Angiotensin II Infused Intrarenally Causes Preglomerular Vascular Changes and Hypertension

Kathleen M. Stevenson, Amanda J. Edgley, Göran Bergström, Katrina Worthy, Michelle M. Kett, Warwick P. Anderson

Abstract—The effects on the renal vasculature and on arterial blood pressure of chronic infusion of low doses of angiotensin II (Ang II) into the renal artery were studied. Sprague Dawley rats were infused continuously with Ang II (0.5, 1.5, or 4.5 ng·kg\(^{-1}\)·min\(^{-1}\)) or vehicle into the right renal artery (contralateral nephrectomy). Intrarenal Ang II infusion for 25 days produced dose-dependent rises (\(P<0.001\)) in awake mean arterial pressure (111±1, 119±5, and 130±3 mm Hg in rats receiving 0.5, 1.5, and 4.5 ng·kg\(^{-1}\)·min\(^{-1}\) Ang II, respectively) compared with 105±1 mm Hg (vehicle). Renal vessel lumen characteristics were assessed with an established, maximally dilated, isosmotic perfused kidney preparation. This revealed a small dose-dependent right shift in the pressure-flow relation (\(P=0.05\)), as well as a dose-dependent right shift and a dose-dependent reduction in the slope of the pressure–glomerular filtration rate relation (\(P=0.04\) and 0.03, respectively). The effects of Ang II infusion on arterial pressure were not affected by the timing of the contralateral nephrectomy but were reduced when the contralateral kidney remained in situ. Acute losartan administration (10 mg/kg IV bolus) produced similar effects on arterial pressure in rats infused with vehicle or Ang II (4.5 ng·kg\(^{-1}\)·min\(^{-1}\)) for 14 days, \(P=0.89\), indicating the lack of systemic spillover of Ang II. Intraperitoneal Ang II (0.5, 1.5, or 4.5 ng·kg\(^{-1}\)·min\(^{-1}\) for 25 days) had no effect on arterial pressure. Thus, chronic intrarenal infusion of low doses of Ang II resulted in changes in the renal vasculature compatible with dose-related structural reductions in the lumen diameter of preglomerular vessels and produced dose-related increases in arterial pressure. (Hypertension. 2000;36:839-844.)

Key Words: angiotensin II ■ kidney ■ perfusion ■ rats ■ vascular resistance

The effects of angiotensin II (Ang II) on cultured vascular smooth muscle cells (VSMCs) in vitro are well known and include hypertrophy, hyperplasia,\(^1\) and increased collagen production.\(^2\) Less is known in vivo, but these growth-promoting effects of Ang II on VSMCs of systemic resistance vessels\(^3,4\) are thought, for example, to be responsible for the progressive rise in arterial blood pressure when low (pressor) doses of Ang II are infused intravenously.\(^5\) Similarly, inhibition of Ang II formation with ACE inhibitors has been shown to reduce vascular hypertrophy in several nonrenal vascular beds.\(^6\)

In the present experiments, we tested whether chronic elevation of Ang II within the renal circulation produces structural changes in the renal vasculature in vivo and hypertension. Ang II has been shown to stimulate mitogenic responses in cultured VSMCs from rat renal preglomerular arterioles,\(^7\) and we have recent evidence that chronic ACE inhibitor treatment of spontaneously hypertensive rats (SHR) leads to structural remodeling of the renal resistance vessel walls.\(^8\) Structural changes in the preglomerular vasculature may have a particular significance in the development and maintenance of hypertension, because the kidney receives 25% of the cardiac output and is a key long-term regulator of arterial pressure.\(^9\) As predicted originally by Goldblatt,\(^10\) reduction in intrarenal vessel diameter may be prohypertensive by mimicking the hemodynamic effects of main renal artery stenosis.

To test whether Ang II caused structural reductions in the lumen of renal resistance vessels,\(^11\) we infused Ang II directly into the renal artery at doses too low to spill into the systemic arterial tree. We used an established functional test of vessel lumen dimensions,\(^8,12,13\) which has been used previously to demonstrate renal vessel lumen changes in a wide variety of hypertensive states, including ACE inhibition in SHR,\(^8\) effects of renal denervation on renal vasculature in SHR,\(^14\) age-dependent changes in the renal vasculature of SHR,\(^12\) and 2-kidney 1-clip hypertensive rats.\(^13\) We also studied the effects of contralateral nephrectomy on the extent of hypertension developed from intrarenal infusion of Ang II.

