Enhanced tubuloglomerular feedback in Cyp1a1-Ren2 transgenic rats with inducible ANG II-dependent malignant hypertension

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Mitchell, Kenneth D., and John J. Mullins. Enhanced tubuloglomerular feedback in Cyp1a1-Ren2 transgenic rats with inducible ANG II-dependent malignant hypertension. Am J Physiol Renal Physiol 289: F1210–F1216, 2005. First published July 20, 2005; doi:10.1152/ajprenal.00461.2004.—The present study was performed to evaluate tubuloglomerular feedback responses in transgenic rats [TGR(Cyp1a1Ren2)] with inducible malignant hypertension and to determine the degree to which feedback responsiveness is modulated by ANG II in these rats. Male Cyp1a1-Ren2 rats were fed a normal diet containing the aryl hydrocarbon indole-3-carbinol (I3C; 0.3%), for 5–6 days to stimulate expression of the Cyp1a1-Ren2 transgene and, thereby, to induce malignant hypertension. Stop-flow pressure (SFP) feedback responses to a late proximal perfusion rate of 40 nl/min were assessed in pentobarbital sodium-anesthetized rats during control conditions and after administration of the AT1 receptor antagonist candesartan (0.1 mg/kg iv). Rats induced with I3C (n = 6) exhibited elevated mean arterial pressure and increased maximal SFP feedback responses compared with noninduced rats (n = 4; 163 ± 4 vs. 130 ± 2 mmHg, P < 0.01 and 16.3 ± 1.4 vs. 11.7 ± 0.5 mmHg, P < 0.05, respectively). Systemic candesartan decreased arterial pressure (to 98 ± 7 and to 101 ± 5 mmHg, respectively, P < 0.001) and attenuated SFP feedback responses (to 2.0 ± 0.4 and to 3.3 ± 0.9 mmHg, respectively, P < 0.01) in both hypertensive and normotensive rats. In additional experiments, peritubular capillary infusion of 10–3 M candesartan did not alter arterial pressure but attenuated feedback responses in both hypertensive (19.3 ± 1.4 to 8.8 ± 0.9 mmHg, P < 0.01, n = 9) and normotensive Cyp1a1-Ren2 rats (9.0 ± 0.8 to 4.7 ± 0.6 mmHg, P < 0.01, n = 7). The present findings indicate that Cyp1a1-Ren2 rats with ANG II-dependent malignant hypertension exhibit augmented tubuloglomerular feedback responses. The data also show that AT1 receptor activation by ANG II contributes to the enhanced feedback responsiveness in Cyp1a1-Ren2 rats with malignant hypertension.

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sion, before the occurrence of severe renal morphological changes that have been observed with more prolonged induction of the Cyp1a1-Ren2 transgene (11). The ANG II dependence of feedback responsiveness was assessed using the selective AT1 receptor antagonist, candesartan (20, 21). In the present study, systemic administration of candesartan elicited marked decreases in blood pressure as well as attenuation of tubuloglomerular feedback responses. Accordingly, additional studies were performed to evaluate the direct effects of AT1 receptor blockade on tubuloglomerular feedback responses in the absence of the confounding influences of decreases in arterial blood pressure. For these experiments, the effects of peritubular capillary infusion of candesartan on tubuloglomerular feedback responses were evaluated in Cyp1a1-Ren2 transgenic rats with malignant hypertension.

**METHODS**

The experimental procedures in this study conform to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Tulane University Health Sciences Center. In vivo micropuncture experiments were performed on adult male Cyp1a1-Ren2 transgenic rats (250–310 g, 13–16 wk of age) (11) bred at Tulane University School of Medicine from stock animals supplied from the University of Edinburgh, Scotland. In one group, male Cyp1a1-Ren2 rats (n = 6) were fed normal rat food containing the aryl hydrocarbon I3C (0.3% wt/wt; diet TD 00554, Harlan-Teklad, Madison, WI) for 5–6 days to induce malignant hypertension. In a second group (n = 4), age-matched male Cyp1a1-Ren2 rats fed normal rat food (diet TD 90229, Harlan-Teklad), which did not contain I3C, served as normotensive controls.

