Role of nNOS in Regulation of Renal Function in Angiotensin II–Induced Hypertension

Luděk Červenka, Herbert J. Kramer, Jan Malý, Jiří Heller

Abstract—Previous studies have indicated that in normotensive rats, NO produced by neuronal NO synthase (nNOS) plays an important role in modulating tubuloglomerular feedback (TGF)–mediated afferent arteriolar constriction. It has also been shown that in angiotensin (Ang) II–infused hypertensive rats, there is a reduced ability of nNOS-derived NO to counteract this vasoconstriction. The present study was performed to (1) assess in vivo renal functional responses to intrarenal nNOS inhibition in control and Ang II–infused rats and (2) determine whether changes in renal function following nNOS inhibition are mediated by unopposed stimulation of Ang II receptor subtype 1 (AT₁). Wistar rats were infused with either saline (SAL) or Ang II (80 ng/min) by osmotic minipumps implanted subcutaneously. Mean arterial blood pressure of SAL- and Ang II–infused rats on day 13 after implantation averaged 121±4 (n=28) and 151±5 (n=30), respectively (P<0.05). There were no differences in glomerular filtration rate (GFR) (0.68±0.09 versus 0.59±0.09 mL · min⁻¹ · g⁻¹), renal plasma flow (RPF) (2.66±0.31 versus 2.34±0.39 mL · min⁻¹ · g⁻¹), and absolute sodium excretion (0.37±0.07 versus 0.42±0.09 μmol · min⁻¹ · g⁻¹), and absolute sodium excretion (0.37±0.07 versus 0.42±0.09 μmol · min⁻¹ · g⁻¹). Intrarenal infusion of SAL did not change GFR, RPF, and sodium excretion in either SAL-infused (n=7) or Ang II–infused rats (n=8). Acute intrarenal administration of the nNOS inhibitor S-methyl-L-thiocitrulline (L-SMTC; 0.3 mg/h) decreased GFR, RPF, and sodium excretion in SAL-infused rats (n=9) by 29±4%, 38±4%, and 70±4% compared with control values (P<0.05). The pretreatment by the AT₁ receptor antagonist candesartan (750 ng IR) in SAL-infused rats (n=7) effectively prevented the decrease in RPF (−3±3%) elicited by nNOS inhibition and resulted in an increase in GFR (+25±12, P<0.05) and a concomitant greater increase in sodium excretion (84±12%, P<0.05) compared with control values. In contrast, in Ang II–infused rats (n=10) intrarenal inhibition of nNOS by L-SMTC did not cause significant decreases in GFR, RPF and sodium excretion (−2±2%, −15±10%, and −14±10%, respectively). These results suggest that in normotensive rats nNOS-derived NO counteracts Ang II–mediated vasoconstriction in the pre- and postglomerular microcirculation. Furthermore, Ang II–infused rats exhibit an impaired ability to release NO by nNOS. Decreased nNOS activity is likely to account at least partially for the enhanced TGF responsiveness in Ang II–infused rats and thus may contribute to the maintenance of hypertension in this model. (Hypertension. 2001;38:280-285.)

Key Words: angiotensin II ■ angiotensin antagonist ■ nitric oxide ■ nitric oxide synthase

The 2-kidney, 1-clip (2K1C) Goldblatt hypertensive rats were studied extensively as a model of hypertension that depends on the renin-angiotensin system and is similar to human renovascular hypertension in many aspects.1,2 It is generally accepted that chronic infusion of initially subpressor doses of angiotensin (Ang) II leads to a slowly developing hypertension that resembles 2K1C Goldblatt hypertension.3

It is well known that tonically produced NO plays an important role as a potent vasodilator in the maintenance of vascular tone; NO is also recognized as a major paracrine regulator of renal microvascular tone.4 It has been shown that increased intrarenal NO synthesis in Ang II–dependent models of hypertension partially attenuates the renal vasoconstriction actions of Ang II and maintains glomerular filtration rate (GFR) and renal blood flow (RBF) in the normal or slightly subnormal range3,5 (for review, see Navar et al6). NO production is regulated by 3 isoforms of the enzyme NO synthase (NOS): endothelial (eNOS), inducible (iNOS), and neuronal (nNOS).7 It has been presumed that in the kidney, eNOS predominates in the delivery of NO. It has been recently shown, however, that nNOS is constitutively expressed in the kidney in the macula densa and endothelial cells of the efferent arterioles.8 It has been also demonstrated that in normotensive rats, NO derived from nNOS plays an important role in counteracting modulation of tubuloglomerular feedback (TGF)–mediated afferent arteriolar constriction.
and exerts an important influence on efferent arteriolar tone.9–11

