Role of AT$_1$ receptors in the renal papillary effects of acute and chronic nitric oxide inhibition

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Ortiz, M. Clara, Lourdes A. Fortepiani, Francisco M. Ruiz-Marcos, Noemí M. Atucha, and Joaquín García-Estan. Role of AT$_1$ receptors in the renal papillary effects of acute and chronic nitric oxide inhibition. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R760–R766, 1998.—Nitric oxide (NO) is a vasodilator substance controlling renal papillary blood flow (PBF) in the rat. In this study we have evaluated the role of AT$_1$ angiotensin II receptors as modulators of the whole kidney and papillary vasoconstrictor effects induced by the acute or chronic inhibition of NO synthesis. Experiments have been performed in anesthetized, euvolemic Munich-Wistar rats prepared for the study of renal blood flow (RBF) and PBF. In normal rats, acute administration of the NO synthesis inhibitor N-nitro-L-arginine methyl ester (L-NAME) increased mean arterial pressure (MAP) and decreases in RBF or PBF secondary to L-NAME. In animals around the left renal artery connected to an electromagnetic flowmeter (Skalar 1401, Skalar Medical, Delft, The Netherlands) and an electromagnetic flowmeter (Periflux PF3; Perimed, Stockholm, Sweden). The laser probe was fixed using 3,5'-cyclic monophosphate formation (26). Its release from the endothelial layer is ideal to counteract the effects of vasoconstrictor substances, and, in this way, many different laboratories have described that NO interacts with other intrarenal or extrarenal systems (13). Especially abundant is the literature regarding the interactions of NO with the renin-angiotensin system. Thus it seems that NO is a potent inhibitor of renin release (13, 26, 30); however, this has not always been unequivocally demonstrated. Similar controversies can be found in the studies dealing with the possible mediation by angiotensin (ANG) II of the renal effects that occur after NO synthesis inhibition. Thus some investigators have reported that ANG II contributes to the renal effects of NO synthesis inhibition (8, 17, 27, 28). Others, however, found that ANG II did not modulate the response to NO inhibition (1, 9, 10, 23).

However, all these studies evaluated renal hemodynamics at the whole kidney level, and the interaction of NO and ANG II in the control of renal blood flow (RBF) in other areas of the kidney has not been completely studied. Thus Ohishi et al. (17) found that the ANG II blockade of AT$_1$ receptors attenuated the vasoconstriction elicited by NO synthesis inhibition in juxtaplomerular afferent and efferent arteriolar perfused in vitro. However, it is not known whether similar effects occur in vivo. In fact, in vivo experiments by Parekh et al. (20) showed that NO modulated the ANG II response of cortical but not outer medullary blood flow. Moreover, the extent of these interactions in the maintenance of papillary blood flow (PBF) has not been evaluated yet. It is possible that, similar to what has been found in other circumstances, a differential control of cortical and papillary blood flow may be present in these circumstances (11, 13, 18). Therefore, in the present study we have evaluated the interactions between NO and ANG II in the control of whole kidney and papillary blood flow. To do this, we have used losartan to analyze the role of AT$_1$ ANG II receptors in the renal effects consequence of the acute or chronic NO synthesis inhibition. Finally, the direct effects of ANG II in the whole kidney and papillary circulations and their modulation by NO have also been investigated.

METHODS

Male Munich-Wistar rats (200–250 g) born and raised in the Animalario of the Universidad de Murcia were used. In all experiments performed, the authors followed the guidelines for the ethical treatment of the animals of the American Physiological Society and the European Union.

