Protective Role of the Angiotensin AT\textsubscript{2} Receptor in a Renal Wrap Hypertension Model

Helmy M. Siragy, Robert M. Carey

Abstract—We evaluated the role of the renal angiotensin II type 2 (AT\textsubscript{2}) receptor in blood pressure regulation in rats with 2-kidney, 1 figure-8 wrap (Grollman) hypertension. Renal wrapping increased systolic blood pressure (SBP). Renal interstitial fluid (RIF) bradykinin (BK), nitric oxide end-products (NOX), and cGMP were higher in the contralateral intact kidney than in the wrapped kidney. In rats with Grollman hypertension, losartan normalized SBP and increased renal function, RIF BK, NOX, and cGMP only in contralateral kidneys. In contrast, PD 123319, a specific AT\textsubscript{2}-receptor antagonist, significantly increased SBP and decreased RIF BK, NOX, and cGMP in both kidneys. Combined administration of losartan and PD 123319 prevented the decrease in SBP and the increase in RIF BK, NOX, and cGMP levels observed with losartan alone. BK-receptor blockade caused a significant increase in RIF BK and a decrease in RIF NOX and cGMP in both kidneys similar to that observed during administration of PD 123319. In rats that underwent sham operation, RIF BK increased in response to angiotensin II, an effect that was blocked by PD 123319. These data demonstrate that angiotensin II mediates renal production of BK, which, in turn, releases nitric oxide and cGMP via stimulation of AT\textsubscript{2} receptors. The increase in blood pressure and the decrease in renal BK, nitric oxide, and cGMP during AT\textsubscript{2}-receptor blockade suggests that the AT\textsubscript{2} receptor mediates counterregulatory vasodilation in Grollman hypertension and prevents a further increase in blood pressure. (Hypertension. 1999;33:1237-1242.)

Key Words: receptors, angiotensin II □ hypertension, renovascular □ bradykinin □ cyclic GMP □ angiotensin II

Angiotensin (Ang) II is established as an important factor in the pathophysiology of renal vascular hypertension. The majority of studies suggest that the renal actions of Ang II are mediated by angiotensin subtype AT\textsubscript{1} receptors. However, AT\textsubscript{2} receptors also are present in the kidney. The physiological actions of Ang II at the AT\textsubscript{2} receptor have been difficult to determine, at least in part, because AT\textsubscript{2} receptors have a low degree of expression compared with AT\textsubscript{1} receptors. We recently demonstrated that AT\textsubscript{2} receptors mediate cGMP\textsuperscript{4} through generation of renal nitric oxide.\textsuperscript{5}

In the present study, we used a hypertensive rat model\textsuperscript{6,7} to investigate the role of the AT\textsubscript{2} receptor in blood pressure regulation. We studied conscious rats with 2-kidney, 1 figure-8 wrap (Grollman) hypertension during normal sodium intake and rats that underwent sham operation and were treated with Ang II. This study was conducted to examine the hypothesis that in Ang II–dependent hypertension, the AT\textsubscript{2} receptor subserves a protective role in blood pressure regulation mediated by AT\textsubscript{2}-receptor augmentation of renal bradykinin (BK), nitric oxide, and cGMP production.

Methods

Renal Microdialysis Technique

To determine the levels of renal interstitial fluid (RIF) BK, nitric oxide end-products (NOX), cGMP, and Ang II, we constructed a microdialysis probe as described previously.\textsuperscript{4,5} The dialysis membrane was obtained from Hospal. In vitro recoveries of cold and radiolabeled Ang II, BK, or cGMP by the dialysis probes were 31% and 45% for Ang II,\textsuperscript{6} 55% and 78% for BK,\textsuperscript{9} and 59% and 70% for cGMP.\textsuperscript{6} Negligible amounts of these peptides stick to the polyethylene tubes of the dialysis probes, as demonstrated by recovery of >99.8% of these substances in the perfusate.\textsuperscript{4,5}