The rats were anesthetized with pentobarbital sodium (50 mg/kg ip) and placed on a thermostatically controlled surgical table to maintain body temperature at 37°C. A tracheostomy was performed and the animals were allowed to breathe air-enriched oxygen, which has been shown to improve the stability of arterial blood pressure of pentobarbital sodium-anesthetized rats (15, 17, 19). The left femoral artery was cannulated to allow monitoring of arterial blood pressure. Blood pressure was monitored with a Statham pressure transducer (model P23 DC) and recorded using a computerized data-acquisition system (MP100 system; BIOPAC Systems, Santa Barbara, CA) with the Accuknowledge software package (version 3.2.4, BIOPAC). The left external jugular vein was cannulated to allow intravenous infusion of solutions and additional doses of anesthetic. The rats were infused intravenously, at a rate of 1.2 ml/h, with isotonic saline containing 6% albumin (bovine; Calbiochem, San Diego, CA) during the surgery and thereafter with isotonic saline containing 1% albumin, 7.5% polyfructosan (Inutest, Lentz, Austria), and 1.5% PAH (Merck, Whitehouse Station, NJ). The left kidney was exposed via a flank incision, freed from surrounding tissue, and placed in a plastic cup. Warm agar was dripped around the kidney to form a saline well. The left ureter was cannulated with polyethylene PE-10 tubing, and urine was collected under mineral oil in tared tubes. On completion of surgery, a 1-h equilibration period was allowed before initiating the experimental protocol.

The experimental protocol consisted of an initial 60-min control period after which the rats received a single intravenous injection of the AT1 receptor antagonist candesartan (0.1 mg/kg; AstraZeneeca, Molndal, Sweden). After a 30-min equilibration period, a 60-min experimental period was initiated. The effectiveness of the blockade of AT1 receptors by candesartan was assessed by determining the magnitude of the pressor response to intravenous bolus injections of 50 ng of ANG II (Sigma; 50 μl in volume) during control conditions, 10 min after administration of candesartan, and at the end of the experiment (some 90 min after candesartan administration). During both the control and experimental periods, timed urine collections and arterial blood samples (each sample being ~300 μl in volume) were obtained to allow determination of whole kidney hemodynamic function. Coincident with the timed urine collections, measurements of the proximal tubule stop-flow pressure (SFP) feedback responses to a late proximal perfusion rate of 40 nl/min were obtained. Surface proximal tubules were mapped by injecting stained (Fast Green) isotonic artificial tubular fluid (ATF) into the randomly selected surface proximal tubules. A wax block, three to four tubular diameters in length, was injected into a middle convolution of a mapped surface proximal tubule using a hydraulic microdrive unit (Trent Wells, Coulterville, CA). A micropipette with a tip diameter of 3–4 μm and attached to a servo-null micropressure system (Instrumentation for Physiology and Medicine, San Diego, CA) was inserted into an early proximal tubule segment to allow continuous monitoring of SFP. Next, a perfusion micropipette filled with stained (Fast Green) isotonic ATF and attached to a microperfusion pump system (Vestavias Scientific, Vestavia Hills, AL) was inserted into a proximal tubule segment distal to the wax block with the pump rate set at zero. Once a stable TF was obtained, the maximal tubuloglomerular feedback response was assessed by continuously monitoring the reduction in SFP in response to a late proximal perfusion rate of 40 nl/min. We previously demonstrated that this orthograde perfusion rate elicits a maximal feedback-mediated reduction in SFP (15, 17, 19). Maximal SFP feedback responses to a late proximal perfusion rate of 40 nl/min were obtained in one to three tubules during both the control and experimental period in each rat. Average SFP responses were derived for each animal for both the control and experimental period.