Surgical Preparation

All experiments were performed in rats fasted for 16 h before the experiment, following a method previously described (18). The animals were anesthetized with thiobutobarbital (Inactin, 100 mg/kg body wt ip, Research Biochemicals International, Natick, MA) and placed on a heated surgical table to maintain rectal temperature at 36.5–37°C. Catheters were inserted into the right femoral artery (to measure blood pressure) and into the right femoral vein (for infusions). A tracheotomy tube was placed to facilitate respiration. The left kidney was exposed by a midline abdominal incision and placed in a holder specially built to isolate the kidney from respiratory motion. Then, the renal papilla was exposed by excising the ureter and was surrounded by moistened cotton. PBF was measured using a laser-Doppler flowmeter (Periflux PF 3; Perimed, Stockholm, Sweden). The laser probe was fixed to a micromanipulator and placed on the papillary surface, always probing the same mid-papillary region at an angle of ~30°. RBF was determined by a 0.8-mm flow probe placed around the left renal artery connected to an electromagnetic flowmeter (Skalar 1401, Skalar Medical, Delft, The Nether-
lands). Zero flow was obtained by carefully occluding the renal artery. Finally, the abdominal opening was covered with a piece of Parafilm (American National Can, Greenwich, CT) to minimize evaporation. All animals received an intravenous infusion of 0.9% NaCl solution containing 1% bovine serum albumin at a rate of 2 ml · 100 g−1·h−1. After surgery, hematocrit was measured and adjusted to 44 ± 1% with 6% albumin. At least 60 min were allowed before starting the experiments (see Experimental Protocols). Mean arterial pressure (MAP), RBF, and PBF were continuously recorded throughout the experiment. PBF was obtained as perfusion units and expressed as volts (100 U corresponding to 1 V). The flowmeter was calibrated by using a colloidal suspension of latex particles (Perimed Motility Standard), which, at room temperature, gives a signal of 250 U (2.5 V, ± 5%). At the end of the experiment, the renal artery was completely occluded to obtain a zero flow reading in the laser-Doppler flowmeter and this value, ~30 U (0.03 V), was subtracted from the signal recorded during the experiment. Then the rat was euthanized by thoracotomy, and the left kidney was removed, blotted dry, and weighed.

**Experimental Protocols**

**Protocol 1. Acute NO synthesis inhibition: effects of acute or chronic AT1 receptor blockade with losartan.** The ability of losartan to interfere with the effects produced by the acute inhibition of NO synthesis was evaluated in three groups of rats, two of them pretreated either acutely or chronically with the AT1 blocker and another one that received losartan after the administration of the NO synthesis inhibitor Nω-nitro-L-arginine methyl ester (L-NAME; Sigma Chemical, Madrid, Spain, 10 mg/kg iv as a bolus). The dose of the latter was selected in preliminary studies as the dose that produced the appropriate degree of AT1 blockade (3.5 ± 0.5). In this group, after obtaining the baseline parameters, losartan was given at the same dose as in protocol 1, and the experimental values were obtained 15 min later when the response had reached a stable level. In these animals, after surgery and stabilization, only the baseline values were obtained.

**Protocol 2. Acute NO synthesis inhibition with control of renal perfusion pressure.** Because it has been shown that PBF varies with the level of renal perfusion pressure (RPP), in these series of experiments, we have controlled RPP throughout the experiment to maintain it at the baseline level. This was done with an adjustable mechanical occluder placed around the abdominal aorta above the level of the renal arteries. These experiments have been performed in the same groups of protocol 1 as follows: 1) acute L-NAME + acute losartan (n = 5), 2) acute losartan + acute L-NAME (n = 5), and 3) chronic losartan + acute L-NAME (n = 6).

**Protocol 3. Chronic NO synthesis inhibition: effects of acute or chronic AT1 receptor blockade with losartan.** In these experiments, chronic NO synthesis inhibition was achieved by adding L-NAME to the drinking water during 2 wk (40 mg·kg−1·day−1). Two groups were studied in this protocol. 1) Chronic L-NAME + acute losartan (n = 6): in these animals, after the stabilization from surgery and obtainment of the basal values, losartan was injected at the same dose as in protocol 1, and the experimental values were obtained 15 min later when the response had reached a stable level. 2) Chronic L-NAME + chronic losartan (n = 6): these animals were also chronically treated with losartan (10 mg·kg−1·day−1 in the drinking water, simultaneously with the NO inhibitor). In these animals, after surgery and stabilization, only the baseline values were obtained.