Methods

Four series of experiments were performed with male Sprague-Dawley rats bred at Monash University (Victoria, Australia). All
experiments were approved in advance by the Monash University Standing Committee on Ethics in Animal Experimentation as being in accord with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Renal artery infusion was achieved through catheterization of the right suprarenal artery and advancement of the catheter tip to the junction with the main renal artery.15 Ang II (0.5, 1.5, or 4.5 mg · kg⁻¹ · min⁻¹) or vehicle (0.9% NaCl with 10 IU heparin sodium/mL) was delivered into the kidney via an osmotic minipump (model 2 ML4, rate 2.5 μL/h; Alza Corporation) attached to the catheter.

Series 1: Infusion of Ang II Into the Renal Artery for 25 Days, With Contralateral Nephrectomy on the Day Infusions Began

At 10 weeks of age, rats were anesthetized (30 mg/kg methohexital sodium and 20 mg/kg pentobarbital sodium IP). A left nephrectomy was performed, and the suprarenal artery was cannulated for the infusion of Ang II at 0.5 (n=5), 1.5 (n=4), or 4.5 (n=9) mg · kg⁻¹ · min⁻¹, or vehicle (n=12). After 25 days of infusion, awake arterial pressure and heart rate were measured; then, rats were prepared for functional determination of renal vessel lumen dimensions.8,14 In brief, pressure-flow—glomerular filtration rate (GFR) relations were constructed in kidneys perfused with collodion solution (isosmotic with plasma), with the renal vasculature maximally dilated (see References 8,12,14,16,17). Maximal vasodilatation of the kidney was confirmed in 4 additional experiments in which infusions of acetylcholine (0.00133 and 1.33 mg/min) did not further dilate the renal vasculature.

Series 2: Intrarenal Infusion of Ang II for 14 Days With Telemetry Monitoring of Blood Pressure and Previous Left Nephrectomy

At 4 weeks after nephrectomy, a telemetry transmitter (Data Sciences International) was implanted in the lower abdominal aorta, and infusions (for 14 days) into the renal artery of vehicle (n=3) or Ang II at 1.5 (n=4) or 4.5 (n=4) ng · kg⁻¹ · min⁻¹ began. Telemetry recordings began after 3 to 7 days, with (DSI Dataquest Labpro Version 3.0 1995; Data Sciences). Systolic and diastolic pressures, heart rate, and activity were recorded for 24-hour periods (12-hour light/dark cycle) twice weekly (data were collected for 60 seconds every 15 minutes).

Series 3: Infusion of Ang II (4.5 ng · kg⁻¹ · min⁻¹, n=7) or Saline Vehicle (n=10) Into the Renal Artery, With the Contralateral Kidney Intact, Including Test of Systemic Spillover of Ang II

On day 14 of the infusion, awake arterial blood pressure was recorded as described earlier. Then, the response to the acute administration of losartan (Ang II type 1 receptor antagonist, 10 mg/kg IV) was recorded for 30 minutes.

Series 4: Control Experiments for Series 1: Intraperitoneal Infusion of Ang II for 25 Days in Uninephrectomized Rats

A minipump was implanted intraperitoneally to deliver either vehicle (n=7) or Ang II at 0.5 (n=5), 1.5 (n=8), or 4.5 (n=8) ng · kg⁻¹ · min⁻¹ (plus left nephrectomy). After 25 days of infusion, awake arterial pressure and heart rate were recorded as described, and ventricular weight and wet and dry kidney weights were recorded.

Statistical Analysis

Data were analyzed with the Systat statistical software package (Version 5.05). Data from the 4 experimental groups was analyzed by 1-way ANOVA with partitioning used to test for dose relatedness. In series I, model II regression was applied to the data obtained from the isolated perfused kidney experiments, and the line of symmetry was fitted to the data.18 For this analysis only, data from rats infused with Ang II at 0.5 ng · kg⁻¹ · min⁻¹ (n=3) and at 1.5 ng · kg⁻¹ · min⁻¹ (n=4) were combined. The SEM for the line of regression was calculated with a model I regression. The slopes of these lines and their intercepts were compared with family regression covariant analysis.19 The assumption that individual experiments exhibited a linear relation was tested with the Pearson correlation coefficient for all individual experiments. In series 3, 1-way ANOVA was used to analyze the effects of treatment on the mean arterial pressure response to losartan. Unless otherwise indicated, values are mean±SEM.

Figure 1. Awake, directly measured mean arterial pressure of individual rats infused continuously for 25 days with either vehicle or Ang II at 0.5, 1.5, or 4.5 ng · kg⁻¹ · min⁻¹ into the renal artery. The horizontal bars show the mean value for each group.

