Angiotensin II and renal medullary blood flow in Lyon rats

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It is well demonstrated that ANG II decreases cortical blood flow, enhances tubular sodium reabsorption, and shifts the pressure-natriuresis relationship toward a higher BP (21). However, its effects on MBF remain unclear. Indeed, a number of studies have demonstrated that the medullary vasculature was poorly sensitive to the vasoconstrictor effects of ANG II compared with the cortical circulation (5, 11, 21, 22). However, Pallone (28) has shown that ANG II induced a potent vasoconstriction of isolated medullary vasa recta in Sprague-Dawley rats, a response also observed in conscious rats (18). Conversely, other investigators have reported that the systemic infusion of ANG II increased papillary blood flow in young Sprague-Dawley and Wistar rats (25, 37) by increasing local medullary synthesis of vasodilator agents such as PGs, nitric oxide (NO), or kinins. Indeed, it has been shown that an inhibition of PG synthesis allowed ANG II to decrease papillary blood flow (30) and that the increase in papillary blood flow caused by ANG II was greatly dependent on the production of NO (27, 37). This was confirmed by Zou et al. (40), who demonstrated that ANG II increased the medullary release of NO. The involvement of kinins was raised by the findings that renal kinins increased papillary blood flow (25) through NO release (20).

Lyon hypertensive rats (LH) exhibit exaggerated renal vasoconstriction and blunted pressure-natriuresis (14) associated with enhanced MFB autoregulation in response to increases in renal perfusion pressure (34). Because their hypertension is fully dependent on an active renin-angiotensin system (12) and because their renal hemodynamics and tubular sodium reabsorption are hypersensitive to ANG II (16), we hypothesized that the MBF of LH rats could be hypersensitive to the effects of ANG II.

To test this hypothesis, MBF responses to graded doses of ANG II were studied in LH rats and compared with the MFB responses of their low-blood-pressure (LL) controls. In addition, we examined the possible mechanisms involved in the increase in MFB caused by ANG II. For that purpose, the specificity of the response was evaluated by comparing the MBF response after ANG II to that of another vasoconstric-
yelephrine (PE). The role of ANG II subtype 1 (AT₁) and subtype 2 (AT₂) receptors in this response was determined using specific antagonists. Finally, the effect of ANG II was evaluated after inhibition of PG synthesis by indomethacin, inhibition of NO production by Nω-nitro-L-arginine methyl ester (L-NAME), and after bradykinin B₂ receptor blockade by HOE-140.

MATERIALS AND METHODS

Animals

Fifteen-week-old male LH and LL rats were used. Animals were housed in controlled conditions (temperature, 21 ± 1°C; humidity, 60 ± 10%; 8:20-h light-dark cycle). They were fed a standard diet (Elevage, Villemoisson-sur-Orge, France) containing 0.3% sodium and tap water ad libitum. Studies were conducted in agreement with our institutional guidelines for animal care.

Surgical Preparation

On the day of the experiment, the rats were anesthetized with inactin (thiobutabarbital, 75 mg/kg body wt ip, Research Biochemicals, Natick, MA) and ketamine (25 mg/kg body wt ip, Merial, Lyon, France) and placed on a heating blanket (model 50–6880, Harvard Apparatus, Edinbrige, KY) to maintain the rectal temperature at 37 ± 0.5°C. A tracheotomy was performed to facilitate breathing. The left jugular and the two femoral veins were cannulated for bolus injections and infusions, respectively. The left carotid artery was cannulated to record the mean BP through a pressure transducer (model P231D, Statham Instrument Division, Gould, Cleveland, OH). To replace fluids lost during surgery, a 5% bovine albumin (fraction V, Sigma, St, Louis, MO) in 0.9% NaCl solution was infused for 30 min at a rate of 33 μl·100 g body wt⁻¹·min⁻¹ and then replaced by 1% bovine albumin in 0.9% NaCl solution infused at the same rate during the experiment (6, 7). Through a midline abdominal incision, an ultrasonic transit-time flow probe (1RB, Transonic Systems, Ithaca, NY) was placed around the left renal artery for continuous recording of the total renal blood flow (RBF) using a transit-time flowmeter (model T106, Transonic Systems). The left kidney was freed from its surrounding tissue and immobilized in a plastic cup to avoid respiration-induced movements. A needle laser-Doppler flow probe (400-μm diameter, model 411, Perimed, Järfalla, Sweden) was inserted perpendicularly into the middle pole of the left kidney through a hole made in the capsule using a 25-gauge needle and advanced to a depth of 5 mm in the medulla (34). This was made using a stereotaxic apparatus (model 900, David Kopf Instruments, Tujunga, CA). The probe was connected to a flowmeter (Laser Doppler System, Periflux 4001 Master, Perimed) for continuous measurement of MBF and was calibrated before the experiment using a motility standard (PF 1001, Perimed). During the experiment, pulsatile arterial pressure, RBF, and MBF were continuously monitored using a computerized recording system (LabVIEW 5.0 software, National Instruments, Austin, TX). Data were sampled every 2 ms and stored on a CD-ROM. Average mean BP, RBF, and MBF were computed off-line.