Animal Preparation

Experiments approved by the University of Virginia Animal Research Committee were conducted in 4-week-old Sprague-Dawley rats (Harlan Teklad, Madison, Wis). The rats were placed under general anesthesia with ketamine (80 mg/kg IM) and xylazine (8 mg/kg IM), and the right and left kidneys were exposed by a midline abdominal incision. In 1 group (n=10), the right or left kidney was selected randomly and a figure-8 renal wrap (Grollman) was performed with a 2.0 silk thread.\textsuperscript{6} A group of rats that underwent sham operation served as controls (n=10). To obtain vascular access, a heparinized polyethylene tube was inserted into the right jugular vein. This tube was flushed daily with 10% heparin in 5% dextrose in water (D,W) and capped with a small piece of copper wire.\textsuperscript{4,5} The exterior end of this tube was secured in place by suturing to skin at the exit site and covered with a stainless-steel spring (to prevent the rats from damaging it). Rats were housed under controlled conditions (temperature, 21 ± 1°C; humidity, 60 ± 10%; and light, 8 to 20 hours). Experiments were started at the same time each day (8 AM) to prevent any diurnal variation of the measured plasma renin activity (PRA) or systemic blood pressure (SBP). For in vivo determinations of RIF BK, NOX, cGMP, and Ang II, the microdialysis probes were placed in the cortex\textsuperscript{4,5} of both kidneys while rats (both hypertensive and normotensive

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control) were under general anesthesia. The probes were implanted on experimental day 5 after wrapping, and all RIF measurements were made on experimental day 7, 48 hours after the probes were implanted. For collection of RIF, the inflow tube of the dialysis probe was connected to a gas-tight syringe filled with lactated Ringer’s solution and perfused at a rate of 3 μL/min. The effluent was collected from the outflow tube of the dialysis probe during 30-minute sample periods.

Analytical Methods
Urinary sodium levels were measured with a NOVA Biomedical analyzer. PRA was measured by radioimmunoassay.\textsuperscript{10} SBP was measured at 30-minute intervals in the tail, and recorded values were averaged for each study period.\textsuperscript{4,5} RIF Ang II and BK levels were measured by enzyme-linked immunosorbent assay.\textsuperscript{9,11} The sensitivity of the assays used is 0.5 pg/mL for Ang II and 1 pg/mL for BK. The assays are 100% specific for BK and Ang II and do not react with any other peptides. RIF nitrate/nitrite (NOX) and cGMP levels in dialysate samples were measured by using an enzyme immunoassay kit.\textsuperscript{4,5} The sensitivity was 2.5 μmol/L and 0.11 pmol/mL for NOX\textsuperscript{12} and cGMP,\textsuperscript{3} respectively, and the specificity was 100% for both. The intra- and interassay cross-reactivity with other cyclic nucleotides was <0.01%.

Effects of AT\textsubscript{1}, AT\textsubscript{2}, or BK B\textsubscript{2}-Receptor Blockade in the Grollman Model
Animals (n=10) were placed in metabolic cages. One day before surgery (control day), while rats were consuming a normal-sodium diet (0.28% NaCl), baseline body weight, PRA, and SBP were measured and a 24-hour urine sample for calculation of urinary volume (UV) and sodium excretion (U\textsubscript{Na}V) was collected. After surgery, we continued to monitor 24-hour UV, U\textsubscript{Na}V, body weight, PRA, SBP, and RIF Ang II, BK, NOX, and cGMP daily for 6 days (experimental days 1 to 6). Animals continued to consume a normal-sodium diet (days 7 to 11), and SBP and RIF BK, NOX, and cGMP were measured during right intracarotid administration (20 μmol/L for 30 minutes), in random order, of (1) D,W vehicle (20 μL/min); (2) losartan, a nonapeptide Ang II antagonist at AT\textsubscript{1} receptors (10 mg/kg);\textsuperscript{5,6} (3) PD 123319 (PD), a specific AT\textsubscript{2}-receptor antagonist (50 μg/kg per minute);\textsuperscript{5,6} (4) losartan (10 mg/kg) and PD (50 μg/kg per minute); (5) icatibant, a potent and specific BK B\textsubscript{2}-receptor antagonist (10 μg/kg per minute);\textsuperscript{13} (6) losartan (10 mg/kg) and icatibant (10 μg/kg per minute); and (7) PD (50 μg/kg per minute) and icatibant (10 μg/kg per minute) combined.