In a recent study, it has been shown that NO derived by nNOS can influence the renal hemodynamics in diabetic rats compared with control rats.12 In contrast, acute nNOS inhibition decreased afferent arteriolar diameter in an in vitro blood-perfused juxtamedullary nephron preparation significantly less in Ang II–infused hypertensive rats than in normotensive rats.13 Acute NOS inhibition by nonselective NOS inhibitor Nω-nitro-L-arginine (L-NNA) caused greater decreases in afferent arteriolar diameter and in renal function in Ang II–infused rats than in normotensive rats, indicating that overall NOS activity is increased in Ang II–infused rats8,14 (for review, see Navar et al).15

In addition, it has been found that Ang II–infused rats exhibit decreased nNOS expression in the renal medulla.15 In view of this information, we hypothesized that Ang II–infused rats have a reduced amount of nNOS in the macula densa. This reduction might partially account for the enhanced TGF activity observed in Ang II–dependent hypertension.16 Enhanced TGF responsiveness combined with an Ang II–dependent augmentation of tubular sodium reabsorption may compromise the ability of the kidney to maintain sufficient sodium excretion at normal arterial pressure level and therefore contribute to hypertension in this model.

Accordingly, the first aim of the present study was to assess in vivo the renal hemodynamics and sodium excretion responses to intrarenal nNOS inhibition in control and Ang II–infused rats. The second major aim of this study was to prove whether the nNOS inhibition–mediated changes in renal hemodynamics and sodium excretion are results of an unopposed Ang II–mediated activation on Ang II type 1 (AT1) receptors. Thus, the effect of intrarenal nNOS inhibition was evaluated in a separate groups of normotensive and Ang II–infused rats after intrarenal pretreatment with the AT1 receptor antagonist candesartan.

Methods

The studies were performed in accordance with the guidelines and practices established by the Institute for Clinical and Experimental Medicine Animal Care and Use Committee and were approved by the University of Bonn Animal Care and Use Committee.

Preparation of Animals

Animals were prepared for experiments as described previously.17 Male Wistar rats (Konárovice, Czech Republic) weighing 160 to 180 g were randomly divided into control (n = 23) and Ang II–infused (n = 25) groups. Rats were anesthetized with thiopental sodium (60 mg/kg IP) to implant osmotic minipumps. In 1 group of rats, osmotic minipumps (model 2002, Alzet Co) containing Ang II (Sigma Chemical Co) at a concentration sufficient to allow an infusion rate of 80 ng/min were implanted subcutaneously at the dorsum of the neck. Osmotic minipumps containing saline (SAL) solution were implanted in the control rats. Animals were fed standard rat chow (SEMED) and tap water ad libitum and were kept on a 12 hour/12 hour light/dark cycle. The acute experiments were performed on day 13 after the implantation of the minipumps.