At the end of the experiment, the left kidney was removed, decapsulated, blotted dry, and weighed. The position of the laser probe into the medulla was checked macroscopically after injection of methylene blue in the hole made by the flow probe. RBF was normalized per gram of the kidney weight. Renal vascular resistance (RVR) was calculated as the ratio of mean BP to RBF. The values of MBF were expressed as arbitrary perfusion units (PU).

Experimental Protocols

Effects of ANG II and PE in control animals. After surgical preparation, 60 min were allowed for stabilization. Baseline values of mean BP, RBF, and MBF were recorded during the last 5 min of stabilization in LH (n = 13) and LL (n = 13) rats. Then, the animals were randomly distributed in two groups receiving either intravenous bolus injections of ANG II (Sigma) at doses of 5, 15, 30, 60, 120, 240, and 480 ng/kg [LH (n = 6) and LL (n = 7)] or intravenous bolus injections of PE (Sigma) at doses of 0.2, 0.6, 1.8, 5.4, 16.2, 48.6, and 145.8 μg/kg [LH (n = 7) and LL (n = 6)]. Consecutive administrations of ANG II or PE were separated by a period of 10 min to allow a full recovery of hemodynamic variables.

Effects of AT₁ or AT₂ receptor blockade in LL rats. Twenty-five minutes after surgical preparation, baseline values of mean BP, RBF, and MBF were recorded for 5 min. Then, losartan (DuPont Merck Pharmaceutical, Wilmington, DE), an AT₁-receptor antagonist, was injected intravenously at the dose of 10 mg/kg in LL rats (n = 7). In another group of LL rats (n = 8), PD-123319 (Sigma), a specific AT₂-receptor antagonist, was infused intravenously at the dose of 50 μg·kg⁻¹·min⁻¹ during the experiment. Twenty-five minutes after administration of these antagonists, the above hemodynamic parameters were recorded once again for 5 min, and then the injections of ANG II (5–480 ng/kg) were performed as described above.

Effects of PGs, NO, or kinin blockade in LL rats. This experiment was performed in three groups of LL rats. Twenty-five minutes after surgical preparation, baseline values of mean BP, RBF, and MBF were recorded for 5 min. Then, the rats received an intravenous injection of indomethacin (Sigma) at a dose of 5 mg/kg (n = 7), 1-NAME at a dose of 10 mg/kg followed by an intravenous infusion at the rate of 0.1 mg·kg⁻¹·min⁻¹ (n = 7), or HOE-140 (Sigma) at a dose of 20 μg/kg followed by an intravenous infusion at the rate of 10 μg·kg⁻¹·min⁻¹ (n = 8). In each group, 25 min after pretreatment, mean BP, RBF, and MBF were recorded once again for 5 min, and then the injections of ANG II (5–480 ng/kg) were performed as described above.