In the present study, systemic administration of candesartan elicited substantial decreases in mean arterial blood pressure as well as pronounced attenuation of tubuloglomerular feedback responses. To evaluate the direct effects of AT1 receptor blockade on feedback responses in the absence of decreases in arterial pressure, additional experiments were performed in hypertensive Cyp1a1-Ren2 rats (n = 5) to determine the effects of peritubular capillary infusion of candesartan on tubuloglomerular feedback responses. Again, Cyp1a1-Ren2 rats were induced with 0.3% I3C for 5–6 days to induce malignant hypertension. The experimental protocol used was similar to that described above except that the SFP feedback responses to a late proximal perfusion rate of 40 nl/min were assessed in the same nephrons during control conditions and during simultaneous peritubular capillary infusion of stained isotonic saline containing 10−3 M candesartan. Candesartan was infused at a rate of 20 nl/min into an adjacent vascular welling point or first-order peritubular capillary for 3–5 min before reassessing the SFP feedback response to a late proximal perfusion rate of 40 nl/min. We previously demonstrated that infusion of control solutions into the peritubular capillaries at a rate of 20 nl/min does not directly influence SFP, single nephron glomerular filtration rate (GFR), or the magnitude of tubuloglomerular feedback-mediated decreases in SFP (17, 19). A peritubular capillary infusion was judged satisfactory if two or more surface convolutions and a distal surface convolution of the nephron under examination were supplied by the infused capillary network. As described previously, peritubular capillary infusions of humoral or pharmacological agents elicit more consistent effects on single nephron hemodynamics when this guideline is followed (17, 19). The concentration of candesartan used in the present study (10−6 M) was chosen on the basis of pilot experiments that demonstrated that it elicited maximal and consistent effects on SFP feedback responses without affecting systemic arterial blood pressure when infused into the peritubular capillaries. For control purposes, the effects of peritubular capillary infusion of candesartan on SFP feedback responses were also assessed in noninduced normotensive Cyp1a1-Ren2 rats (n = 5).

At the end of each experiment, the left kidney was removed, decapsulated, blotted dry, and weighed. Urine volume was determined gravimetrically. Inulin and PAH concentrations in both urine and plasma were measured by standard spectrophotometry. Plasma and
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following administration of candesartan. In addition, candesar-

**RESULTS**

Chronic dietary administration of 0.3% I3C to Cyp1a1-Ren2 rats (n = 6) for 5–6 days resulted in the development of hypertension (163 ± 4 vs. 130 ± 2 mmHg, P < 0.01; Fig. 1). The rats induced with I3C had reduced body weight compared with noninduced rats (276 ± 10 vs. 304 ± 11 g, P < 0.05). The hypertensive rats also demonstrated severe lethargy, piloerection, and adoption of hunched posture, which are clinical manifestations of malignant hypertension in the rat (11, 12, 35, 36). This confirms previous observations that chronic dietary administration of 0.3% I3C induces malignant hypertension in the Cyp1a1-Ren2 transgenic rats (11). As shown in Fig. 1, the magnitudes of the pressor responses to bolus injections of 50 ng of ANG II were not different between the two groups. In both normotensive and hypertensive rats, the pressor responses to ANG II were markedly attenuated (43 ± 2 to 4 ± 1 and 49 ± 3 to 5 ± 1 mmHg, respectively, P < 0.01 in both cases) following administration of candesartan. In addition, candesar-
tan administration elicited pronounced decreases in mean arterial pressure in both hypertensive and normotensive Cyp1a1-
Ren2 transgenic rats (from 163 ± 4 to 98 ± 7 and from 130 ± 2 to 101 ± 5 mmHg, respectively, P < 0.01 in both cases). The magnitude of the decrease in mean arterial pressure elicited by candesartan was greater in the hypertensive rats than in the normotensive rats (−65 ± 3 vs. −29 ± 5 mmHg, P < 0.01).

As shown in Figs. 2 and 3, basal values for GFR and RPF in the hypertensive rats were lower than the corresponding values in the noninduced normotensive rats (0.78 ± 0.07 vs. 1.06 ± 0.04 and 2.26 ± 0.21 vs. 3.10 ± 0.23 ml·min⁻¹·g⁻¹, respectively, P < 0.05 in both cases). Candesartan administration decreased GFR (from 0.78 ± 0.07 to 0.36 ± 0.05 ml·min⁻¹·g⁻¹, P < 0.01) in the hypertensive rats but did not alter GFR in the normotensive rats (1.06 ± 0.04 vs. 1.03 ± 0.10 ml·min⁻¹·g⁻¹; Fig. 2). RPF did not change in either group following candesartan administration (Fig. 3). As shown in Fig. 4, the basal value for filtration fraction in the hypertensive rats was not different from that in the noninduced normotensive rats (35.5 ± 3.6 vs. 35.0 ± 2.8%). Candesartan significantly decreased filtration fraction in the hypertensive rats (to 16.2 ± 1.5%, P < 0.001) but not in the normotensive rats (29 ± 3.2%).