**Protocol 4. Effects of ANG II administration: role of NO.** In these experiments (n = 7), after stabilization from surgery and the obtainment of baseline parameters, the animals received ANG II (Sigma) at doses of 100 and 300 ng·kg−1·min−1 iv for 10 min each, with enough time between doses to allow for the recovery of the measured parameters (~10 min). Then L-NAME was administered intravenously at the dose of 10 mg/kg and, ~15 min later, the ANG II infusions were repeated.

**Plasma Renin Activity Determination**

Plasma renin activity (PRA) was determined by radioimmunoassay (Sorin Biomedica Diagnostics, Saluggia, Italy) in blood samples (500 μl) obtained with 6% EDTA in the following situations: 1) in control animals (n = 5), a basal sample after surgery and stabilization and another sample 15 min after the administration of a bolus of 10 mg/kg iv of L-NAME, and 2) in chronic L-NAME-treated rats (n = 7) after surgery and stabilization.

**Statistical Methods**

Data are presented as the means ± SE. Significance of the differences in measured values within the groups was evaluated using an analysis of variance for repeated measures, followed by Duncan’s multiple-range test. The differences in measured values between groups were analyzed using a two-way analysis of variance followed by Duncan’s multiple-range test. Differences were considered statistically significant at a P level < 0.05.

**RESULTS**

**Protocol 1. Acute NO Synthesis Inhibition: Effects of Acute or Chronic AT1 Receptor Blockade With Losartan**

The data obtained in this protocol are represented in Fig. 1, while Fig. 2 shows the percentage changes elicited in each variable by the administration of L-NAME. In the first group composed of control animals, the administration of L-NAME changed significantly all three parameters studied. Thus MAP increased from 117.1 ± 4.1 to 157.9 ± 4.8 mmHg (a 35.0 ± 1.7% increase), RBF decreased from 6.2 ± 0.3 to 3.1 ± 0.3 ml·min−1·g−1 (a 50.8 ± 3.3% reduction), and PBF descended from 2.31 ± 0.06 to 1.39 ± 0.08 U (a 40.0 ± 2.7% decrease). Administration of losartan to these animals slightly but significantly lowered MAP (to 147.7 ± 4.2 mmHg) and did not statistically change RBF (3.3 ± 0.3 ml·min−1·g−1) or PBF (1.36 ± 0.11 U). Basal hematocrit in these animals was 44.3 ± 0.5.
and increased slightly after L-NAME administration (45.9 ± 0.6) and remained similar after losartan (45.3 ± 0.4).

In the second group, acute administration of losartan decreased MAP significantly from 112.3 ± 2.4 to 102.3 ± 2.5 mmHg and PBF from 2.32 ± 0.11 to 2.19 ± 0.14 U, while RBF increased significantly from 7.7 ± 0.6 to 8.4 ± 0.8 ml·min⁻¹·g⁻¹. The subsequent injection of L-NAME significantly changed the three parameters, increasing MAP 23.8 ± 2.7% and decreasing RBF 38.5 ± 3.0% and PBF 35.6 ± 3.5%. However, whereas both the elevation in MAP and the decrease in RBF were lower in comparison with the control group, the decrease in PBF was similar in these two groups. Basal hematocrit was 45.4 ± 0.5 and was well maintained throughout the experiment.

In the third group, the animals chronically treated with losartan also showed a lower baseline MAP (105.5 ± 2.8 mmHg) and higher RBF (8.3 ± 0.7 ml·min⁻¹·g⁻¹) compared with group 1 of control untreated animals but similar PBF (2.44 ± 0.05 U). The subsequent administration of L-NAME decreased RBF 37.8 ± 5.9%, a value significantly different than that observed in the control group, and increased MAP 32.5 ± 2.6% and decreased PBF 41.8 ± 3.3%, both values similar to those observed in the first group of this protocol. Basal hematocrit in this group was 44.2 ± 0.6% and was well maintained during the experiment.