Renal Function Studies

On the day of the experiment, rats were anesthetized with thiopental sodium (60 mg/kg IP) and placed on a thermoregulated table so that their body temperature could be maintained at 37°C to 37.5°C. A tracheostomy by PE-240 tubing was performed to maintain a patent airway, and the exterior end of the tracheal cannula was placed inside a small plastic chamber into which a humidified 95% O2, 5% CO2 mixture was continuously passed. This procedure markedly improves the stability of arterial pressure in anesthetized rats.17 The right jugular vein was catheterized with PE-50 tubing for infusion of solutions. A PE-50 tube was inserted into the right femoral artery for measurement of continuous arterial blood pressure and blood sampling. Mean arterial pressure (MAP) was monitored with a Tesla pressure transducer (model LMP 102) and recorded on a chart recorder (model T2 4100, Laboratorní Přístroje Praha). The left kidney was exposed by a flank incision, isolated from surrounding tissue, and placed in a Lucite cup to keep it stable. A tapered PE-10 catheter was inserted into the left renal artery via the left femoral artery for selective intrarenal administration. This catheter was kept patent by continuous infusion of heparinized isotonic SAL at a rate of 4 µL/min. In a previous study, it was verified that this procedure allows selective administration of drugs without spillover to the systemic circulation.17 During surgery, an isotonic SAL solution containing bovine albumin (6%) (Sigma Chemical Co) was infused at a rate of 20 µL/min. After surgery, an isotonic SAL solution containing albumin (1%), p-aminohippurate sodium (PAH, Merck) (1.5%), and polyfructosan (Inutest, Laevosan) (7.5%) was infused at the same infusion rate. After completion of the surgical procedures, an equilibrium period of 60 minutes was allowed for the animals to establish steady state before we began two 30-minute control clearance periods. After this, either a continuous intrarenal infusion of the nNOS inhibitor S-methyl-L-thiocitrulline (L-SMTC; Sigma Chemical Co) at a rate of 0.3 mg/h or a SAL solution (infusion rate, 4 µL/min) was started in both SAL- and Ang II–infused rats throughout the remaining clearance periods. After a 15-minute delay, the two 30-minute experimental clearance periods were performed. This dose of L-SMTC was chosen to approximately match the most efficient dose (10 µmol/L) used by Ichihara et al in a study employing in vitro blood-perfused juxtamedullary nephron preparation. In their study, it was shown that this dose of L-SMTC is highly specific for nNOS. In a separate groups of SAL- and Ang II–infused rats, the effects of nNOS inhibition after AT, receptor blockade were evaluated. After the control periods, rats received a bolus injection of candesartan (750 ng IR), and after a 5-minute delay, the intrarenal infusion of L-SMTC was started. After another 10-minute interval, two 30-minute experimental clearance periods were performed. As shown in our previous study, this dose of candesartan is sufficient to prevent the renin vasocpressor and vasoconstrictor effects of Ang II.17 Thus, the following experimental groups of rats were examined: group 1 (n = 7), SAL-infused + intrarenal SAL infusion; group 2 (n = 8), Ang II–infused + intrarenal SAL infusion; group 3 (n = 9), SAL-infused + intrarenal L-SMTC infusion; group 4 (n = 10), Ang II–infused + intrarenal L-SMTC infusion; group 5 (n = 7), SAL-infused + intrarenal candesartan + intrarenal L-SMTC infusion; group 6 (n = 7), Ang II–infused + intrarenal candesartan + L-SMTC infusion; group 7 (n = 5), SAL-infused + intrarenal candesartan; and group 8 (n = 5), Ang II + intrarenal candesartan.

Analytical Procedures, Calculations, and Statistical Analyses

Urine volume was measured gravimetrically; inulin and PAH concentrations, colorimetrically. Two blood samples were collected at the midpoints to calculate inulin and PAH clearances. Hematocrit was assessed for each blood sample. Inulin clearance was used as an index of GFR; PAH clearance, as an index of renal plasma flow (RPF). Sodium and potassium concentrations were determined by flame photometry. RBF was estimated from the PAH clearance and hematocrit values but without correction for PAH extraction. Renal vascular resistance (RVR) and fractional sodium and potassium excretion rates were calculated by standard formulas. Data are expressed as mean ± SEM. Statistical comparisons within groups were conducted by the use of ANOVA for repeated measurements, followed by Newman-Keuls test. One-way ANOVA was used for comparisons between groups. Values exceeding the 95% probability limits (P < 0.05) were considered statistically significant.
Basal Values of Blood Pressure, Renal Function and Electrolyte Excretion From the Left Kidneys in SAL-Infused and Ang II-Infused Rats

