Enhanced renal vascular responsiveness to angiotensin II in hypertensive ren-2 transgenic rats

SEVERINA M. JACINTO,1 JOHN J. MULLINS,2 AND KENNETH D. MITCHELL1

1Department of Physiology, Tulane University School of Medicine, New Orleans, Louisiana 70112; and 2Centre for Genome Research, University of Edinburgh, Edinburgh EH9 3JQ, United Kingdom

Jacinto, Severina M., John J. Mullins, and Kenneth D. Mitchell. Enhanced renal vascular responsiveness to angiotensin II in hypertensive ren-2 transgenic rats. Am. J. Physiol. 276 (Renal Physiol. 45): F315–F322, 1999.—The present study was performed to evaluate renal vascular responsiveness (RVR) to ANG II in hypertensive transgenic rats [TGR; strain TGR(mRen2)27] harboring the mouse ren-2 renin gene. Renal blood flow (RBF) responses to either intravenous or intrarenal arterial administration of ANG II were assessed in pentobarbital sodium-anesthetized female heterozygous TGR (9–12 wk old) and age-matched transgene-negative Hanover Sprague-Dawley rats (HanSD). Intravenous bolus injections of 15 and 30 ng ANG II elicited dose-dependent increases in mean arterial blood pressure (AP) and increases in RBF in both TGR and HanSD. However, the magnitude of the increases in AP was greater in TGR than in HanSD (24 ± 1 vs. 17 ± 2 mmHg and 33 ± 2 vs. 25 ± 1 mmHg, respectively, P < 0.05 in both cases). Similarly, the magnitude of the decrease in RBF elicited by intravenous administration of 15 ng of ANG II was greater in TGR than HanSD (−62 ± 3 vs. −52 ± 5%, P < 0.05). Intrarenal arterial administration of 1.5 and 3 ng ANG II did not alter mean AP in either group but elicited larger decreases in RBF in TGR than in HanSD (−24 ± 2 vs. −13 ± 1% and −41 ± 5 vs. −30 ± 2%, respectively, P < 0.05 in both cases). In contrast, intrarenal arterial administration of norepinephrine (40 and 80 ng) elicited smaller decreases in RBF in TGR than in HanSD (−24 ± 3 vs. −40 ± 6% and −51 ± 9 vs. −71 ± 8%, respectively, P < 0.05 in both cases), indicating that TGR do not exhibit a generalized increase in RVR to endogenous vasoconstrictors. Furthermore, the enhanced RVR to ANG II does not appear to reflect an impaired RVR to endogenous vasodilator factors since intrarenal administration of bradykinin and acetylcholine elicited larger increases in RBF in TGR than in HanSD. The present findings indicate that hypertensive TGR exhibit exaggerated renal and peripheral vascular responses to ANG II, which likely contributes to an increased renal and peripheral vascular resistance and thereby to the hypertension in TGR.

Acetylcholine; arterial blood pressure; bradykinin; endothelium-dependent vasodilators; hypertension; norepinephrine; renal blood flow; renal hemodynamics; renal vascular resistance.

The transgenic rat line TGR(mRen2)27 was constructed by insertion of the mouse ren-2 renin gene including its flanking sequences into the genome of the Hanover Sprague-Dawley (HanSD) rat (26). Expression of the ren-2 renin gene, which is a duplicated form of the renin structural gene and is present in mouse strains expressing high levels of submandibular gland renin, results in severe hypertension in both male and female rats of this line (3, 26). Evidence obtained from a variety of studies indicates that the hypertension that occurs in ren-2 transgenic rats (TGR) is ANG II dependent and that activation of AT1 receptors by ANG II is largely responsible for the hypertension in this model (5, 11, 13, 17, 24, 26, 33). There is also growing recognition that ANG II exerts a substantial modulatory influence on renal hemodynamics and excretory function in hypertensive TGR and that ANG II-dependent alterations in renal hemodynamics and tubular reabsorptive function contribute importantly to the inability of the kidney to maintain normal rates of sodium excretion at normotensive pressures and thereby to the hypertension in this model (12, 13, 20, 24, 31). The sustained elevation of renal arterial pressure would be expected to suppress renal renin secretion and thus reduce both plasma and kidney tissue ANG II levels. However, it has been shown that, despite the hypertension, plasma and kidney tissue ANG II levels in anesthetized hypertensive TGR are not markedly different from those in transgene-negative normotensive control rats (23). This finding that plasma and intrarenal ANG II levels are maintained in hypertensive TGR suggests that the hypertension in this model is not reducing circulating and intrarenal ANG II levels. In this regard, it is possible that the ANG II dependence of the elevated arterial blood pressure as well as of renal function in the face of normal plasma and kidney tissue ANG II levels may reflect enhanced peripheral and renal vascular responsiveness to ANG II in hypertensive TGR. Although it has been reported that other models of hypertension, such as the spontaneously hypertensive rat and ANG II-infused hypertensive rat models, exhibit enhanced renal vascular responsiveness to ANG II (1, 4, 7, 8, 14, 16, 34), little information is available regarding the responsiveness of the peripheral and renal vasculature to ANG II in TGR.

