Angiotensin Dependence of Endothelium-Mediated Renal Hemodynamics

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Endothelium-derived relaxing factor has been shown to regulate renal blood flow, and inhibition of its synthesis increases blood pressure and renal vascular resistance and decreases renal blood flow. Using the substrate antagonist Nω-nitro-l-arginine methyl ester (L-NAME), we tested whether renal vasoconstriction induced by endothelium-derived relaxing factor synthesis inhibition could be mediated in part by angiotensin II. In 14 control rats, 10 mg/kg body wt L-NAME increased blood pressure from 106±6 to 126±6 mm Hg (p<0.001), increased renal vascular resistance by 74% (from 19.3±2.6 to 33.6±2.9 resistance units), and decreased renal blood flow by 34% (from 5.9±0.5 to 3.9±0.3 ml · min⁻¹ · g kidney wt⁻¹, p<0.005). When six rats were treated with 10 mg/kg body wt of the angiotensin receptor antagonist DuP 753, L-NAME increased blood pressure from 84±4 to 106±4 mm Hg (p<0.001); however, renal vascular resistance increased by only 27% (from 13±2 to 17±3 resistance units, p<0.01; p<0.05 different from control value) and renal blood flow was unchanged. Likewise, after pretreatment of six rats with 32 μg/100 g body wt of the angiotensin converting enzyme inhibitor enalaprilat, L-NAME increased blood pressure from 88±5 to 124±6 mm Hg (p<0.001) and renal vascular resistance by 54% (from 12±1 to 18±3 resistance units, p<0.01; p<0.05 different from control value) but renal blood flow was unchanged. Additionally, in enalaprilat-treated rats L-NAME caused a transient increase in renal blood flow that was not apparent in rats pretreated with a kinin analogue antagonist or indomethacin. Thus, inhibition of endothelium-derived relaxing factor synthesis produces an angiotensin-mediated decrease in renal blood flow that is independent of L-NAME’s systemic pressor effect. This suggests that renal endothelium-derived relaxing factor buffers the vasoconstrictor influence of endogenous angiotensin, particularly in the kidney.

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Key WORDS • endothelium-derived relaxing factor • nitric oxide • arginine • kininase II • kinins • angiotensin II • prostaglandins • renal circulation

The regulation of renal circulation is controlled by a number of factors, including intrinsic or myogenic autoregulation,1 tubuloglomerular feedback,2 and various vasoactive factors.3 Some of these factors, such as endothelium-derived relaxing factor (EDRF), endothelin, and prostacyclin (PGI₂), are endogenous products of the renal endothelium. The importance of EDRF, presumably nitric oxide or an NO-containing compound,4–6 in maintaining normal renal blood flow (RBF) has been demonstrated by a number of investigators. Inhibition of EDRF synthesis using either Nω-nitro-l-arginine methyl ester (L-NAME) or N⁰-monomethyl-l-arginine (L-NMMA)7,8 results in decreased RBF9–11 and increased renal vascular resistance (RVR). This increase in RVR is presumably due to removal of intrinsic EDRF-mediated tonic renal vasodilation.9,12 Decreased RBF is seen in the presence of a large increase in renal perfusion pressure (i.e., blood pressure). Baylis et al9 have demonstrated in rats that the decrease in RBF caused by inhibition of EDRF synthesis was accompanied by a disproportionate decrease in glomerular filtration rate (GFR) compared with the change in RBF, resulting in an increased filtration fraction (FF). These investigators suggested that under basal conditions, tone release of EDRF is important in maintaining normal RBF and renal function. Previous studies using direct intrarenal infusion of angiotensin II (Ang II)13–15 resulted in decreased RBF and GFR but increased FF. Similar disproportionate changes in RBF and GFR, induced by either EDRF synthesis inhibitors or Ang II infusion, suggest that the renal vasoconstriction associated with EDRF synthesis inhibition may be mediated, at least in part, by Ang II. Thus EDRF within the renal vasculature could buffer Ang II by opposing Ang II-mediated vasoconstriction.