<table>
<thead>
<tr>
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<th>SAL-Infused (n=28)</th>
<th>Ang II-Infused (n=30)</th>
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<tbody>
<tr>
<td>MAP, mmHg</td>
<td>121±4</td>
<td>151±5*</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>246±11</td>
<td>257±12</td>
</tr>
<tr>
<td>GFR, mL·min⁻¹·g⁻¹</td>
<td>0.68±0.09</td>
<td>0.59±0.09</td>
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<tr>
<td>RPF, mL·min⁻¹·g⁻¹</td>
<td>2.66±0.31</td>
<td>2.34±0.39</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg/mL · min · g)</td>
<td>23±4</td>
<td>38±2*</td>
</tr>
<tr>
<td>Sodium excretion, μEq · min⁻¹ · g⁻¹</td>
<td>0.37±0.07</td>
<td>0.42±0.09</td>
</tr>
<tr>
<td>Potassium excretion, μEq · min⁻¹ · g⁻¹</td>
<td>0.68±0.13</td>
<td>0.57±0.09</td>
</tr>
<tr>
<td>Fractional sodium excretion, %</td>
<td>0.46±0.11</td>
<td>0.47±0.06</td>
</tr>
<tr>
<td>Fractional potassium excretion, %</td>
<td>29.1±5.1</td>
<td>25.4±4.7</td>
</tr>
<tr>
<td>Urine flow, μL · min⁻¹ · g⁻¹</td>
<td>6.1±0.7</td>
<td>6.6±1.1</td>
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*P<0.05 vs SAL-infused group.

Results
Basal values of body weight, blood pressure, renal hemodynamics, and electrolyte excretion rates from left kidneys in SAL-infused and Ang II-infused rats are summarized in the Table. As expected, arterial pressure and RVR were significantly higher in Ang II-infused rats than in SAL-infused rats. There were no significant differences in hemodynamic function and sodium excretion between groups. Thus, to evaluate renal functional responses to experimental manipulations, we used percentage change as a marker throughout the experimental periods.

Effects of Intrarenal L-SMTC and Candesartan on Arterial Pressure
Intrarenal infusion of L-SMTC did not change MAP significantly in either SAL-infused or Ang II-infused rats (125±6 to 122±5 and 150±7 to 147±5 mm Hg, respectively). The pretreatment by candesartan also did not elicit significant changes in arterial pressure (123±3 to 121±4 and 147±5 to 144±4 mm Hg, respectively). Similarly, the administration of candesartan alone did not change MAP either in SAL-infused or in Ang II-infused rats (119±4 to 120±3 and 151±3 to 148±5). SAL vehicle alone also did not influence MAP either in SAL-infused or in Ang II-infused rats (124±4 to 125±6 and 149±4 to 152±8 mm Hg, respectively).

Effects of Intrarenal L-SMTC and Candesartan on GFR, RPF, and RVR
As shown in Figure 1 (top), L-SMTC elicited significant decreases in GFR in SAL-infused rats (−29±4%, P<0.05). Intrarenal pretreatment by candesartan prevented decreases in GFR elicited by L-SMTC and even elicited a significant increase in GFR in the second experimental period (+25±12, P<0.05%) in SAL-infused rats. Intrarenal administration of candesartan alone caused a slight but significant increase in GFR in SAL-infused rats (+13±3%, P<0.05%). In contrast, in Ang II-infused rats L-SMTC administration did not significantly change GFR (−2±2%), and also either pretreatment by candesartan or administration of candesartan alone did not influence GFR significantly (+5±4 and −3±3%). As with GFR responses, L-SMTC administration elicited significant decreases in RPF in SAL-infused rats (−38±4%, P<0.05) and did not significantly change RPF in Ang II-infused rats (−15±10%) (Figure 1, bottom). Likewise, candesartan prevented decreases in RPF in SAL-infused rats to L-SMTC (−3±3%) and did not significantly influence RPF in Ang II-infused rats (+4±3%). Moreover, the administration of candesartan alone caused a significant increase in RPF in SAL-infused rats (+14±2%, P<0.05) and did not significantly change RPF in Ang II-infused rats (+4±3%). Time-control rats (given the SAL vehicle only) did not show significant changes in GFR and RPF in either the SAL-infused (+4±2 and +3±2%, respectively) or the Ang II-infused rats (+2±2 and −3±3%, respectively). RVR was not significantly changed by administration of L-SMTC or by pretreatment with candesartan in Ang II-infused groups (37±3 to 41±3 and 36±2 to 35±4 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹, respectively). Intrarenal infusion of L-SMTC, however, elicited a significant increase in RVR in SAL-infused rats (24±3 to 34±3 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹, P<0.05). Intrarenal pretreatment by candesartan prevented increases in RVR to L-SMTC infusion in SAL-infused rats (25±3 to 24±3 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹). The administration of candesartan alone did not significantly influence RVR either in SAL-infused or Ang II-infused rats (23±2 to 21±3 and 39±4 to 37±3 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹). Time-control rats did not show any change in RVR.