Statistical Analysis

Values are means ± SE. The between-strain differences reported in Table 1 were analyzed using Student’s t-test for

Table 1. Baseline blood pressure and renal hemodynamics in 15-wk-old anesthetized rats

<table>
<thead>
<tr>
<th></th>
<th>LH (n=13)</th>
<th></th>
<th>LH (n=8)</th>
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<th>LH (n=7)</th>
<th></th>
<th>LH (n=6)</th>
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<tr>
<td>n</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mean BP, mmHg</td>
<td>121 ± 4</td>
<td>8.0 ± 0.3</td>
<td>16 ± 1</td>
<td>145 ± 6</td>
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<tr>
<td>RBF, ml·min⁻¹·g⁻¹ KW</td>
<td>162 ± 3†</td>
<td>6.8 ± 0.2*</td>
<td>24 ± 1*</td>
<td>147 ± 8</td>
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<td></td>
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<tr>
<td>RVR, mmHg·ml·min⁻¹·g⁻¹ KW</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>MBF, PU</td>
<td></td>
<td></td>
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</table>

Values are means ± SE. n, No. of rats; LH, Lyon hypertensive rats; LL, Lyon low-blood-pressure rats; BP, blood pressure; RBF, renal blood flow; RVR, renal vascular resistance; MBF, renal medullary blood flow; KW, kidney wt; PU, perfusion units. *P < 0.01 and †P < 0.001 vs. LL rats.

F366 ANGIOTENSIN II AND RENAL MEDULLARY BLOOD FLOW

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unpaired data. The between-strain differences in the dose-response curves of ANG II and PE were analyzed using a two-way analysis of variance followed by a Fisher multiple-range test. The dose-related effects of ANG II and PE within groups and the effects of treatment were analyzed using one-way analysis of variance. A difference was considered to be statistically significant at $P < 0.05$.

RESULTS

Effects of ANG II and PE in Control Animals

As shown in Table 1, LH rats differed from LL rats by a higher mean BP and a decreased RBF, leading to elevated RVR; baseline MBF did not differ between LH and LL rats.

Typical recordings of mean BP, RBF, and MBF in response to the four highest doses of ANG II and PE in one LL and one LH rat are depicted in Figs. 1 and 2, respectively. In LH and LL rats, both drugs increased mean BP and decreased RBF. Interestingly, ANG II, but not PE, elicited a biphasic response in MBF (Figs. 1 and 3A). In LL rats, the initial rapid and short lasting ($<1$ min) decrease (vasoconstrictor component) was followed by a marked and long-lasting ($>2$ min) increase (vasodilator component). In LH rats, the de-
crease in MBF was more pronounced than in LL controls, whereas the delayed vasodilation was significantly blunted over the range of ANG II doses (Figs. 1 and 3A).

As shown in Fig. 3A, mean BP responses to the lowest doses (5–30 ng/kg) of ANG II were significantly higher ($P < 0.05$) in LH than in LL rats. RBF dose dependently decreased after ANG II injections in both strains, and this decrease was significantly greater ($P < 0.001$) in LH than in LL rats (until the dose of 120 ng/kg). Finally, over the entire range of ANG II doses and in both strains, the decreases in MBF were less marked than those in RBF ($−8 \pm 1\%$ for MBF and $−20 \pm 2\%$ for RBF in LL rats; $−17 \pm 2\%$ for MBF and $−35 \pm 5\%$ for RBF in LH rats for the ANG II dose of 30 ng/kg).

As shown in Fig. 3B, PE elicited similar mean BP and RBF responses to those for ANG II. RBF decreased nearly to zero flow with the highest doses, which is not meaningful. Concerning MBF, the decrease was more marked in LH than in LL rats. In contrast, no delayed vasodilation was observed after PE in both LL and LH rats (Figs. 2 and 3B).

Effects of AT$_1$ or AT$_2$ Receptor Blockade in LL Rats

As shown in Table 2, losartan significantly decreased mean BP and increased RBF in LL rats. Treatment with PD-123319 did not significantly modify mean BP or RBF. Finally, neither losartan nor PD-123319 altered baseline MBF.