Results

Effects on Arterial Pressure

Series 1: Infusion of Ang II Into the Renal Artery for 25 Days, With Contralateral Nephrectomy on the Day Infusions Began

Intrarenal infusion of Ang II caused a dose-dependent rise in mean arterial pressure (P<0.001). After 25 days of infusion, mean arterial pressure was 105±1 mm Hg (n=12) in rats infused with vehicle and 111±1 mm Hg (n=5), 119±5 mm Hg (n=4), and 130±3 mm Hg (n=9) in rats infused with Ang II at 0.5, 1.5, or 4.5 ng · kg⁻¹ · min⁻¹, respectively (Figure 1). Ang II infusion resulted in dose-related increases in the ratio of right ventricle to body weight (P=0.004) but not in the ratio of right ventricle to body weight (P=0.72), heart rate (P=0.21), body weight gain (P=0.42), or ratio of wet (P=0.43) or dry (P=0.29) kidney weight to body weight (Table 1).

Series 2: Intrarenal Infusion of Ang II for 14 Days With Telemetry Monitoring of Blood Pressure and Previous Left Nephrectomy

By 8 to 11 days of vehicle or Ang II (1.5 or 4.5 ng · kg⁻¹ · min⁻¹) infusion, there were significant dose-related increases in both systolic and diastolic arterial pressure for both day and night (Figure 2).

Series 3: Infusion of Ang II (4.5 ng · kg⁻¹ · min⁻¹, n=7) or Saline Vehicle (n=10) Into the Renal Artery, With the Contralateral Kidney Intact, Including Test of Systemic Spillover of Ang II

On day 14, awake mean arterial pressure was higher in rats receiving Ang II (4.5 ng · kg⁻¹ · min⁻¹) into the renal artery (128±3 mm Hg, n=6) than that in rats receiving vehicle (110±2 mm Hg, n=11; P<0.001). The administration of
losartan (10 mg/kg IV) resulted in similar reductions in mean arterial pressure in rats infused with vehicle (−8.7 ± 1.9 mm Hg) and in rats infused with Ang II (−9.1 ± 1.7 mm Hg, P = 0.89; Figure 3).

Series 4: Control Experiments for Series 1: Intraperitoneal Infusion of Ang II for 25 Days in Uninephrectomized Rats
There were no dose-dependent effects of intraperitoneal infusion of Ang II on mean arterial pressure (P = 0.81) with the same doses as had been administered intrarenally. After 25 days of infusion, mean arterial pressure was 110 ± 2 mm Hg (n = 7) in vehicle-infused rats and 107 ± 1 mm Hg (n = 5), 110 ± 1 mm Hg (n = 8), and 110 ± 3 mm Hg (n = 8) in rats infused with Ang II at 0.5, 1.5, or 4.5 ng · kg⁻¹ · min⁻¹, respectively.

Assessment of Effects on Renal Vessel Structure
After 25 days of infusion of vehicle or Ang II, the kidneys from the rats of series 1 were perfused with isosmotic colloid solution to test whether the 25-day Ang II infusion (0.5, 1.5, or 4.5 ng · kg⁻¹ · min⁻¹) had caused changes in resistance vessel diameter in the maximally vasodilated state. The pressure-flow and pressure-GFR relations for all doses are summarized in Table 2.

There was a significant linear relation between renal perfusion pressure and perfusate flow within each individual rat experiment (R² = 0.98 to 1; Figure 4). Analysis of the relation between arterial distending pressure and perfusate flow for group data (Table 2) indicated that there was a small but significant dose-dependent change in elevation (P = 0.05) but no significant effect of Ang II on slope (P = 0.57).

For analysis of the pressure-GFR relation, arterial distending pressure was expressed as its natural logarithm (ln; Figure 4). There was a significant linear relation between arterial distending pressure and GFR within each individual experiment (R² = 0.92 to 1). There was a significant dose-dependent right shift of the relation between renal arterial distending pressure and GFR (P = 0.04) and a dose-dependent change in the slope of this relation (P = 0.03; Table 2). In addition, Ang II infusion resulted in a dose-dependent increase in the lowest perfusion pressure at which urine could be collected (P < 0.001: 51.5 ± 4.3, 57.8 ± 5.1, 62.8 ± 3.7, and 71.8 ± 2.7 mm Hg for kidneys infused with vehicle or Ang II at 0.5, 1.5, or 4.5 ng · kg⁻¹ · min⁻¹, respectively). There was similar tubular reabsorption of fluid between groups (ie, similar urinary-to-plasma inulin ratio). In addition, Ang II infusion resulted in a dose-dependent increase in the lowest perfusion pressure at which urine could be collected (P < 0.001).