Protocol 2. Acute NO Synthesis Inhibition With Control of RPP

Table 1 shows the data obtained in this protocol together with the results of protocol 1, in which RPP was not controlled. As observed, maintaining RPP at the baseline level slightly decreased PBF values when compared with the values observed in the animals of protocol 1. However, these differences were not statistically significant. Similarly, the PBF values were not statistically different in the three groups.

Protocol 3. Chronic NO Synthesis Inhibition: Effects of Acute or Chronic AT₁ Receptor Blockade With Losartan

Figure 3 shows data from protocol 3. In the first group, rats that received L-NAME in the drinking water for 15 days had elevated MAP (176.4 ± 3.5 mmHg) and reduced RBF (4.4 ± 0.5 ml·min⁻¹·g⁻¹) and PBF (1.49 ± 0.09 U). The acute administration of losartan decreased MAP to 162.4 ± 4.7 mmHg and elevated RBF to 5.2 ± 0.3 ml·min⁻¹·g⁻¹ and PBF to 1.83 ± 0.12 U, and these changes were all statistically significant. Hematocrit in these animals was 45.6 ± 0.2 and did not change significantly after losartan injection. Figure 3 also shows the basal values of the second group.

Table 1. Comparison of the PBF responses obtained in the groups of protocols 1 and 2 without and with control of RPP

<table>
<thead>
<tr>
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<th>PBF at Spontaneous RPP</th>
<th>PBF at Controlled RPP</th>
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<tr>
<td></td>
<td>RPP</td>
<td>PBF</td>
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<tr>
<td>Basal-L-NAME-Los</td>
<td>147.7±4.2</td>
<td>1.36±0.11</td>
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<tr>
<td>Basal-Los-L-NAME</td>
<td>139.5±3.1</td>
<td>1.42±0.08</td>
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<tr>
<td>Chronic Los-L-NAME</td>
<td>126.3±2.6</td>
<td>1.38±0.05</td>
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Data are means ± SE. PBF, papillary blood flow; RPP, renal perfusion pressure; L-NAME, N°-nitro-L-arginine-methyl ester; Los, losartan.
group of animals simultaneously and chronically treated with L-NAME and losartan. As observed, MAP was lower than in the previous group (139.3 ± 4.1 mmHg), but still higher than in the control group of protocol 1 (117.1 ± 4.1 mmHg). RBF was normalized (6.4 ± 0.5 ml·min⁻¹·g⁻¹), but PBF (1.68 ± 0.08 U) was still lower than in the control group (2.31 ± 0.06 U) and not different from the value observed in the first group of this protocol. Hematocrit in this group was 43.4 ± 1.3.

Protocol 4. Effects of ANG II Administration:
Role of NO

Baseline MAP (118.3 ± 3.0 mmHg), RBF (6.7 ± 0.2 ml·min⁻¹·g⁻¹), and PBF (2.33 ± 0.07 U) were all significantly and dose dependently changed by both doses of ANG II. As observed in Fig. 4, MAP was increased 7.9 ± 1.0% by the dose of 100 ng·kg⁻¹·min⁻¹ and 22.9 ± 2.3% by the dose of 300 ng·kg⁻¹·min⁻¹. RBF decreased 24.9 ± 1.9 and 38.4 ± 3.9%, respectively, and PBF increased 8.8 ± 1.8 and 13.4 ± 2.3%, respectively. Acute inhibition of NO synthesis with L-NAME increased MAP to 156.3 ± 2.9 mmHg and decreased RBF to 4.4 ± 0.3 ml·min⁻¹·g⁻¹ and PBF to 1.60 ± 0.08 U. In this situation, both doses of ANG II also increased MAP, but less than in the previous instance (5.1 ± 1.2 and 9.4 ± 3.6%, respectively), and decreased RBF (17.1 ± 3.9 and 38.5 ± 7.1%, respectively) in a similar amount to that observed in the basal situation. However, PBF responses were blunted in comparison with the basal situation and increased slightly with the lower dose (2.9 ± 2.6%) and decreased with the higher dose (4.4 ± 3.9%). The hematocrit in these experiments was 44.5 ± 0.2 in the basal period and did not change significantly throughout the experiment.