Effects of AT\textsubscript{1}, AT\textsubscript{2}, and BK B\textsubscript{2}-Receptor Blockade on U\textsubscript{Na}V and Renal Blood Flow
In a different group of anesthetized rats (n=10), the protocol described above was repeated for measurement of individual kidney U\textsubscript{Na}V, renal total blood flow (RBF), cortical blood flow (RCBF), and medullary blood flow (RMBF) responses to administration of losartan, PD, or icatibant (at the doses cited above, either alone or combined). Urine from each kidney was collected directly by inserting a polyethylene tube into each ureter. RBF was measured by placing a flow probe around the renal arteries. RCBF and RMBF were monitored by laser Doppler flowmeter. The optic fibers of the laser Doppler flowmeter were placed in renal cortex and medulla.

Effects of Ang II and AT\textsubscript{1}- and AT\textsubscript{2}-Receptor Blockade on RIF BK in Normotensive Rats
To evaluate whether the observed changes in RIF BK in rats with Grollman hypertension during AT\textsubscript{2}- and AT\textsubscript{2}-receptor blockade were related to changes in renal Ang II secondary to renal wrap, we repeated the above study (days 7 to 11) in conscious animals (n=10) during normal sodium intake. RIF BK was monitored during a control period (D,W) was infused into the right carotid artery at 20 μL/min for 30 minutes) and during a treatment period (30 minutes), during which (1) D,W (20 μL/min), (2) Ang II (30 ng/kg per minute), (3) losartan (10 mg/kg), or (4) PD (50 μg/kg minute), alone or combined, were administered intravenously. The dose of Ang II was determined from a dose-pressor response curve for Ang II.\textsuperscript{4,5} We chose the largest dose of Ang II that did not elicit any rise in blood pressure.

Statistical Analysis
Comparisons among pharmacological agents and controls were examined by ANOVA, including a repeated-measures term, using the general linear models procedure of the Statistical Analysis System. Multiple comparisons of individual pairs of effect means were conducted by using values of least square means pooled variance. Data are expressed as mean±SE. Statistical significance was identified at P<0.05.

Results
Changes in PRA and RIF Ang II Responses to Unilateral Renal Wrap
PRA and RIF Ang in control rats were 1.5±1 ng/mL per hour and 145±20 fmol/min, respectively, and did not change after surgery. Rats with Grollman hypertension had a significant increase in PRA, from 1.6±1.0 to 27.0±5.0 ng/mL per hour (P<0.0001), by day 6 after surgery. Similarly, Ang II significantly increased from 142±22 to 300±30 fmol/min (P<0.0001) in wrapped kidneys and decreased from 145±26 to 70±10 fmol/min (P<0.0001) in the contralateral kidney of rats with Grollman hypertension.

Twenty-Four-Hour UV, U\textsubscript{Na}V, and Blood Pressure Responses to Unilateral Renal Wrap in Conscious Rats
In control animals, there were no significant changes in 24-hour UV, U\textsubscript{Na}V, or SBP. Rats with Grollman hypertension had a significant (P<0.0001) and progressive decrease in 24-hour UV (Figure 1A), U\textsubscript{Na}V (Figure 1B), and SBP (Figure 1C).