Our studies have been designed to determine the role played by Ang II in the decrease in RBF seen after EDRF synthesis inhibition. In the first series of studies, we demonstrated the decrease in RBF in response to L-NAME. Next we investigated the effect of L-NAME on RBF in rats pretreated with either of two different inhibitors of the renin-angiotensin system, the Ang II receptor antagonist DuP 733 and the angiotensin converting enzyme inhibitor enalaprilat. We hypothesized that if endogenous Ang II is an important mediator of
the renal hemodynamic response to inhibition of EDRF synthesis, then both agents should attenuate the decrease in RBF seen when EDRF synthesis is inhibited. Since angiotensin converting enzyme (kininase II) inhibition also potentiates endogenous kinins and kinins are known to stimulate EDRF, we also studied the effect of a kinin analogue antagonist after enalaprilat on the response to L-NAME. Finally, since endothelial cells produce the vasodilator PG12 and this can also be stimulated by kinins, we studied the effect of cyclooxygenase inhibition by indomethacin in the presence of enalaprilat on the response to L-NAME.

**Methods**

Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, Mass.) weighing 320–450 g fasted overnight but were allowed free access to water. On the day of the experiment they were anesthetized with 125 mg/kg body wt i.p. thiobutabarbital (Inactin, Andrew Lockwood Co., Milwaukee, Wis.) and placed on a heating pad to maintain constant body temperature. The rats were surgically prepared with a tracheostomy using PE-260 tubing (Fisher Scientific, Chicago, Ill.) for spontaneous breathing of room air. Then the femoral artery was catheterized using PE-50 tubing to monitor femoral blood pressure (BP) using a Statham pressure transducer (Viggo-Spectramed, Oxnard, Calif.). The femoral vein was catheterized using PE-50 tubing for 1) supplemental administration of 1 ml plasma from a donor rat nephrectomized 16–24 hours earlier, 2) a constant infusion of saline at 40 μl/min, and 3) administration of drugs. The left kidney was exposed through an abdominal incision. The renal artery was dissected from the renal vein and fitted with a noncannulating 1.5-mm electromagnetic flow probe connected to a flowmeter (Carolina Medical Electronics, Inc., King, N.C.). The flow probe was calibrated in vivo by treating the rat with heparin, cannulating the renal artery distal to the probe using PE-260 tubing (Fisher Scientific, Chicago, Ill.) for 30 minutes. Then 10 mg/kg body wt L-NAME was given, and BP and RBF were recorded over 30 minutes. After this period, the rats received 32 μg/100 g body wt enalaprilat (Merck Sharp & Dohme, West Point, Pa.), an angiotensin converting enzyme inhibitor. Basal BP and RBF were monitored over 30 minutes. Then the rats were treated with a bolus of 10 mg/kg body wt L-NAME, and BP and RBF were again recorded over 30 minutes.

**Effect in rats pretreated with enalaprilat.** Six anesthetized rats were prepared as described above. After surgery, the rats were allowed a 30-minute recovery period during which BP and RBF were recorded. After this period, the rats received 32 μg/100 g body wt enalaprilat (Merck Sharp & Dohme, West Point, Pa.), an angiotensin converting enzyme inhibitor. Basal BP and RBF were monitored over 30 minutes. Then the rats were treated with a bolus of 10 mg/kg body wt L-NAME, and BP and RBF were again recorded over 30 minutes.

**Effect in rats pretreated with kinin analogue antagonist.** Six anesthetized rats were prepared as described above. After surgery, BP and RBF were allowed to stabilize (15 minutes). We then initiated a constant infusion of 10 μg/min of a kinin analogue antagonist. We used the decapetide kinin analogue [DArg-Arg-Pro-Hyp-Gly-Thi-Ser-O-Phe-Thi-Arg] trifluoroacetic acid [L-4-hydroxy-L-proline (Hyp), β-(2-thienyl) L-alanine (Thi)] (Bachem Inc., Torrance, Calif.) Basal BP and RBF were monitored for 15 minutes before the rats received a bolus of 10 mg/kg body wt L-NAME, and then BP and RBF were monitored again over the final 30 minutes.