PRA determination. In control animals, PRA was 5.3 ± 0.7 ng ANG I·ml⁻¹·h⁻¹ and decreased slightly, but not significantly, after acute L-NAME administration (4.8 ± 0.9). PRA was also lower in the chronic L-NAME-treated rats (4.2 ± 1.0), but this value did not reach statistical significance compared with the other PRA values.

DISCUSSION

The present results suggest the existence of a differential interaction between NO and ANG II, depending on the duration of the NO synthesis inhibition achieved. Thus, in the acute studies, L-NAME importantly decreased PBF and this effect was not prevented or reversed by the blockade of the AT₁ ANG II receptors, indicating that the acute reduction of PBF induced by the NO synthesis inhibitor is not mediated by ANG II.
However, chronic inhibition of NO synthesis also reduces PBF, but this effect is partly dependent on the stimulation of AT$_1$ ANG II receptors.

It is known that the renal medulla is capable of producing a great amount of NO (2, 26), and thus the acute inhibition of NO synthesis results in an important reduction of PBF (12, 18). We have recently shown that the renal papillary vasoconstrictor effect elicited by the NO synthesis inhibitor L-NAME is not modified by previous prostaglandin synthesis inhibition with indomethacin (18), and the present results show that ANG II blockade with losartan also does not modify the L-NAME effect. Moreover, when RPP was prevented from increasing, similar results were obtained, therefore indicating that the differences in RPP observed in the experimental groups are not contributing to the PBF level. This agrees with previous results (18) indicating that acute NO synthesis inhibition renders the papillary circulation very insensitive to changes in RPP. Although the possible mediation of other vasoconstrictor factors has not been evaluated yet, these results suggest that the reduction of PBF elicited by acute NO inhibition is a consequence of the disappearance of the tonic release of NO into the medullary environment.

Previous observations have shown that NO functions as an important factor that counteracts the renal effects of vasoconstrictor substances, such as ANG II (8, 20, 25). Then, it may be hypothesized that the immediate disappearance of NO brought about by administration of the NO synthesis inhibitor would have allowed the expression of the vasoconstrictor effects of ANG II in the papillary circulation. However, previous investigations by several laboratories have shown that ANG II does not decrease PBF in the rat, which may even increase in some circumstances (4, 6, 11, 16). Also, the present results demonstrate that two pressor doses of ANG II that reduce RBF to an important degree increase PBF, although in a relatively modest way. This result is in accordance with previous results by Nobes et al. (16), who showed that this effect was due to the intrarenal production of kinins and independent of the level of RPP. Interestingly, our data indicate that the elevation of PBF brought about by ANG II is greatly dependent on an increased production of NO, because it was reduced at the low dose and reversed at the highest dose by the NO synthesis inhibitor. This result is not contradictory with the data by Nobes et al. (16), because it has been suggested that the renal effects of the kinins are mediated by NO (26). Therefore, the present results suggest that NO is an important physiological antagonist of ANG II in the renal papillary circulation, where it can effectively maintain a normal blood flow to this important kidney zone, despite important reductions of blood flow to the cortical regions. However, even when NO was inhibited, the PBF effects of ANG II were small, thus suggesting that, under physiological conditions, this powerful vasoconstrictor is not an important controller of blood flow in the renal papilla.