The present study was performed to assess the peripheral and renal vascular responsiveness to ANG II in hypertensive TGR. Mean arterial blood pressure and renal blood flow responses to either intravenous or intrarenal arterial administration of ANG II were assessed in both hypertensive TGR and age-matched transgene-negative control rats. In the present study, administration of ANG II elicited significantly greater increases in mean arterial blood pressure and decreases in renal blood flow in TGR than in HanSD, indicating that hypertensive TGR exhibit exaggerated peripheral and renal vascular responsiveness to ANG II.
II. To determine whether the augmented vascular responsiveness is specific for ANG II or represents a generalized increase in vascular responsiveness to endogenous vasoconstrictors, additional experiments were performed to evaluate the arterial blood pressure and renal blood flow responses to norepinephrine. Finally, to gain insight as to whether the enhanced renal and peripheral vascular responsiveness to ANG II reflects an impaired vascular responsiveness to endogenous vasodilator factors, we also assessed the renal blood flow and arterial blood pressure responses to administration of the endothelium-dependent vasodilators bradykinin and acetylcholine.

METHODS

Experiments were performed on 9- to 12-wk-old female heterozygous TGR of the hypertensive rat line TGR(mRen2)27 (Ref. 26) and age-matched transgene-negative HanSD. All rats used in the present study were bred at Tulane University School of Medicine from stock animals supplied from the Centre for Genome Research, University of Edinburgh. The rats were allowed free access to food and tap water until the day of the experiment.

The rats were anesthetized with pentobarbital sodium (50 mg/kg ip) and placed on a surgical table thermostatically controlled to maintain body temperature at 37°C. A tracheostomy was performed and the animals were allowed to breathe air enriched with oxygen, which has been shown to markedly improve the stability of arterial blood pressure of pentobarbital sodium-anesthetized rats (23, 24). A catheter was inserted into the right femoral artery to allow monitoring of arterial blood pressure. Blood pressure was monitored with a Statham pressure transducer (model P23 DC) and recorded on a computer (model PS-166; Gateway 2000, North Sioux City, SD) using a computerized data-acquisition system (MP100 system; BIOPAC Systems, Santa Barbara, CA) with the AcqKnowledge software package (version 3.2.4, BIOPAC). The left jugular vein and right femoral vein were cannulated to allow infusion of solutions and additional anesthetic. The animals were infused intravenously, at a rate of 1.2 ml/h, with isotonic saline containing 1% albumin (bovine; Sigma, St. Louis, MO) during surgery and thereafter with isotonic saline containing 1% albumin. The left kidney was exposed via a flank incision, freed from surrounding tissue, and placed in a Lucite cup. The left ureter was cannulated to ensure unrestricted urine flow. A tapered and curved PE-10 catheter was inserted into the left femoral artery and advanced until its tip was ∼1–2 mm into the left renal artery. The left renal arterial catheter was kept patent by continuous infusion of heparinized isotonic saline at a rate of 10 µl/min. An ultrasonic transit-time flow probe (IRB; Transonic Systems, Ithaca, NY) attached to a Transonic flowmeter (model T106) was placed around the left renal artery to allow continuous monitoring of renal blood flow. Renal blood flow was also continuously recorded by computer using the computerized data-acquisition system. On completion of surgery, a 1-h equilibration period was allowed before initiation of the experimental protocol.