Figure 1. Changes in GFR (top) and RPF (bottom) in response to L-SMTC in SAL-infused (□) and Ang II-infused (●) rats. Effects of intrarenal pretreatment by candesartan on GFR and RPF responses to L-SMTC in SAL-infused (□) and Ang II-infused (●) rats. GFR and RPF responses to intrarenal administration of candesartan alone in SAL-infused (●) and Ang II-infused (●) rats. Values are mean±SE. *P<0.05 vs corresponding control periods.
Effects of Intrarenal L-SMTC and Candesartan on Sodium Excretory Function

As shown in Figure 2, intrarenal administration of L-SMTC caused marked decreases in absolute and fractional sodium excretion in SAL-infused rats (−70±4 and −64±5%, P<0.05 in both cases). In contrast, intrarenal administration of L-SMTC did not significantly influence either absolute (−14±10%) or fractional (−5±4%) sodium excretion in Ang II-infused rats. Intrarenal pretreatment by candesartan elicited comparable increases in absolute sodium excretion in both SAL-infused and Ang II-infused rats (+84±21 and +129±35%, P<0.05 in both cases). The administration of candesartan alone caused significant increases in absolute sodium excretion in SAL-infused and Ang II-infused rats (+113±29 and +61±13%, P<0.05 in both cases). Likewise, fractional sodium excretion increased about 2-fold either by pretreatment (+107±23 and +102±29%, P<0.05 in both cases) or by administration of candesartan alone (+106±27 and +84±16, P<0.05 in both cases) in SAL-infused and Ang II-infused rats. No significant changes in potassium excretion were found in any of the groups.

Discussion

The major finding of the present study is that selective intrarenal nNOS inhibition by L-SMTC elicited marked decreases in renal hemodynamics and sodium excretory functions in normotensive rats and did not significantly influence renal function in Ang II–infused hypertensive rats. This finding is in a good agreement with the previous studies demonstrating an important role for nNOS in buffering TGF-mediated afferent arteriolar vasoconstriction in normotensive rats.9–11 In line with our finding is also the recent observation made by Ichihara et al10 employing the in vitro blood-perfused juxtamedullary nephron preparation that the decrease in afferent arteriolar diameter in response to L-SMTC administration was significantly less in Ang II–infused rats compared with control rats.

It has been also shown that nNOS activity, nNOS mRNA, and renin mRNA are increased in AT1A receptor gene and angiotensinogen gene knockout mice.18,19 In addition, studies evaluating the effects of sodium intake on renin, angiotensin, and nNOS expression in the renal cortex have shown that the expression was negatively correlated with sodium intake.20 Moreover, it has been demonstrated that nNOS activity is decreased in macula densa cells in nonclipped kidneys of 2K1C Goldblatt hypertensive rats and in rats hypertensive by administration of deoxycorticosterone acetate (DOCA) + salt (DOCA-salt rats).21,22 Taken together, these findings support the assumption that renin release and nNOS are regulated in parallel (for a review, see Kurtz and Wagner23). Therefore, it would be conceivable that such models of hypertension, such as 2K1C Goldblatt, DOCA-salt, and Ang II–infused rats, characterized by low intrarenal renin levels, have reduced nNOS activity. However, in a recent study, an elevated nNOS immunostaining was found in Ang II–infused rats.23 To reconcile this obvious contradiction, it could be assumed that the enzyme activity but not the protein level of nNOS is decreased in macula densa cells of Ang II–infused rats.