Our results are also similar to data of Parekh et al. (20), who have recently demonstrated in acutely L-NAME-pretreated rats that ANG II doses that decrease cortical blood flow by 40% do not affect outer medullary blood flow. Due to the important presence of ANG II receptors in the rat renal medulla, these results seem to be paradoxical. However, by using high-resolution electron microscopic autoradiography, Zhuo et al. (32) have demonstrated that ANG II binding sites are absent in the inner medulla of the rat and that the primary sites for ANG II binding are in the inner stripe of the outer medulla and, more specifically, only in the interstitial cells located between the tubules and the vasa recta bundles. Whether the interstitial cells participate in the control of medullary blood flow is not clear yet, but they are known to synthesize prostaglandins and have a contractile function (7). In this sense, recent results indicate that vasodilatory prostaglandins counteract the vasoconstrictor effects of ANG II in the rat renal outer medulla in vivo (21) and in isolated microperfused outer medullary vasa recta (19).

Different than these acute studies, administration of the AT$_1$ ANG II receptor blocker to L-NAME hypertensive rats produced renal vasodilatory effects both at the whole kidney level and in the papillary circulation. Our results show that these rats made hypertensive by chronically inhibiting NO synthesis show a reduced renal PBF, as well as the decrease in RBF previously observed (5). This result is in agreement with data showing that a chronic infusion of L-NAME into the medullary interstitium that selectively reduces PBF produces arterial hypertension (15). It is likely that the reduced PBF found in our L-NAME hypertensive rats contributes to the maintenance of the elevated blood pressure levels and the severely blunted pressure diuresis and natriuresis response characteristic of this NO-deficient model (5). Although the acute administration of NO synthesis inhibitors also reduces the pressure diuresis and natriuresis response, the administration of losartan in this setting does not seem to have any beneficial effect (9). However, whether ANG II receptor blockade improves the pressure diuresis and natriuresis response of L-NAME hypertensive rats is not known yet. It is tempting to speculate that, because losartan increased PBF in these hypertensive animals, the pressure diuresis and natriuresis should also improve. However, this has not yet been proven.

Several investigators have shown that the renin-angiotensin is involved in the maintenance of the arterial hypertension exhibited by models of chronic NO synthesis inhibition (22, 24, 31). Our results are in keeping with these studies, because acute losartan administration decreased MAP and elevated blood flows, although without reaching normal levels, both in the renal cortical and papillary circulation of these animals. Interestingly, the chronic administration of losartan simultaneously with the NO synthesis inhibitor further decreased blood pressure and normalized RBF. It is likely that the smaller effect of acute losartan is the consequence of the blockade of the immediate direct pressor or constricting effects of the peptide. However, chronic losartan would probably also block other ANG II-dependent effects which, acting throughout the phase
of chronic NO deficiency, would not disappear after the acute blockade. Among them, activation of the sympathetic nervous system and structural alterations in resistance vessels could well be involved.

However, the lower PBF of the L-NAME-treated animals was not normalized by the concurrent chronic administration of losartan, and, in fact, this value was similar to the one observed in the other group of L-NAME-treated rats that received the acute dose of losartan. Again, this result suggests that the percentage of the PBF reduction due to ANG II, even with the chronic absence of NO, is not too great. It is possible, therefore, that the lack of NO is the main mechanism responsible for the lower PBF of the NO-deficient hypertensive rats. However, other vasoconstrictor factors, such as the sympathetic nervous system and endothelin, may also be contributing to the reduced PBF present in the L-NAME hypertensive rats.

The present results indicate that the involvement of ANG II in the renal papillary effects induced by L-NAME is very different depending on the type of NO synthesis inhibition achieved, either acute or chronic. The mechanisms by which losartan increases PBF in the chronic hypertensive rats are not known, but they may be related to the vasodilator effect elicited by the AT$_1$ receptor blocker at the whole kidney level. Also, it is possible that the chronic deficiency of NO renders the papillary circulation more sensitive to the vasoconstrictor effects of ANG II, as it happens after the acute inhibition of NO synthesis shown by the present results. Another possibility is that vasodilatory prostaglandins may not compensate for the chronic absence of NO (5). Thus it has been shown that the chronic administration of L-NAME is not accompanied by an elevated excretion of vasodilatory prostaglandins (14).