Despite the markedly elevated mean arterial blood pressure, the basal values for resting SFP (i.e., SFP measured during conditions of zero distal nephron volume delivery) in the hypertensive rats were not significantly different from those in

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**B**

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<td>Con</td>
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<th>ANG II Pressor Response (mmHg)</th>
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<td>Con</td>
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**Fig. 1.** Effects of administration of candesartan (Cand; 0.1 mg/kg iv) on mean arterial blood pressures (A) and the pressor responses to intravenous administration of ANG II (B) in noninduced normotensive Cyp1a1-Ren2 transgenic rats (filled bars) and in hypertensive Cyp1a1-Ren2 transgenic rats (hatched bars). **P < 0.01 compared with corresponding control (Con) value. †P < 0.001 compared with noninduced rats.
the normotensive rats (44.8 ± 1.5 vs. 41.0 ± 0.4 mmHg). Candesartan administration decreased resting SFP in both groups, although SFP fell to a greater extent in the hypertensive rats than in the normotensive rats (13.2 ± 3.1 vs. -4.3 ± 0.7 mmHg, P < 0.05), presumably as a consequence of the larger fall in mean arterial pressure elicited by candesartan in the hypertensive rats. The effects of systemic administration of candesartan on the magnitude of the maximal SFP tubuloglomerular feedback response to a late proximal perfusion rate of 40 nl/min are summarized in Fig. 5. During control conditions, the magnitude of the maximal SFP feedback response in the hypertensive Cyp1a1-Ren2 rats averaged 16.3 ± 1.4 mmHg, a value significantly higher (P < 0.05) than the corresponding value in the noninduced normotensive rats (11.7 ± 0.5 mmHg). As shown in Fig. 5, systemic candesartan administration decreased the magnitude of the maximal SFP feedback response in both the normotensive (to 3.3 ± 0.7 mmHg, P < 0.01) and hypertensive rats (to 2.0 ± 0.4 mmHg, P < 0.01).

The effects of peritubular capillary infusion of 10⁻³ M candesartan on the magnitude of the SFP feedback responses to a late proximal perfusion rate of 40 nl/min in normotensive and hypertensive Cyp1a1-Ren2 rats are shown in Fig. 6. In these additional experiments, Cyp1a1-Ren2 rats induced with I3C for 5–6 days exhibited higher mean arterial pressure (170 ± 5 vs. 123 ± 4 mmHg, P < 0.001) and augmented SFP tubuloglomerular feedback responses (19.3 ± 1.4 vs. 9.0 ± 0.8 mmHg, P < 0.01) compared with noninduced rats. As shown in Fig. 6, peritubular capillary infusion of candesartan did not alter resting SFP in either group but substantially decreased the magnitude of the maximal SFP feedback response from 9.0 ± 0.8 to 4.7 ± 0.6 mmHg (P < 0.01, n = 7) in the normotensive group.
rats and from 19.3 ± 1.4 to 8.8 ± 0.9 mmHg (P < 0.01, n = 9) in the hypertensive rats. The degree of attenuation of feedback responses elicited by peritubular capillary infusion of candesartan was not significantly different between the two groups (−47.1 ± 5.8 vs. −54.2 ± 4.3%, not significant).

**DISCUSSION**

The present study was performed to evaluate tubuloglomerular feedback responses in Cyp1a1-Ren2 transgenic rats with inductive malignant hypertension and to determine the ANG II dependence of feedback responsiveness in these rats. Malignant hypertension is a form of severe hypertension characterized by fibrinoid necrosis of arterioles and vascular damage in many tissues, including the kidney (11, 12, 14, 35, 36). The Cyp1a1-Ren2 transgenic rat line allows the induction of ANG II-dependent malignant hypertension (11). This transgenic rat line was generated by inserting a mouse Ren2 renin gene into the genome of the Fischer 344 rat (11). Extrarenal Ren2 renin gene expression is induced by the administration of the aryl hydrocarbon I3C, resulting in the development of ANG II-dependent malignant hypertension (11). Such induction of Ren2 renin gene expression using a benign and naturally occurring dietary supplement leads to the development of ANG II-dependent hypertension as a result of increased renin gene expression and plasma renin levels, which are not subject to normal physiological feedback control mechanisms. In the present study, induction of the Ren2 renin gene by dietary administration of 0.3% I3C for 5–6 days resulted in the development of hypertension. The hypertension was associated with a marked decrease in body weight, and the rats also exhibited extreme lethargy, assumption of a hunched posture, and piloerection, which are clinical manifestations of malignant hypertension in the rodent (11, 12, 22, 35, 36). Acute blockade of AT$_1$ receptors with candesartan resulted in a rapid normalization of mean arterial blood pressure (Fig. 1) in the six rats studied. This finding indicates that activation of AT$_1$ receptors, by ANG II generated as a consequence of induction of the Cyp1a1-Ren2 transgene, is responsible for the hypertension in Cyp1a1-Ren2 transgenic rats.

