure diuresis response is not dependent on the activation of AT1 receptors. This is in agreement with data from a study performed by Majid et al. (19), who reported that the effect of L-NAME blunting pressure diuresis was unaffected by pretreatment with losartan in dogs. These results may be because the impairment of pressure diuresis and natriuresis produced by angiotensin II is not mediated by the AT1 receptor subtype (14). The elevation of sodium and water excretion produced by valsartan in L-NAME-
pretreated rats in our study was greater than the effect of valsartan alone, and it may be a result of the fact that renal tissue angiotensin II increases after NO synthesis blockade (33). In this regard, Romero et al. (25) postulated that at low RPP, the low flow and shear stress should reduce NO production, and this might contribute to the increase in renin secretion; at high RPP, shear stress and NO increase within the kidney, contributing to inhibit renin secretion. Therefore, after NO synthesis inhibition, renin secretion rate increases (28), and this, associated with the absence of NO restraint of the tubular effects of angiotensin, may contribute to the effect of L-NAME on sodium and water excretion.

In the present study, blockade of AT2 receptors with PD-123319 in rats given L-NAME normalized the slope of the pressure diuresis and natriuresis relationship. This interaction between the renin-angiotensin system and NO on pressure diuresis may result from the elevation of endogenous intrarenal angiotensin produced by NO synthesis blockade (33), because the subtype AT2 comprises 5–10% of renal angiotensin receptors and because PD-123319 seems to affect pressure diuresis only when angiotensin II is elevated by intravenous infusion (14), whereas it has no renal effects in rats maintained on a low-sodium diet (15). The mechanism by which PD-123319 increases the slope of the pressure natriuresis response in rats treated with L-NAME is unknown. However, it has been recently reported that AT2 receptor blockade potentiates the angiotensin-induced prostaglandin E2 (PGE2) production by activation of the AT1 receptor subtype (30), and it is well known that PGE2 urinary excretion increases as arterial pressure rises, whereas cyclooxygenase blockade reduces both urinary prostaglandin excretion and pressure natriuresis (1, 11, 24). Therefore, it may be hypothesized that the effects of PD-123319 on pressure diuresis may be mediated through intrarenal prostaglandins.

In summary, the results of the present study indicate that the impairment induced by NO synthesis blockade on the pressure diuresis response depends on the presence of an intact renin-angiotensin system functioning through activation of AT2 angiotensin receptors.

Perspectives

In recent years, considerable advances have been made in our understanding of the role of the pressure diuresis and natriuresis response controlling sodium excretion in normal conditions and in hypertension. This mechanism of control of sodium excretion is thought to be nonadaptable and responsible for the long-term control of arterial pressure. The malfunction of pressure diuresis leads to arterial hypertension, an important risk factor in cardiovascular disease. It has recently been postulated that NO may be the mediator linking increases in arterial pressure with reduced tubular sodium reabsorption. According to this hypothesis, arterial pressure is dependent on the mechanisms regulating the renal actions of NO. A better understanding of the interactions between NO and other renal hormones may help in the prevention and treatment of arterial hypertension and its cardiovascular consequences.

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