The protocol consisted of evaluating the mean arterial blood pressure and renal blood flow responses to either intravenous or intrarenal arterial bolus administration of the vasoconstrictors ANG II and norepinephrine and the endothelium-dependent vasodilators bradykinin and acetylcholine (all obtained from Sigma). The vasoactive agents were administered intravenously in small volumes (50 and 100 µl) that did not directly alter mean arterial blood pressure or renal blood flow. Similarly, intrarenal arterial administrations of the vasoactive agents were made in small volumes of 10 or 20 µl that did not directly influence renal blood flow. Just before the intrarenal arterial administration of each test agent, the intrarenal infusion rate was increased from 10 to 100 µl/min so as to deliver the entire dose rapidly into the kidney. After recovery of renal blood flow to baseline values (within ∼2–3 min), the intrarenal saline infusion rate was returned to 10 µl/min. No discernible changes in renal blood flow were observed in response to either intrarenal arterial bolus administration of 20 µl of isotonic saline or to an increase in the rate of intrarenal saline infusion from 10 to 100 µl/min for 3 min. A single vasoconstrictor agent and a single vasodilator agent were administered both intravenously and intrarennally to each rat. The order in which different doses of the same vasoactive agent were administered and the order of administration of the different vasoactive agents was randomized. In pilot experiments, repeated administration of the same dose of a given vasoactive agent elicited comparable changes in arterial pressure and renal blood flow when a 10-min period was allowed between successive injections. Accordingly, at least 15 min were allowed between successive intrarenal and/or intravenous injections of different doses of the same test agent or between successive administration of different vasoactive agents.

Statistical analyses were performed using one-way ANOVA, one-way repeated measures ANOVA, and two-way repeated measures ANOVA followed by Student-Newman-Keuls test where appropriate. Statistical significance was defined as P < 0.05. All data are expressed as means ± SE.

RESULTS

The mean arterial blood pressures of the 9- to 12-wk-old female TGR averaged 156 ± 4 mmHg (n = 18) and were significantly higher (P < 0.001) than those of the age-matched HanSD (121 ± 3 mmHg, n = 16). Despite the markedly higher mean arterial pressures, however, basal renal blood flow in the TGR averaged 5.22 ± 0.28 ml·min⁻¹·g⁻¹, a value not significantly different from that of normotensive HanSD (4.68 ± 0.22 ml·min⁻¹·g⁻¹). This finding confirms our previous observation that renal vascular resistance is markedly elevated in hypertensive TGR (24) and is consistent with the demonstration that the hypertension in TGR is characterized by a generalized increase in peripheral vascular resistance (11).

The mean arterial blood pressure and renal blood flow responses to intravenous and intrarenal arterial bolus administration of ANG II are summarized in Figs. 1–3. Intravenous bolus administration of ANG II (15 and 30 ng) elicited dose-dependent increases in mean arterial pressure and decreases in renal blood flow in both TGR and HanSD. As shown in Fig. 1A, however, the magnitude of the increases in mean arterial pressure elicited by intravenous bolus administration of 15 and 30 ng of ANG II was greater in the TGR than in the HanSD (24 ± 1 vs. 17 ± 2 mmHg and 33 ± 2 vs. 25 ± 1 mmHg, respectively, P < 0.05 in both cases). Similarly, as shown in Fig. 2A, intravenous administration of 15 ng of ANG II elicited a significantly larger decrease in renal blood flow in TGR than in HanSD (∼62 ± 3 vs. ∼52 ± 5%, P < 0.05). However, intravenous administration of 30 ng of ANG II pro-
duced comparable decreases in renal blood flow in both groups (−81 ± 3 vs. −83 ± 2%, NS). Figure 3A shows the maximum decreases in renal blood flow produced by intrarenal arterial administration of ANG II. Selective intrarenal arterial administration of 1.5 and 3.0 ng of ANG II did not alter mean arterial pressure in either group but elicited substantially larger decreases in renal blood flow in TGR than in HanSD (−24 ± 2 vs. −13 ± 1% and −41 ± 5 vs. −30 ± 2%, respectively, P < 0.05 in both cases) (Fig. 3A). Collectively, these findings indicate that hypertensive TGR exhibit exaggerated peripheral and renal vascular responsiveness to ANG II.