AT$_1$ blockade by losartan abolished the effects of ANG II on mean BP, RBF, and the vasoconstrictor and vasodilator components of the MBF response in LL rats (Fig. 4). In contrast, the hemodynamic responses to ANG II remained unchanged after blockade of AT$_2$ receptors by PD-123319 (Fig. 4).

Effects of PGs, NO, or Kinin Blockade in LL Rats

As shown in Table 2, indomethacin did not significantly modify mean BP and RBF but significantly decreased baseline MBF. In response to subsequent administrations of ANG II, the decrease in RBF did not significantly differ between indomethacin-pretreated

Table 2. Effects of different treatments in 15-wk-old anesthetized LL rats

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean BP (mmHg)</th>
<th>RBF (ml·min$^{-1}$·g$^{-1}$)</th>
<th>MBF (PU)</th>
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</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>7</td>
<td>Before 122 ± 7</td>
<td>7.9 ± 0.4</td>
<td>183 ± 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 99 ± 6‡</td>
<td>10.2 ± 1.0‡</td>
<td>180 ± 17</td>
</tr>
<tr>
<td>PD-123319</td>
<td>8</td>
<td>Before 108 ± 4</td>
<td>9.5 ± 0.5</td>
<td>165 ± 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 114 ± 6</td>
<td>9.0 ± 0.4</td>
<td>153 ± 7</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>7</td>
<td>Before 117 ± 5</td>
<td>7.6 ± 0.3</td>
<td>192 ± 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 111 ± 4</td>
<td>7.2 ± 0.2</td>
<td>135 ± 17§</td>
</tr>
<tr>
<td>L-NAME</td>
<td>7</td>
<td>Before 120 ± 6</td>
<td>8.7 ± 0.5</td>
<td>168 ± 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 142 ± 6‡</td>
<td>5.7 ± 0.3§</td>
<td>94 ± 3§</td>
</tr>
<tr>
<td>HOE-140</td>
<td>8</td>
<td>Before 117 ± 4</td>
<td>7.9 ± 0.5</td>
<td>221 ± 21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 112 ± 3</td>
<td>8.4 ± 0.6</td>
<td>208 ± 24</td>
</tr>
</tbody>
</table>

Values are means ± SE. *n*, No. of rats. Doses are as follows: losartan (10 mg/kg iv); PD-123319 (50 µg·kg$^{-1}$·min$^{-1}$ iv); indomethacin (5 mg/kg iv); N$^\text{ω}$-nitro-L-arginine methyl ester (L-NAME; 10 mg/kg iv followed by 0.1 mg·kg$^{-1}$·min$^{-1}$ iv); HOE-140 (20 µg/kg iv followed by 10 µg·kg$^{-1}$·min$^{-1}$). *P < 0.05, ‡P < 0.01, §P < 0.001 vs. before.
and control LL rats (Fig. 5). Interestingly, from the lowest ANG II dose (15 ng/kg), indomethacin significantly enhanced the ANG II-induced dose-dependent decrease in MBF (P < 0.001) and markedly attenuated (P < 0.001) the increase in MBF by ~90% (Fig. 5).

L-NAME administration significantly increased baseline mean BP and decreased RBF and MBF (Table 2). The decrease in RBF elicited by increasing doses of ANG II was blunted and rapidly reached a maximal level in L-NAME-pretreated animals compared with controls (Fig. 5). The ANG II-induced medullary vasoconstriction (from 15 ng/kg) was significantly enhanced (P < 0.001) by L-NAME, whereas medullary vasodilation was lowered by ~80% only for the highest doses of ANG II (Fig. 5).

Treatment with HOE-140 had no effect on baseline values of mean BP, RBF, and MBF (Table 2). The decreases in RBF and MBF (Fig. 5) induced by ANG II were significantly enhanced by HOE-140 treatment (P < 0.001 for both parameters). Finally, HOE-140 attenuated the medullary vasodilation (by ~40%) for the highest doses of ANG II only (Fig. 5).