**Effect in rats pretreated with kinin antagonist before enalaprilat.** Six anesthetized rats were prepared as described above. After surgery, BP and RBF were allowed to stabilize (15 minutes). We then initiated a constant infusion of 10 μg/min of the same kinin analogue antagonist. Fifteen minutes after the start of the infusion of the kinin antagonist, the rats were given a bolus of 32 μg/100 g body wt enalaprilat. BP and RBF were monitored for 30 minutes. Then the rats received a bolus of 10 mg/kg body wt L-NAME, and BP and RBF were monitored over the final 30 minutes.

**Effect in cyclooxygenase-inhibited rats treated with enalaprilat.** Six anesthetized rats were prepared as described above. After surgical instrumentation, the rats were given a 5 mg/kg body wt bolus of indomethacin (Sigma). After the surgical procedure, the rats were allowed a 30-minute recovery period during which BP and RBF were monitored. After this period, the rats received a bolus of 32 μg/100 g body wt enalaprilat, and basal BP and RBF were monitored for an additional 30 minutes. Then 10 mg/kg body wt L-NAME was given, and BP and RBF were monitored for the final 30 minutes.

**Analysis**

Blood flow to the left kidney was determined directly from the flowmeter and normalized to milliliters per minute per gram kidney weight. The BP and RBF were used to calculate RVR. Units for RVR are millimeters of mercury per milliliter per minute per gram kidney weight and will be designated hereafter as resistance units (RU). Groups were compared using one-way analysis of variance and then further analyzed using Dunnett's t test. We used a probability (or adjusted probability) value of less than 0.05 to represent statistical significance.
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RBF by 30% ($p<0.005$), and increased RVR by 74% ($p<0.001$).

Effect in Rats Pretreated With DuP 753
These six rats weighed 326±14 g, and the left kidneys weighed 1.29±0.06 g. The initial BP was 99±4 mm Hg, and RBF was 6.9±0.6 ml·min⁻¹·g kidney wt⁻¹.

Administration of DuP 753 decreased basal BP to 84±4 mm Hg ($p<0.01$). Although there was no change in RBF (6.82±0.70 ml·min⁻¹·g kidney wt⁻¹), there was a small decrease in RVR (from 14.7±1.5 to 13.2±1.6 RU, $p<0.01$). As shown in Figure 1, after DuP 753 L-NAME significantly increased BP by 22±2 mm Hg ($p<0.001$), RBF did not change, and RVR increased by only 27% ($p<0.01$). This was only a third as much as the increase seen in control rats in response to L-NAME ($p<0.05$).

Effect in Rats Pretreated With Enalaprilat
These six rats weighed 345±7 g, and the left kidneys weighed 1.39±0.05 g. The initial BP was 99±4 mm Hg, and RBF was 6.42±0.60 ml·min⁻¹·g kidney wt⁻¹.

Administration of enalaprilat decreased basal BP to 88±5 mm Hg ($p<0.001$), increased RBF by 23% (to 7.9±0.6 ml·min⁻¹·g kidney wt⁻¹, $p<0.001$), and decreased RVR from 16.4±1.8 to 11.7±1.4 RU ($p<0.001$). As shown in Figure 2, L-NAME significantly increased BP by 35±4 mm Hg ($p<0.001$), which was 63% greater than the increase seen in control rats or after DuP 753 pretreatment ($p<0.05$). There was no change in RBF in response to L-NAME after 10 minutes in enalapril-treated rats, but RVR increased by 54% ($p<0.01$), which was significantly less than the increase seen in control rats ($p<0.05$).

Effect in Rats Pretreated With Kinin Analogue Antagonist
These six rats weighed 322±9 g, and the left kidneys weighed 1.34±0.05 g. The initial BP was 101±3 mm Hg, and RBF was 6.9±0.47 ml·min⁻¹·g kidney wt⁻¹.

The kinin antagonist did not significantly change basal BP, RBF, or RVR. As shown in Figure 3, after the rats received the kinin antagonist, L-NAME significantly increased BP by 21±4 mm Hg ($p<0.005$). Similar to the response to L-NAME in control rats, RBF decreased by 27% ($p<0.001$) and RVR increased by 66% ($p<0.001$).

Effect in Rats Pretreated With Kinin Antagonist Before Enalaprilat
These six rats weighed 335±7 g, and the left kidneys weighed 1.37±0.5 g. The initial BP was 98±4 mm Hg, and RBF was 6.9±0.47 ml·min⁻¹·g kidney wt⁻¹.