Overall, the present results suggest that NO is a very important vasodilator factor in the renal papillary circulation and that its deficiency cannot be compensated by other vasodilator substances.

Our results also show that, contrary to what was observed in the hypertensive animals, ANG II does not seem to participate in the whole kidney vasoconstrictor effects elicited by the acute inhibition of NO synthesis. Thus, although the percentage decrease in RBF produced by L-NAME was lower in the presence of either acute or chronic administration of losartan, the absolute decrease in RBF was of a similar magnitude in the untreated and losartan-treated animals. Therefore, ANG II did not interfere with the ability of L-NAME to reduce RBF. However, the presence of losartan vasodilates the kidney and this helps to maintain a higher RBF than in the untreated animal. It is important to notice that these differences between acute or chronic NO inhibition occur in the absence of significant changes in PRA. Thus PRA was not significantly different in these situations, and this may be the result of two opposing stimuli on renin release: on the one hand, a tendency to increase due to the disappearance of NO, on the other hand, a tendency to decrease due to the elevation in blood pressure. It seems that the latter is the predominant stimulus, at least in our experimental conditions, because a tendency for lower PRA values was observed after both the acute or chronic NO synthesis inhibition. In any case, these PRA measurements do not help in determining the reason of the different effect of losartan in the acute or chronically NO-inhibited animals. It is possible that the intrarenal levels of ANG II change in a different manner not reflected by the systemic renin values. Clearly, more studies are needed to evaluate the intrarenal interactions between NO and ANG II.

Interestingly, only the acute pretreatment with losartan also blunted the pressor effect of the NO inhibitor. It has been suggested that losartan can increase the production of NO (3), and it is possible that the chronic administration of losartan results in a higher production of NO than after its acute injection. Alternatively, it is also possible that the chronic blockade of AT$_1$ ANG II receptors produces a vasodilating effect mediated by the activation of AT$_2$, by circulating ANG II (29).

In summary, the present results show that there is a differential role for ANG II in the modulation of the whole kidney and papillary circulations in response to L-NAME administration. Thus acute inhibition of NO synthesis decreases renal and papillary blood flow by an effect independent of the activation of the AT$_1$ ANG II receptors. However, chronic inhibition of NO synthesis also reduces PBF and RBF and this effect is partly dependent on the activity of the AT$_1$, ANG II receptors.

Perspectives

The knowledge of the interactions among NO and ANG II in the control of intrarenal blood flow is far from complete. The present results, obtained in anesthetized Munich-Wistar rats, confirm previous observations showing that ANG II, contrary to its role on the cortical circulation, has little vasoconstrictor effect in the papillary circulation. This seems to be due to the stimulating action of ANG II on medullary NO production, which maintains an adequate perfusion to the deeper zone of the kidney despite very important reductions of total renal blood flow. This stresses the role of medullary NO as one of the important factors, prostaglandins being the other one (18), controlling papillary blood flow in the rat. Our results also disclose that ANG II participates in the renal papillary effects consequence of the inhibition of NO synthesis only when NO production is chronically inhibited. Thus the blockade of AT$_1$, ANG II receptors prevents the renal vasoconstriction and, importantly, reduces the elevated blood pressure levels shown by the L-NAME hypertensive animals, but without completely correcting the reduced papillary blood flow characteristic of this model. This may be relevant to studies dealing with the role of ANG II in the development and maintenance of NO-deficient arterial hypertension and suggests that the renal medullary consequences of the NO-deficient hypertension would not only be reversed with the blockade of AT$_1$, ANG II receptors.
REFERENCES