DISCUSSION

The major findings of the present work are that 1) ANG II injection induces a dose-dependent biphasic MBF response characterized by a rapid decrease followed by a durable increase; this response is specific to ANG II, as it is not seen after PE; 2) in response to ANG II, LH rats exhibit an increased medullary vasoconstriction and a blunted medullary vasodilation compared with LL rats; 3) both the ANG II-induced medullary vasoconstriction and vasodilation are mediated by AT₁ receptors; and 4) the medullary vasodilation is mainly due to a release of PGs and NO.

The importance of MBF in the long-term control of BP has been demonstrated by experiments showing...
that a primary reduction in MBF allowed the development of hypertension (24), whereas an increase in MBF can lower hypertension (17). Previous studies suggested that LH rats are prone to retain sodium, because their pressure-natriuresis is blunted (14) and they are salt sensitive (8). The mechanisms involved in this sodium retention are unknown but may involve altered MBF regulation (34). Because hypertension in LH rats is dependent on an active renin-angiotensin system (12), we examined the response of MBF to ANG II in LH compared with LL rats. For that purpose, MBF was measured using a laser-Doppler flow probe as previously described (34).

In LL rats, ANG II induced a brief decrease in MBF that was less marked than that for total RBF. This result is in good agreement with the experiments showing that, in normotensive rats, MBF is less sensitive to the vasoconstrictor effect of ANG II than the cortical circulation (5, 6, 11, 21). This initial response was followed by a marked and long-lasting vasodilation, thus leading to a biphasic response that does not appear related to the manner in which ANG II was administered. Indeed, 1) MBF did not change after injection of an equivalent volume of saline; 2) the responses to ANG II were dose dependent, although the increasing bolus doses of ANG II were injected at a constant volume; and 3) in rats pretreated with losartan, ANG II, given in the same manner to untreated rats, did not modify MBF. In addition, although such a biphasic response to ANG II is at variance with studies demonstrating that ANG II infusion induces only medullary vasodilation (2, 25, 37), a similar response to ANG II injection was recently reported by Rajapakse et al. (31) in anesthetized rabbits. Interestingly, the long-lasting and dose-dependent increase in MBF induced by ANG II was not observed with PE, despite a similar systemic and renal vasoconstriction. Although the arterial pressure was not controlled in our study, the ANG II-induced increase in MBF has been shown to occur even if the increase in arterial pressure was prevented by an aortic clamp (2, 25). Taken together, these observations show that the biphasic MBF response is specific to ANG II and demonstrate that the increase in MBF induced by ANG II is not related to an increase in renal perfusion pressure. It has been shown that ANG II, but not PE, is able to increase Ca2+ dependent NO synthase activity in renal medulla (23). This observation presumably explains why PE did not induce renal medullary vasodilation as did ANG II in LL rats.

No baseline differences in MBF could be observed between LH and LL rats. In contrast, MBF responses to ANG II differed between the two strains. LH rats exhibited a more marked decrease in MBF. These results are in accordance with previous studies demonstrating that the medullary circulation of the spontaneously hypertensive rat (SHR) is more sensitive to the vasoconstrictor effect of ANG II compared with that of normotensive Wistar-Kyoto rats (6). Similar results have been also observed in Dahl salt-sensitive rats (36). The increased medullary sensitivity to ANG II seen in these hypertensive rats was partly explained by a deficit in NO (13, 36). However, our results differ from those observed in spontaneously hypertensive and Wistar-Kyoto rats in which a medullary vasodilation was not observed after the vasoconstriction induced by ANG II (6). LH rats also differed from LL rats by a blunted increase in MBF after ANG II. The contribution of this abnormality to the hypertension of LH rats remains to be clarified. However, it might be of pathophysiological importance, because 1) the blunted medullary vasodilation favors the vasoconstrictor and antinatriuretic effects of ANG II within the kidney and thus may contribute to the ANG II-induced decrease in sodium excretion; and 2) in LH rats, the decreased renal sodium excretion was found to be sensitive to ANG II (16).