The mean arterial blood pressure and renal blood flow responses to intravenous and intrarenal administration of norepinephrine are also summarized in Figs. 1–3. As with ANG II, intravenous bolus administration of acetylcholine (100 and 200 ng) elicited decreases in renal blood flow in TGR and normotensive HanSD. However, the decreases in mean arterial pressure (−46 ± 5 and −53 ± 2 mmHg, respectively) and increases in renal blood flow (−24 ± 2 and −42 ± 3%, respectively) in the TGR. However, the magnitude of the norepinephrine-induced increases in mean arterial pressure and decreases in renal blood flow in the TGR was not different from that observed in the HanSD (Figs. 1B and 2B). In contrast, and as shown in Fig. 3B, intrarenal arterial administration of norepinephrine, at doses (40 and 80 ng) that did not alter mean arterial blood pressure, elicited significantly smaller decreases in renal blood flow in the TGR than in the HanSD (−24 ± 3 vs. −40 ± 6% and −51 ± 9 vs. −71 ± 8%, respectively, P < 0.05 in both cases).

Figures 4–6 summarize the mean arterial blood pressure and renal blood flow responses to intravenous and intrarenal arterial administration of the endothelium-dependent vasodilators acetylcholine and bradykinin in both TGR and HanSD. As shown in Figs. 4 and 5, intravenous bolus administration of acetylcholine (100 and 200 ng) elicited decreases in mean arterial blood pressure and increases in renal blood flow in both hypertensive TGR and normotensive HanSD. However, the decreases in mean arterial pressure (−46 ± 5 and −53 ± 2 mmHg, respectively) and increases in renal...
blood flow (23 ± 3 and 34 ± 5%, respectively) elicited by intravenous administration of 100 and 200 ng of acetylcholine in the TGR were not different in magnitude from those in the HanSD (Figs. 4A and 5A). Similarly, intravenous administration of 1 and 2 µg of bradykinin elicited comparable increases in renal blood flow in HanSD and TGR (20 ± 3 vs. 19 ± 2% and 22 ± 3%, respectively) (Fig. 5B). However, intravenous administration of 1 and 2 µg of bradykinin elicited larger decreases in mean arterial blood pressure in TGR than in HanSD (−38 ± 4 vs. −23 ± 4 mmHg and −50 ± 5 vs. −32 ± 4 mmHg, respectively, P < 0.05 in both cases) (Fig. 4B).

The maximum increases in renal blood flow elicited by selective intrarenal arterial administration of acetylcholine and bradykinin in TGR and HanSD are summarized in Fig. 6. Intrarenal arterial administration of acetylcholine, at doses (10 and 20 ng) that did not alter mean arterial blood pressure, elicited increases in renal blood flow in both groups. Although intrarenal arterial injection of 10 ng of acetylcholine elicited comparable increases in renal blood flow in HanSD and TGR (7 ± 1 vs. 9 ± 2%, NS), intrarenal arterial administration of 20 ng of acetylcholine elicited a larger increase in renal blood flow in TGR than in HanSD (15 ± 2 vs. 10 ± 1%, P < 0.05) (Fig. 6A). Similarly, intrarenal arterial administration of bradykinin, at doses (200 and 800 ng) that did not alter mean arterial pressure, elicited larger increases in renal blood flow in TGR than in HanSD (14 ± 2 vs. 9 ± 1% and 25 ± 2 vs. 18 ± 2%, respectively, P < 0.05 in both cases). These findings therefore indicate that hypertensive TGR exhibit exaggerated renal vasodilator responses to endothelium-dependent agonists.