When rats pretreated with the kinin antagonist were given enalaprilat, basal BP decreased to 84±4 mm Hg ($p<0.001$), RBF increased by 14% (from 6.7±0.47 to 7.55±0.33 ml·min⁻¹·g kidney wt⁻¹, $p<0.005$), and RVR decreased from 14.9±1.3 to 11.2±0.7 RU ($p<0.001$), similar to what we observed after enalaprilat alone. As shown in Figure 4, L-NAME significantly increased BP by 22±2 mm Hg ($p<0.005$), but this change was similar to that in control rats and only 63% of that seen with L-NAME after enalaprilat alone. There was no change in RBF, and RVR increased by only 35% ($p<0.001$). The increase in RVR was significantly attenuated compared with that in control rats ($p<0.05$).
Effect in Cyclooxygenase-Inhibited Rats Treated With Enalaprilat

These six rats weighed 329±10 g, and the left kidneys weighed 1.47±0.07 g. The initial BP was 98±4 mm Hg, and RBF was 5.30±0.35 ml·min⁻¹·g kidney wt⁻¹.

In the presence of indomethacin, enalaprilat decreased basal BP to 88±5 mm Hg (p<0.001), but basal RBF was increased by 9% (to 5.79±0.46 ml·min⁻¹·g kidney wt⁻¹, p<0.05). RVR decreased by 17%, from 18.8±1.1 to 15.6±1.0 RU (p<0.001). As shown in Figure 5, L-NAME significantly increased BP by 33±2 mm Hg (p<0.001). This was similar to the response seen after enalaprilat alone (Figure 2) and was greater than the change seen in control rats (p<0.05). Despite thepressor response to L-NAME, RBF decreased by only 8% (p<0.05) in indomethacin plus enalaprilat rats, approximately one quarter the response seen in control rats. RVR increased by 51% (p<0.001).
Transient Acute Changes in Renal Blood Flow and Renal Vascular Resistance

Although all of the data we present here represent steady-state conditions, either before or 10 minutes after L-NAME, we observed some interesting differences in the initial response to L-NAME. These transient changes in RBF and RVR are shown in Figure 6.

In rats treated with DuP 753 there was a transient 3% increase in RBF at 1 minute (from 6.8 ± 0.70 to 7.1 ± 0.72 ml·min⁻¹·g kidney wt⁻¹, p < 0.005) that rapidly dissipated to basal levels; RVR did not change (11.9 ± 0.9 versus 12.5 ± 1.2 RU). In enalaprilat-treated rats, while we saw no changes in RBF in the steady state, we did observe a transient renal vasodilation resulting in a 15% increase in RBF (from 7.9 ± 0.6 to 9.2 ± 1.1 ml·min⁻¹·g.
Our results suggest that a major component of the decrease in RBF observed after inhibition of EDRF synthesis is mediated by Ang II. This conclusion is based on the observation that both DuP 753 and enalaprilat, two inhibitors of the renin-angiotensin system that act through different pathways, attenuated the renal vasoconstrictor response to L-NAME without altering its systemic pressor effect. Therefore, the reported tonic release of EDRF, which seems to regulate both BP and renal perfusion, may be particularly important in balancing the intrarenal effects of Ang II. Interestingly, interrupting this apparent relation between EDRF and Ang II within the kidney dissociates the renal response from the systemic response to L-NAME. Since the systemic pressor response was not attenuated, the presumed increase in total peripheral resistance after L-NAME must be due to vasoconstrictor influences other than that of Ang II. It is also possible that the decrease in cardiac output associated with EDRF synthesis inhibition could be attenuated with Ang II blockade. The apparent dissociation of the renal from the systemic responses to L-NAME in our study suggests that local interactions between EDRF and endogenous vasoconstrictor influences (such as Ang II in the kidney) may be an important factor in selectively regulating organ blood flow.