The nature of the receptor subtypes and the mechanisms involved in ANG II-induced MBF response were examined in LL rats only because these animals exhibit marked vasodilation. It is evident that the mechanisms involved in LL rats could differ from those in LH rats. Most of the biological actions of ANG II are known to be mediated through AT1 receptors. However, recent evidence suggests that AT2 receptors may be important in the regulation of BP and renal function by counterbalancing the vasoconstrictor and antinatriuretic actions of AT1 receptors (3). The role of AT1 receptors was examined using their specific antagonist losartan at the dose usually used (38). We observed that losartan not only suppressed the ANG II-induced medullary vasconstriction but also the secondary vasodilation, thus demonstrating that the increase in MBF is AT1 receptor mediated. Moreover, this response is likely related to a secondary release of vasoconstrictors, because 1) it occurred subsequent to and durably after ANG II administration; 2) AT1 receptors are localized not only in renal cortical vasculature but also in the vasa recta of the outer and inner medulla (1, 39); and 3) the activation of AT1 receptors increases the release of local vasodilators (23, 35). The role of AT2 receptors in ANG II effects was examined using PD-123319 infused at a dose demonstrated to be highly specific for AT2 receptors (15, 19). The lack of influence of PD-123319 on the systemic and renal effects of ANG II showed that the involvement of AT2 receptors was negligible in our experimental conditions. Similar results have been recently reported by Badzynska et al. (2) in normotensive rats, in which no change in ANG II-induced cortical and MBF was observed after treatment with PD-123319.

In the present work, only baseline MBF decreased markedly after treatment with indomethacin. The effect of endogenous PGs on medullary blood perfusion was also observed by other investigators (25, 26, 32) and is in good agreement with the fact that the rate of synthesis and tissue concentration of PGs is higher in the renal medulla than in the cortex (35). Indomethacin did not significantly modify the decrease in total RBF induced by ANG II but enhanced the vasoconstrictor effects of ANG II on MBF. These results are in good agreement with those of Parekh and colleagues (29,
In the Lyon hypertensive rats, the medullary vasodilation appears to involve the release of PGs by indomethacin because of the marked hemodynamic changes induced by 1-NAME before ANG II administration. Therefore, it is likely that RBF and MBF rapidly reached their minimal levels because they cannot decrease further. These results provide evidence that the medullary vasodilation evoked by ANG II injections not only depends on PGs but also on the release of NO. Indeed, the AT1 receptor activation is known to increase NO production in the medulla by increasing the Ca2+-dependent NO synthase activity. In this regard, it has been shown that a decrease in the release of NO into tubules by inhibiting prostaglandin synthesis. However, an early study showed that the increasing indomethacin-induced sodium concentrations in the renal medulla did not decrease papillary plasma flow.

To determine whether kinin formation participated in ANG II-induced medullary vasodilation, the animals were pretreated with HOE-140, a specific bradykinin B2 receptor antagonist. This treatment did not modify the baseline systemic and renal hemodynamics in LL rats nor change their mean BP response to ANG II. However, HOE-140 enhanced the vasoconstrictor effects of ANG II on RBF as well as on MBF. The contribution of kinins to ANG II-induced medullary vasodilation was observed only at the highest doses of ANG II. This suggests that in LL rats, kinins were more involved in buffering renal vasoconstriction. In the present work, the AT1 receptor-mediated medullary vasodilator response to low doses of ANG II is mainly due to the release of PGs, whereas the vasodilator response to high doses of ANG II has additional NO- and kinin-dependent components.

In conclusion, the present work shows that intravenous ANG II injection in LL rats induces a biphasic medullary response characterized by an initial vasoconstriction followed by a vasodilation. Both responses are AT1 receptor mediated. The medullary vasodilation is unlikely due to systemic or renal vasoconstriction, as it was not seen in response to PE. At low ANG II doses, the medullary vasodilation appears to involve the release of PGs, while the response to higher ANG II doses also involves NO and kinins. LH rats differ from LL rats by an exaggerated medullary vasoconstriction response to ANG II and a blunted medullary vasodilation. As the renal medullary circulation appears to be an integral component of the long-term regulation of arterial pressure, the functional consequences of the altered MBF response to ANG II might contribute to the impaired pressure-natriuresis and hypertension in LH rats.

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REFERENCES