DISCUSSION

The present study demonstrates that ANG II, administered intravenously, elicits significantly greater increases in mean arterial blood pressure and decreases in renal blood flow in hypertensive TGR as compared with age-matched normotensive HanSD controls. Furthermore, the data show that intrarenal arterial administration of ANG II, at doses that do not alter mean arterial blood pressure, elicits substantially greater increases in renal blood flow and decreases in mean arterial blood pressure in hypertensive TGR versus HanSD controls.
reductions in renal blood flow in TGR than in HanSD. Collectively, the present findings indicate that hypertensive ren-2 transgenic rats exhibit enhanced renal and peripheral vasoconstrictor responses to ANG II and are consistent with the previous observation that isolated aortic segments obtained from male heterozygous ren-2 transgenic rats are more sensitive to the vasoconstrictor effects of ANG II (2). Such enhanced peripheral and renal vascular responsiveness to ANG II would likely enable the prevailing circulating and intrarenal ANG II levels in TGR, which have been shown not to be markedly different from those in normotensive control rats (23), to exert greater vasoconstrictor effects and thereby contribute to an increased peripheral and renal vascular resistance in TGR. This manner, and as proposed for the spontaneously hypertensive rat (16, 18), the augmented renal vascular responsiveness to ANG II would likely contribute importantly to the hypertension in TGR.

Although the mechanisms responsible for the observed increases in peripheral and renal vascular responsiveness to ANG II in hypertensive TGR remain unclear, it is possible that they occurred secondary to increases in the number and/or affinity of vascular ANG II receptors. It has recently been demonstrated, however, that aortic, atrial, and ventricular ANG II AT1 receptor mRNA expression are downregulated in adult ren-2 transgenic rats (27). Such findings would argue against the possibility that increased AT1 receptor number is responsible for the augmented renal and peripheral vascular responsiveness to ANG II in hypertensive TGR. It is possible that the enhanced vascular responsiveness to ANG II may reflect an increased sensitivity of the AT1 receptor signal transduction pathway in vascular smooth muscle of hypertensive

![Graph A](image)

**Fig. 5.** Maximum increase in RBF elicited by intravenous bolus administration of acetylcholine (100 and 200 ng) (A) and bradykinin (1 and 2 µg) (B) in normotensive HanSD (solid bars, n = 6 or 7) and hypertensive TGR (hatched bars, n = 8 or 9).

![Graph B](image)

**Fig. 6.** Maximum increase in RBF elicited by selective intrarenal bolus administration of acetylcholine (10 and 20 ng) (A) and bradykinin (200 and 800 ng) (B) in normotensive HanSD (solid bars, n = 7 or 8) and hypertensive TGR (hatched bars, n = 6–9). *P < 0.05 vs. HanSD.
vasculature and contributes to the impaired renal function. Whether such a circumstance occurs in the renal vasculature remains to be elucidated.

An alternative explanation is that the increased vascular sensitivity to ANG II observed secondary to hypertension-induced vascular hypertrophy and/or remodeling of arterial vessels. Indeed, augmented contractile responses would be expected in the vasculature of hypertensive TGR due to the existence of arterial hypertrophy, as has been reported in several studies. In this regard, it has been demonstrated that there is increased wall thickness in the aorta, coronary arteries and arterioles, and renal arteries and arterioles of hypertensive TGR (3, 30). In addition, it has been shown that mesenteric arteries of ren-2 transgenic rats exhibit medial hypertrophy (32). More recently, it was demonstrated that first- and second-order mesenteric resistance vessels isolated from TGR display an increased wall thickness and media content compared with vessels from control HanSD (10). In view of these findings, and to the extent that the increased media content of resistance vessels may contribute to an enhanced sensitivity to vasoconstrictors, one would predict that the vasculature of TGR might be more sensitive to the actions of vasoconstrictor stimuli. If this were the case, then one would predict that TGR should exhibit a generalized increase in vascular responsiveness to endogenous vasoconstrictor agents. However, in the present study, intravenous administration of norepinephrine produced comparable changes in mean arterial blood pressure and renal blood flow in both TGR and HanSD (Figs. 1 and 2). Furthermore, intrarenal arterial administration of norepinephrine, at doses that did not alter blood pressure, elicited substantially smaller decreases in renal blood flow in TGR than in HanSD (Fig. 3). Thus the present data do not support the idea that the vasculature of TGR exhibit a generalized increase in responsiveness to vasoconstrictor agents; rather, they indicate that the augmented renal and peripheral vascular responsiveness may likely be specific for ANG II. The present observation that TGR exhibited a decreased renal vascular responsiveness to norepinephrine also indicates that the augmented vascular responses to ANG II did not occur merely as a consequence of the elevated basal levels of peripheral and renal vascular resistance. Although the mechanisms responsible for the decreased renal vascular responsiveness to norepinephrine cannot be determined from the present data, it was recently demonstrated that despite an increased α-adrenoceptor density, hypertensive TGR exhibit reduced positive inotropic responses to α1 agonists and reduced phospholipase C activity in the papillary muscles of the left ventricle (29). These findings were taken to indicate that there is a desensitization of the α-adrenergic signal transduction pathway in hypertensive TGR. Whether such a circumstance occurs in the renal vasculature and contributes to the impaired renal vascular responsiveness to norepinephrine in TGR remains to be elucidated.