Cyp1a1-Ren2 rats with malignant hypertension exhibited significantly decreased values of GFR and RPF. This observation that both GFR and RPF were markedly reduced indicates that preglomerular vascular resistance is markedly elevated in Cyp1a1-Ren2 transgenic rats with malignant hypertension. The present data do not, however, allow determination of the relative contribution of the direct preglomerular vasoconstrictor actions of ANG II (1, 2, 5, 16, 19) and the autoregulatory response to the increase in arterial blood pressure to the marked reduction of renal hemodynamic function in these rats. Regardless of the mechanism, it is clear that Cyp1a1-Ren2 rats with malignant hypertension exhibit markedly increased renal vascular resistance and that the ability of the preglomerular vasculature to prevent the transmission of the systemic hypertension to the glomerular capillaries appears to be intact at this stage of the pathogenesis of malignant hypertension. In the present study, candesartan administration decreased GFR in the hypertensive rats but not in the normotensive rats. It is likely that the GFR decreased, in part, as a consequence of the associated pronounced reduction of arterial blood pressure. Indeed, candesartan administration decreased blood pressure by more than 60 mmHg in the hypertensive rats. Such a pronounced and rapid drop in arterial blood pressure, together with the loss of the postglomerular vasoconstrictor effect of ANG II, would likely have acted to offset the preglomerular vasodilatory effects of AT$_1$ receptor blockade to maintain normal levels of glomerular capillary pressure and GFR in the hypertensive rats.

In contrast to the decrease in GFR and despite the marked drop in arterial blood pressure, RPF in the hypertensive rats remained unaltered following blockade of AT$_1$ receptors. Thus as shown in Fig. 4, candesartan elicited a marked decrease in filtration fraction in the hypertensive rats. Although this could have occurred as a consequence of predominant postglomerular dilatation, it should be recognized that parallel dilation of both the pre- and postglomerular vascular resistance vessels will also decrease filtration fraction (16). Thus dilation of both afferent and efferent arteriolar resistance vessels could have contributed to the decreased filtration fraction and to the preservation of RPF in the hypertensive rats following AT$_1$ receptor blockade with candesartan. The present data do not allow determination of the quantitative extent to which vasodilation of the pre- and postglomerular resistance elements contributed to the reduced filtration fraction following AT$_1$ receptor blockade. However, in view of the evidence that ANG II exerts vasoconstrictor effects on both the afferent and efferent arterioles (1, 2, 5, 16), it seems likely that dilation of both the afferent and efferent arterioles contributed to the decreased filtration fraction and to the maintenance of RPF after AT$_1$ receptor blockade. It is possible that autoregulatory adjustments of preglomerular vascular resistance also contributed to the maintenance of RPF under these conditions. Further studies are required to elucidate the specific mechanisms responsible for the reduced filtration fraction and the preservation of RPF following AT$_1$ receptor blockade in rats with malignant hypertension. Whatever the mechanism, the present data indicate that AT$_1$ receptor regulation of afferent and efferent arteriolar tone is required to maintain GFR in this form of malignant hypertension.

Previous investigations showed that ANG II exerts a substantial modulatory influence on the sensitivity of the tubuloglomerular feedback mechanism in various models of hypertension (3, 9, 15, 16, 18, 25). However, little is known about the influence of ANG II on tubuloglomerular feedback responses in ANG II-dependent malignant hypertension. It has been demonstrated that induction of malignant hypertension in Cyp1a1-Ren2 rats is associated with severe renal morphological changes including myointimal proliferation and fibrinoid necrosis and endarteritis obliterans of interlobular and afferent arterioles (11). Such severe renal vascular changes would likely act to impair autoregulatory-mediated adjustments in preglomerular vascular resistance, which would be reflected as attenuated tubuloglomerular feedback responses. In the present study, however, the magnitude of the maximal SFP tubuloglomerular feedback response in Cyp1a1-Ren2 transgenic rats with malignant hypertension was significantly higher than that in noninduced normotensive control rats. This indicates that the reactivity of the preglomerular vascular resistance elements that mediate glomerular capillary pressure feedback responses is intact at this early stage (5–6 days) of the development of malignant hypertension. Thus our findings demonstrate that tubuloglomerular feedback responsiveness is augmented dur-
ing the early development phase of hypertension before the development of severe preglomerular vascular damage (11). One would predict that continued exposure of the preglomerular vasculature to the elevated arterial pressure would contribute to the progression of severe renal vascular damage, which, in turn, would act to impair tubuloglomerular feedback-mediated alterations in afferent arteriolar resistance. Additional studies are required to address this issue.