The vascular endothelium plays an important role in modulating vascular tone through the production of endothelium-derived factors such as EDRF, endothelin, and PGI2. The importance of basal EDRF release on systemic or renal vascular tone has been demonstrated by a number of investigators. In anesthetized rats, systemic EDRF synthesis inhibition with L-NMMA or L-NAME treatment is accompanied by increased mean BP and systemic vascular resistance and decreased heart rate and cardiac output. In the kidney, increased renal perfusion after L-NAME treatment is accompanied by decreased RBPF and increased RVR. This suggests that EDRF is an important regulator of renal hemodynamics, EDRF synthesis inhibition results in a disproportionate decrease in GFR compared with RBF, resulting in an increased FF. This suggests preferential vasoconstriction of the efferent arteriole, an observation similar to results obtained using intrarenal infusion of Ang II, leading us to hypothesize that the renal vasoconstriction in this model was mediated by Ang II.

Similar to the studies previously cited, we found that L-NAME increased BP, decreased RBF, and increased RVR in control rats. However, if rats were treated with either inhibitor of the renin-angiotensin system (DuP 753 or enalaprilat), the decrease in RBF was not observed while the increase in RVR was greatly attenuated. This suggests that the renal vasoconstriction in response to EDRF synthesis inhibition is primarily due to Ang II. There are three possible mechanisms by which EDRF synthesis inhibition could lead to Ang II-mediated renal vasoconstriction. First, inhibition of the vasodilator influence of renal EDRF could unmask the counteracting Ang II-mediated renal vasoconstriction. Second, EDRF could be acting directly to inhibit renin release so that L-NAME would result in renal vasoconstriction due to a disinhibition of renin release. This would potentiate Ang II-induced vasoconstriction concurrent with removal of EDRF-induced vasodilation. Finally, as suggested by Ito et al., EDRF synthesis inhibition could result in

**Discussion**

Our results suggest that a major component of the decrease in RBF observed after inhibition of EDRF synthesis is mediated by Ang II. This conclusion is based

**Figure 6.** Line plots show transient responses of renal blood flow (top) and renal vascular resistance (RVR) (bottom) during the first 5 minutes after N\(^\text{ω}-\text{nitro-L-arginine methyl ester (L-NAME)}\) in control (c, n=6), DuP 753- (o, n=6), enalaprilat- (Δ, n=6), enalaprilat plus indomethacin- (●, n=6), and enalaprilat plus kinin antagonist- (□, n=6) treated rats. *p<0.05 difference between control and experimental groups.
increased sensitivity of the renal resistance vessels to vasoconstrictors such as Ang II. Regardless of the mechanism, we suggest that EDRF normally buffers Ang II's vasoconstrictor effect in the kidney.

Since the renal response to L-NAME can be dissociated from the systemic response by Ang II inhibition, this suggests a unique relation between Ang II and EDRF regulating resistance within the kidney. Since EDRF can be stimulated by calcium entry as well as by shear force, both of which could result from actions of Ang II, it is possible that Ang II may directly or indirectly stimulate EDRF production, leading to equilibrium between these contradictory vasoactive factors. It is important to note that while Ang II inhibition eliminates the decrease in RBF after L-NAME, there was still a significant though attenuated increase in RVR. This suggests that EDRF synthesis inhibition in the absence of Ang II unmasks either the effect of other endogenous vasoconstrictors or intrinsic vascular tone, or both. The lesser magnitude of this component of RVR suggests that such factors play a secondary role when Ang II is present. However, it could be that the decrease in BP seen in our anesthetized rats after DuP 753 or enalaprilat could reduce the stimulation of EDRF by reducing shear stress, thus accounting for the lack of change when EDRF synthesis was inhibited. Thus, the response to EDRF synthesis inhibition could be dependent on the basal BP or, specifically, renal perfusion pressure. However, we observed no attenuation of the systemic pressor response after inhibiting the renin-angiotensin system. Further, similar studies by Tolins and Raij used a partially agonistic peptide Ang II antagonist that actually increased BP compared with controls but demonstrated an attenuation of the RBF response to EDRF synthesis inhibition qualitatively similar to that which we have demonstrated.