It is also possible that the exaggerated renal and peripheral vascular responsiveness to ANG II may reflect an impaired vascular responsiveness to endogenous vasodilators. In this regard, various animal models of hypertension as well as essential hypertensive patients have been shown to exhibit impaired endothelium-dependent vasorelaxation (15, 19, 21, 28). In the present study, however, intravenous bolus administration of the endothelium-dependent vasodilator bradykinin elicited larger decreases in mean arterial pressure in TGR than in HanSD (Fig. 4). In addition, the magnitude of the increases in renal blood flow elicited by the intravenous administration of either acetylcholine or bradykinin was similar in both TGR and HanSD (Fig. 5). Furthermore, selective intrarenal arterial administration of either acetylcholine or bradykinin elicited larger increases in renal blood flow in TGR than in HanSD (Fig. 6). The present findings that hypertensive TGR exhibit exaggerated peripheral and renal vasodilator responses to endothelium-dependent agonists are consistent with the recent observations that female TGR exhibit enhanced pressor responses to acute blockade of nitric oxide synthesis (6) and that acute blockade of nitric oxide synthesis elicits larger increases in afferent arteriolar resistance and decreases in glomerular filtration rate in hypertensive male TGR than in normotensive control rats (9). Thus it seems unlikely that impaired peripheral and renal vascular responsiveness to endothelium-dependent vasodilators is responsible for the enhanced peripheral and renal vasoconstrictor responses to ANG II in hypertensive TGR. Indeed, the enhanced renal vascular responsiveness to endothelium-dependent vasodilators may act to buffer the renal vasoconstrictor effects of endogenous ANG II and thus contribute to the maintenance of renal blood flow in hypertensive TGR.

It should be recognized that the present experiments were performed in anesthetized, surgically stressed rats, which have been shown to have an increased activity of the renin-angiotensin system compared with unanesthetized rats. Furthermore, anesthesia and surgical stress are well known to alter the activity of the autonomic nervous system as well as alter extracellular fluid volume status. Thus it is possible that the changes in neurohumoral and volume status induced by anesthesia and surgical stress were different in TGR and HanSD and that this contributed to the observed differences between the vascular responsiveness to ANG II in the two groups. However, we have previously reported that plasma and intrarenal ANG II levels in anesthetized hypertensive TGR are not markedly different from those in normotensive HanSD (23). In addition, we have found that, when measured under experimental conditions identical to those of the present study, the arterial hematocrit of 9- to 12-wk-old female heterozygous TGR averaged 47 ± 1% (n = 7), a value not different from that in normotensive HanSD (48 ± 1%, n = 7) (unpublished observation). These findings suggest that the augmentation of vascular responsive-
ness to ANG II in hypertensive TGR did not occur secondary to differences between the neurohumoral and volume status of TGR and HanSD induced by anesthesia and surgical stress.

In summary, the present findings indicate that hypertensive TGR exhibit exaggerated renal and peripheral vascular responsiveness to ANG II not due to an impaired vascular responsiveness to enhanced vascular responsiveness to ANG II in TGR is likely specific for ANG II and does not represent a generalized increase in vascular responsiveness to endogenous vasoconstrictors. Furthermore, the data show that hypertensive TGR exhibit enhanced peripheral and renal vascular responsiveness to endothelium-dependent vasodilators, indicating that the enhanced vascular responsiveness to ANG II in TGR is not due to an impaired vascular responsiveness to endothelium-derived vasodilators. The enhanced renal and peripheral vascular responsiveness to ANG II might contribute importantly to an increased renal and peripheral vascular resistance and thereby to the hypertension in TGR.

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Address for reprint requests: K. D. Mitchell, Department of Physiology, SL39, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, LA 70112.

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