Changes in SBP in Conscious Rats With Grollman Hypertension in Response to AT\textsubscript{1}-, AT\textsubscript{2}-, and BK B\textsubscript{2}-Receptor Blockade
There were no changes in SBP in response to AT\textsubscript{1}-, AT\textsubscript{2}-, or BK B\textsubscript{2}-receptor blockade in control animals. In rats with Grollman hypertension (Figure 2A), there was a significant increase in SBP after unilateral renal wrap (P<0.0001). On day 7 after wrapping, administration of the AT\textsubscript{2}-receptor blocker (PD) or the BK B\textsubscript{2}-receptor antagonist (icatibant) further increased SBP (P<0.05). In contrast, the AT\textsubscript{1}-receptor blocker (losartan) decreased SBP in rats with Grollman hypertension from 181±7 to 134±10 mm Hg (P<0.001) (Figure 2A). SBP during losartan treatment was not significantly different in hypertensive rats and controls. In rats with unilateral renal wrap, combined administration of PD and losartan or of icatibant and losartan completely prevented the decrease in SBP that was observed with losartan alone. Combined administration of PD and icatibant increased SBP to the same levels observed with individual administration of PD or icatibant.

Changes in Split Renal Excretory Function, RCBF, and RMBF in Response to AT\textsubscript{1}-, AT\textsubscript{2}-, and BK B\textsubscript{2}-Receptor Blockade in Anesthetized Grollman Rats
In control rats, both kidneys had similar urine flow rate (UV), U\textsubscript{Na}V, RBF, RCBF, and RMBF measurements at baseline on
day 7 before any pharmacological agents were administered (Figure 2); these values did not change in response to unilateral renal wrapping (—●—) or sham operation (—○—). Data are mean±SE. *P<0.05 and **P<0.0001 vs respective controls and sham-operated rats.

Figure 1. Twenty-four-hour UV (A), U\textsubscript{NaV} (B), and SBP (C) in conscious rats (n=10) during normal-sodium intake in response to unilateral renal wrapping (—●—) or sham operation (—○—). Data are mean±SE. *P<0.05 and **P<0.0001 vs respective controls and sham-operated rats.

Figure 2. SBP (A) and U\textsubscript{NaV} (B) in anesthetized rats that underwent sham operation (n=10) or anesthetized rats with unilateral renal wrap (n=10) during normal sodium intake in response to administration of D\textsubscript{5}W (V), losartan (L), PD, and icatibant (I), either alone or combined. A, Data for sham-operated animals (●) and animals with unilateral renal wrap (□) are shown. B, Solid bars represent contralateral unwrapped kidneys, and open bars represent wrapped kidneys. Data are mean±SE. *P<0.05. **P<0.001 vs corresponding vehicle. +P<0.05 vs contralateral kidney. ++P<0.001. ***P<0.0001 vs sham.

U\textsubscript{NaV} observed with losartan alone in rats with Grollman hypertension. Combined administration of PD and icatibant decreased UV and U\textsubscript{NaV} to the same levels as observed with PD or icatibant alone.

RBF was 5.2±0.4 mL/min in control animals and did not change in response to AT\textsubscript{1}-, AT\textsubscript{2}-, or BK B\textsubscript{2}-receptor blockade. RBF was 1.0±0.02 mL/min in wrapped kidneys and 9.2±1.0 mL/min in contralateral kidneys, respectively. RBF increased in response to losartan in both wrapped and contralateral kidneys by 4.2% and 15%, respectively (P<0.0001), whereas PD and icatibant decreased RBF only in contralateral kidneys by 8% and 10%, respectively (P<0.0001). Similarly RCBF was significantly lower in wrapped (67%, P<0.0001) than in contralateral kidneys. RCBF increased in response to losartan in both wrapped and contralateral kidneys by 4.2% and 15%, respectively (P<0.0001), whereas PD and icatibant decreased RBF only in contralateral kidneys by 8% and 10%, respectively (P<0.0001). Similarly RCBF was significantly lower in wrapped (67%, P<0.0001) than in contralateral kidneys. RCBF increased in response to losartan in both the wrapped (3.7%) and contralateral (13%) kidneys (P<0.001). PD decreased RCBF (P<0.001) in contralateral kidneys (7.3%). PD and icatibant, alone or combined, did not affect RCBF in wrapped kidneys. Administration of losartan and PD together decreased RCBF in the wrapped kidneys to the same extent as PD alone. In contralateral kidneys, PD blocked the increase in RCBF due to losartan. Icatibant, alone or combined with PD, decreased RCBF to the same extent as PD and blocked the vasodilatory effect of losartan in the contralateral kidney.