The previous studies have shown that a compensatory increase in NOS activity counteracts the vasoconstrictor influences of elevated circulating and intrarenal Ang II levels on renal hemodynamics, and NO is likely the major vasodilator substance that helps to maintain RBF and GFR in Ang II–dependent model of hypertension within the normal range (for review, see Navar et al4). However, our results suggest that NO derived by nNOS does not participate in the renoprotective effects of NO described in Ang II–infused rats. This hypothesis is supported not only by the observation that Ang II–infused rats exhibit attenuated vasoconstrictor responses to acute nNOS inhibition but also by the finding of a decreased expression of nNOS in the renal medulla in these animals.15 In contrast to Ang II–infused rats, renal hemodynamic responses to acute nNOS inhibition are enhanced in diabetic rats compared with control rats.12 In addition, nNOS inhibition in Dahl salt-resistant rats caused a development of salt-sensitive hypertension.24 These results indicate that NO derived from nNOS plays an important role in the regulation of renal function and blood pressure. Thus, these findings suggest that the nNOS activity is inappropriately reduced in Ang II–infused rats and might partially account for the enhanced TGF responsiveness and increased RVR observed in Ang II–dependent hypertension.

The second major observation is that pretreatment by the AT1 receptor antagonist candesartan prevented the decreases in renal hemodynamics in normotensive control rats. In addition, the administration of candesartan alone elicited significant increases in GFR and RPF in SAL-infused rats. These results indicate that decreases in GFR and RPF in...
response to L-SMTC in normotensive rats are mediated via unopposed Ang II–mediated activation of AT1 receptors. Moreover, these data suggest that increases in renal hemodynamics are elicited by AT1 receptor blockade. Increases in GFR in SAL-infused rats could be caused not only by the vasodilatory actions on renal microvasculature but also by increases in the glomerular filtration coefficient caused by blockade of endogenous Ang II at the glomerulus. The specific mechanisms underlying the renal hemodynamic responses to intrarenal AT1 receptor blockade require further studies. As summarized in Figure 3, the substantial greater increases in both absolute and fractional sodium excretion compared with slight increases in GFR in normotensive control and Ang II–infused hypertensive rats strongly indicate that the blockade of tubular AT1 receptors markedly contributes to increases in urinary sodium excretion.

Of interest is our observation that both pretreatment by AT1 receptor antagonist and administration of AT1 receptor antagonist alone caused increases in GFR and RPF in normotensive SAL-infused rats but did not change GFR and RPF in Ang II–infused hypertensive rats. This is in obvious discrepancy with our previous study in 2K1C Goldblatt hypertensive rats where an increase was demonstrated in cultured proximal tubule, whereas their expression in glomeruli decreased. Thus, it is possible that the Ang II–infused rats may have the same pattern of AT1 receptor expression as rats fed the low-sodium diet. Upregulation of tubular AT1 receptors in Ang II–infused rats may be important in mediating enhanced tubule sodium reabsorption in states of elevated intrarenal Ang II levels, and this contributes to the hypertensinogenic effects of Ang II.

Our data, the marked increases in fractional sodium excretion and no change in renal hemodynamics in response to AT1 receptor blockade in Ang II–infused rats, would support this hypothesis. Moreover, this assumption is further supported by the recent finding made by Harrison-Bernard et al33 that in Ang II–infused rats, AT1 receptor binding is decreased in glomeruli and not significantly altered in the proximal tubules. It is obvious, however, that studies to address the regional intrarenal AT1 receptor expression in Ang II–infused hypertensive rats will be required.

Another possible explanation why intrarenal administration of candesartan did not significantly increase GFR and RPF in our study might be that structural changes in glomeruli of Ang II–infused rats diminished vasodilatory response of glomerular vasculature to AT1 receptor blockade. This possibility is supported by findings that Ang II–infused rats reveal prominent and widespread renal injury characterized by focal and segmental glomerulosclerosis, glomerular hypertrophy on day 13 of infusion.34 To address this issue, studies evaluating renal functional responses to AT1 receptor blockade in the course of Ang II–induced hypertension will be required.

In summary, the present data indicate that in normotensive rats nNOS derived NO counteracts Ang II–mediated vasoconstriction in the pre- and postglomerular microcirculation. Ang II–infused hypertensive rats exhibit impaired ability to release NO caused by nNOS. This inappropriately decreased nNOS activity likely partially accounts for the enhanced TGF activity in Ang II–infused rats. Enhanced TGF responsiveness combined with increased renal vascular resistance might contribute to a compromised ability of the kidney to respond to blood pressure elevations by appropriate increases in sodium excretion and thus contribute to the maintenance of hypertension in this model.
References

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