Despite the enhanced tubuloglomerular feedback responsiveness, resting SFP under control conditions in the hypertensive rats was not significantly different from that in the normotensive rats. This finding is consistent with previous observations in the nonclipped kidney of two kidney, one clip Goldblatt hypertensive rats (3) and may reflect an enhanced myogenic responsiveness of the afferent arteriole. In essence, it is possible that in addition to an enhanced tubuloglomerular feedback responsiveness, the myogenic component of autoregulatory-mediated adjustments in afferent arteriolar tone is also enhanced in Cyp1a1-Ren2 rats with malignant hypertension. To the extent that this is the case, this would act to prevent glomerular pressure from increasing when distal nephron solute and fluid delivery are interrupted and, in this manner, contribute to the maintained resting SFP in this form of hypertension. In both the hypertensive and normotensive rats, the magnitudes of the maximal SFP feedback responses were markedly attenuated after systemic administration of the AT$_1$ antagonist candesartan. The magnitude of the maximal SFP feedback response was inhibited by 87.3 $\pm$ 3.0% in the hypertensive rats and by 71.7 $\pm$ 8.1% in the normotensive rats following systemic administration of candesartan. There was no significant difference between groups in the degree of attenuation of SFP feedback responses by intravenously administered candesartan.

It is unlikely that the observed attenuation of SFP feedback responses by systemic candesartan occurred entirely as a consequence of blockade of the direct modulatory influence of ANG II on the tubuloglomerular feedback mechanism. Indeed, it is possible that the decreases in blood pressure per se contributed importantly to the attenuation of feedback responses observed following systemic candesartan administration. However, peritubular capillary infusion of candesartan, at a dose that did not decrease arterial blood pressure, markedly attenuated SFP feedback responses in both normotensive and hypertensive Cyp1a1-Ren2 rats. In these experiments, peritubular candesartan administration attenuated the magnitude of the maximal SFP feedback response by 54% in the hypertensive rats and by 47% in the noninduced normotensive controls. These findings suggest that at least one-half of the observed reduction of SFP feedback responsiveness elicited by systemic candesartan administration was due to blockade of the direct modulatory effect of AT$_1$ receptor activation by ANG II on the tubuloglomerular feedback mechanism. Taken together, the results of the present study indicate that tubuloglomerular feedback responses are enhanced in hypertensive Cyp1a1-Ren2 transgenic rats and that ANG II, acting via AT$_1$ receptors, contributes to the enhancement of feedback responsiveness during the development of malignant hypertension in Cyp1a1-Ren2 transgenic rats. Such a maintained modulatory influence of ANG II on feedback responsiveness can be considered inappropriately high for the level of arterial blood pressure and likely contributes to an inability of the kidney to maintain normal rates of sodium excretion except at hypertensive arterial pressures (16).

In summary, the present findings demonstrate that Cyp1a1-Ren2 transgenic rats with malignant hypertension have reduced GFR and RPF and enhanced SFP tubuloglomerular feedback responses. The data also show that AT$_1$ receptor activation, by ANG II generated as a consequence of induced expression of the Cyp1a1-Ren2 transgene, exerts a pronounced modulatory influence on tubuloglomerular feedback responsiveness and renal hemodynamics in these transgenic rats. Such ANG II-dependent influences might contribute to an inability of the kidneys to maintain normal rates of sodium excretion at normotensive pressures and attenuate the natriuretic response to the ANG II-mediated elevation of arterial pressure. In this manner, the modulatory influence of ANG II on renal hemodynamics and tubuloglomerular feedback responsiveness could contribute to the development of malignant hypertension in Cyp1a1-Ren2 rats.

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