None of the treatments described above caused any significant changes in RMBF in the Grollman model.
RIF BK, NOX, and cGMP Response to Unilateral Renal Wrap and AT₁-, AT₂-, or BK B₂-Receptor Blockade in Rats With Grollman Hypertension

In animals that underwent sham operation, RIF BK, NOX, and cGMP did not change with AT₁-, AT₂-, or BK B₂-receptor blockade (data not shown). Animals with a unilateral renal wrap had a significant decrease in RIF BK, NOX, and cGMP (Figure 3A through 3C) in the wrapped kidney on day 7 (P<0.01). Seven days after surgery, RIF BK, NOX, and cGMP in the contralateral kidney increased significantly compared with values in controls and the wrapped kidney (P<0.0001). RIF BK, NOX, and cGMP significantly increased in the contralateral kidney (Figure 3A through 3C), but not in the wrapped kidney, in response to AT₁-receptor blockade with losartan. AT₂-receptor blockade with PD significantly decreased RIF BK, NOX, and cGMP in the wrapped and contralateral kidneys. Combined administration of losartan and PD decreased RIF BK, NOX, and cGMP in both wrapped and contralateral kidneys to the same levels observed with icatibant alone.

Figure 4. RIF BK responses to Ang II (AII), losartan (L), and PD, alone or combined, in conscious rats (n=10) during normal sodium intake. ■ indicates values for contralateral kidneys before treatment; and □, values for wrapped kidneys. Data are mean±SE. *P<0.05. **P<0.0001 vs respective vehicle treatment. ***P<0.0001 vs corresponding contralateral kidney.

RIF BK Responses to Ang II, Losartan, and PD in Normotensive Conscious Rats (n=10)

RIF BK (Figure 4) increased during Ang II infusion (P<0.0001). Losartan and PD, alone or combined, did not change RIF BK in the absence of exogenous Ang II. Combined administration of Ang II and losartan increased RIF BK from 66±5 to 250±12 pg/min (P<0.0001), a response that was greater than that produced by Ang II alone (P<0.05). The increase in RIF BK in response to Ang II was blocked completely by coadministration of PD (P<0.0001). Simultaneous administration of Ang II, losartan, and PD did not cause a significant change in RIF BK levels and nullified the RIF BK response to Ang II (P<0.0001).

Discussion

This study demonstrates, to our knowledge for the first time, a novel mechanism whereby the Ang AT₂ receptor mediates counterregulatory vasodilation and protects against a further increase in BP in Ang II–dependent renal wrap hypertension. We further determined that this protective vasodilator response is mediated by the renal production of BK and nitric oxide.

We used the 2-kidney, 1 wrap (Grollman) model of renal vascular hypertension, in which blood pressure increased progressively over a period of 7 days. We demonstrated the dependence of blood pressure on Ang II by (1) an ∼17-fold increase in PRA, (2) increased RIF Ang II levels in the wrapped kidney, and (3) normalization of blood pressure with the AT₁-receptor antagonist losartan. These data confirm that activation of the renin-angiotensin system mediates the blood pressure changes observed in this animal model through stimulation of the AT₁ receptor. The observed reduction in UV and U₅⁺V observed in rats with Grollman hypertension can be attributed to increased activity of the renin-angiotensin system because AT₁-receptor blockade with losartan caused
significant diuresis and natriuresis and lowered blood pressure.

The results of the present study clearly demonstrate that the contralateral, nonwrapped kidney is not depleted of Ang II. The source of this Ang II is not clear. Because renal renin content and renal renin mRNA have been reported to be reduced in the nonclipped kidney of 2K1C rats, Ang II could be taken up by renal tissue. We recently reported a significant reduction in AT₂-receptor protein in the wrapped kidney and maintenance of the receptor protein in the contralateral kidney. In contrast, AT₁-receptor protein was downregulated in the contralateral kidney, leading to relatively greater expression of the AT₂ receptor in that kidney.