As a qualifying note, Inactin anesthesia modifies various regulatory reflex mechanisms, particularly increasing basal plasma renin activity (from around 2–3 up to 9–12 ng angiotensin I·ml⁻¹·hr⁻¹ in our laboratory). This may amplify the renal influence of Ang II and the systemic responses to Ang II inhibition. However, the interaction between Ang II and systemic pressor response after inhibiting the renin-angiotensin system. Further, similar studies by Tolins and Raij used a partially agonistic peptide Ang II antagonist that actually increased BP compared with controls but demonstrated an attenuation of the RBF response to EDRF synthesis inhibition qualitatively similar to that which we have demonstrated.

We observed that the systemic pressor response to L-NAME in the presence of enalaprilat was about 67% greater than that with DuP 753, yet in each case RBF was unchanged. Thus, renal perfusion was autoregulated in the absence of Ang II with either treatment, despite a greater increase in RVR with enalaprilat than with DuP 753. The greater pressor response to L-NAME in enalaprilat-treated rats could be related to increased endogenous kinin concentrations caused by angiotensin converting enzyme (kininase II) inhibition. Kinins are known stimuli of EDRF. Therefore, in enalaprilat-treated rats L-NAME removed a greater dilator component, resulting in a 35 mm Hg increase in BP and a 54% increase in RVR. While we found that the kinin antagonist alone did not modify the response to L-NAME, in enalaprilat plus kinin antagonist–treated rats L-NAME resulted in only a 22 mm Hg increase in BP and a 35% increase in RVR, similar to that reported with DuP 753. The stimulation of EDRF by kinins, potentiated through kininase II inhibition, suggests that significant portions of the systemic and renal responses to angiotensin converting enzyme inhibition in these normotensive rats are mediated through kinins' stimulation of EDRF.

Previously, many studies of EDRF have been carried out in vitro under conditions in which prostaglandin synthesis was blocked. The rationale has been that the endothelium-derived vasodilator PGI2 might obscure EDRF-mediated changes. We have previously reported that angiotensin converting enzyme inhibition results in an increased vascular PGI2 (but not PGE2) synthesis and that this response could be reversed with a kinin antagonist. To determine whether prostaglandins might account for a component of our results, we repeated our protocol using L-NAME together with enalaprilat in indomethacin-treated rats. We found that there were no differences in the response to L-NAME in enalaprilat-treated rats with or without indomethacin when BP and RBF were stable. Therefore, the response to L-NAME in angiotensin converting enzyme–inhibited rats is predominantly due to EDRF inhibition and not the result of kinin-stimulated prostaglandin synthesis.

Despite our findings that there were no changes in the RBF response to L-NAME in enalaprilat-treated rats when BP and RBF were stable, we did observe a curious transient 15% increase in RBF that peaked 1 minute after L-NAME administration but had dissipated within 4 minutes. This increased RBF was 4–5 times greater in the enalaprilat-treated group compared with a slight change seen in the DuP 753–treated group. In the group treated with enalaprilat plus either indomethacin or the kinin antagonist, we found that the transient increase in RBF was eliminated. While these results suggest that the transient increase in RBF following EDRF synthesis inhibition in enalaprilat-treated rats is mediated somehow through kinin stimulation of prostaglandin synthesis, it is not obvious what the actual mechanism of this unusual response to L-NAME might be. However, Doni et al have reported that EDRF can suppress bradykinin-stimulated PGI2 synthesis, presumably through the formation of cyclic guanosine monophosphate. Thus, with enalaprilat potentiation of endogenous kinins, L-NAME could withdraw EDRF inhibition of PGI2, leading to the transient (bradykinin- and prostaglandin-mediated) vasodilation we observed.

In summary, we observed that EDRF synthesis inhibition with L-NAME results in a decrease in RBF in the presence of a large increase in BP and consequently in renal perfusion pressure. However, blocking the renin-angiotensin system with either DuP 753 or enalaprilat dissociated the systemic pressor effect from the renal vascular response to L-NAME. This suggests that the increase in RVR after L-NAME administration is mediated by Ang II. The potentiation of the pressor response to L-NAME after enalaprilat, but not after DuP 753, suggests that a significant portion of the systemic effect of angiotensin converting enzyme inhibition in normotensive rats is mediated through kinin-stimulated EDRF. These observations suggest that en-
endothelial modulation of RBF is largely due to a unique interaction between EDRF and Ang II within the kidney, contrary to what exists in the general systemic circulation.

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