In this study, we hypothesized that in Ang II-dependent renal wrap hypertension, Ang II acts via the AT₁ receptor in a counterregulatory manner to decrease blood pressure. We clearly demonstrated that the increase in blood pressure in Grollman hypertension is mediated by the AT₁ receptor because AT₁-receptor blockade normalized the blood pressure response to renal wrap. The salient finding of the study, however, was that AT₂-receptor blockade with PD prevented the hypotensive response to AT₁-receptor blockade in this animal model of hypertension. In this study, it is not clear what mechanism maintains blood pressure during combined AT₁ and AT₂ blockade. It is likely that less than total blockade of the AT₁ receptor combined with decreased production of BK and nitric oxide during AT₂-receptor blockade balances the hypotensive effect of losartan. In addition, AT₁-receptor blockade alone increased blood pressure slightly. These data strongly suggest that in Ang II-dependent hypertension, tonic endogenous stimulation of the AT₂ receptor protects against an additional increase in blood pressure mediated through the AT₁ receptor. The data further suggest that at least some of the hypotensive action of AT₁-receptor blockade is mediated via the AT₂ receptor.

Having demonstrated the counterregulatory role of the AT₂ receptor in Ang II-dependent hypertension, we sought to clarify the mechanisms of vasodilation subserved by the AT₂ receptor in this form of hypertension. A major finding of the study was that this protective role is mediated by BK. We demonstrated that the increase in BK was significantly inhibited in both the contralateral and wrapped kidneys by AT₂-receptor blockade, suggesting that increased intrarenal BK production in the kidney is mediated by the AT₂ receptor. The present study does not explain the cause of decreased BK and cGMP production in the wrapped kidney, but it is possible that downregulation of the AT₂ receptor may play a role.

The present observations that AT₂ receptor blockade significantly reduced bradykinin, NOX and cGMP suggested that bradykinin may stimulate nitric oxide and cGMP in this model of Ang II-dependent hypertension. This interpretation was strengthened by the observation that the specific BK B₂-receptor antagonist, icatibant, decreased NOX and cGMP to baseline levels in the contralateral kidneys of these animals. This is consistent with the recent report that the AT₂ receptor induced an increase of cGMP in rat aortic tissue through BK release. The observed increase in RIF BK in the contralateral kidney in the Grollman model suggests a protective mechanism.

The decrease in NOX and cGMP during BK-receptor blockade suggests that the protective effect of the AT₂ receptor is mediated by stimulation of nitric oxide via BK release. Alternatively, it is possible that nitric oxide was stimulated directly by Ang II at the AT₂ receptor without BK as an intermediate.

In the present study, we demonstrated that AT₂ receptor stimulation is directly linked to BK release because Ang II stimulated renal BK and this response was completely abolished by AT₂ but not AT₁-receptor blockade. In rats with Grollman hypertension, the reduction in BK with AT₂-receptor blockade was associated with decreased NOX, cGMP, and renal excretory and hemodynamic functions. Blocking the BK B₂ receptor mimicked (to the same magnitude) the effects of AT₂-receptor blockade on renal NOX, cGMP, and excretory and hemodynamic functions. The close correlation between AT₂-receptor activity and the release of these renal vasodilatory substances confirms our hypothesis that the AT₂ receptor plays a role in counterbalancing the vasoconstrictor effects of increased Ang II activity.

In conclusion, we showed in a 2-kidney, 1-wrap model of renal vascular hypertension that AT₁ receptor stimulation mediates the increase in blood pressure and that the AT₂ receptor mediates counterregulatory vasodilation and protects against an additional increase in blood pressure. Elimination of the hypotensive effect of AT₁-receptor inhibition by concurrent AT₂-receptor blockade suggests that at least some of the beneficial effects of the AT₁-receptor blockade are mediated by the AT₂ receptor. We also demonstrated that the protective effect of the AT₂ receptor is mediated by generation of renal BK, nitric oxide, and cGMP in the contralateral (nonischemic) kidney and that these mechanisms may play a role in the pressure natriuresis of the nonischemic kidney in renal vascular hypertension.

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