TABLE 1. Values for Heart Rate, Change in Body Weight, and Heart and Kidney Weights After 25-day Intrarenal Infusion of Vehicle or Ang II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saline (n=12)</th>
<th>0.5 (n=5)</th>
<th>1.5 (n=4)</th>
<th>4.5 (n=9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔBody weight, g</td>
<td>+54.79±8.00</td>
<td>+53.27±8.32</td>
<td>+40.30±9.70</td>
<td>+52.18±4.60</td>
<td>0.42</td>
</tr>
<tr>
<td>Left ventricle, g/100 g body wt</td>
<td>0.167±0.004</td>
<td>0.187±0.005</td>
<td>0.180±0.004</td>
<td>0.183±0.005</td>
<td>0.004</td>
</tr>
<tr>
<td>Right ventricle, g/100 g body wt</td>
<td>0.053±0.003</td>
<td>0.050±0.007</td>
<td>0.046±0.002</td>
<td>0.051±0.004</td>
<td>0.72</td>
</tr>
<tr>
<td>Kidney dry weight, g/100 g body wt</td>
<td>0.085±0.002</td>
<td>0.092±0.003</td>
<td>0.083±0.002</td>
<td>0.085±0.002</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

Figure 2. Diastolic (open columns) and systolic (cross-hatched columns) pressures measured by telemetry at days 8 to 11 during infusion of either vehicle or Ang II at 1.5 or 4.5 ng · kg⁻¹ · min⁻¹ intrarenally. Values shown are for 12 hours of light (DAY, top) and 12 hours of darkness (NIGHT, bottom).

Figure 3. Mean arterial pressure before and after a bolus dose of losartan (10 mg/kg IV) on day 14 of infusion of either vehicle or Ang II at 4.5 ng · kg⁻¹ · min⁻¹ into the renal artery.
TABLE 2. Values for the Intercept (a) and the Slope (b) of the Relationship Between Arterial Distending Pressure and Perfusate Flow and for the Relationship Between Arterial Distending Pressure and GFR for Rats Infused for 25 Days With Vehicle or Ang II

<table>
<thead>
<tr>
<th>Group</th>
<th>Arterial Distending Pressure-Flow Relationship (Flow=a+b(pressure))</th>
<th>Arterial Distending Pressure-GFR Relationship (GFR=a+b(ln pressure))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>a: $-4.4 \pm 0.7$, b: $0.7 \pm 0.1$</td>
<td>a: $-5.0 \times 10^3 \pm 3.2 \times 10^2$, b: $1.5 \times 10^2 \pm 7.5 \times 10^0$</td>
</tr>
<tr>
<td>0.5 ng combined with 1.5 ng Ang II $\cdot$ kg $^{-1} \cdot$ min $^{-1}$</td>
<td>a: $-5.9 \pm 0.9$, b: $0.8 \pm 0.1$</td>
<td>a: $-4.2 \times 10^3 \pm 4.6 \times 10^2$, b: $1.2 \times 10^2 \pm 1.3 \times 10^2$</td>
</tr>
<tr>
<td>4.5 ng Ang II $\cdot$ kg $^{-1} \cdot$ min $^{-1}$</td>
<td>a: $-7.3 \pm 1.2$, b: $0.7 \pm 0.1$</td>
<td>a: $-3.5 \times 10^3 \pm 6.6 \times 10^2$, b: $1.1 \times 10^2 \pm 1.5 \times 10^2$</td>
</tr>
<tr>
<td>P dose dependent</td>
<td>a: $0.05$, b: $0.57$</td>
<td>a: $0.04$, b: $0.03$</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

Discussion

The infusion of low doses of Ang II directly into the kidney appears to have resulted in changes in the renal vasculature that are suggestive of structural remodeling of the preglomerular resistance vessels around a narrowed lumen. It also resulted in hypertension. Ang II has a number of growth-related effects on VSMCs in vitro and in vivo, including the stimulation of several growth factors and effects on extracellular matrix production. The proliferative effects of Ang II have also been shown specifically for VSMCs harvested from the renal vasculature. In addition, the acute infusion of Ang II directly into the renal artery in anesthetized rats has been shown to cause an increased renal expression of the early growth response genes Egr-1 and c-fos. However, the present study appears to be the first description of the potential for Ang II to cause long-term vascular changes when infused into a local vascular bed in vivo.

A well-established functional assay was used to detect structural remodeling of the local vascular bed; this technique was developed by Gothberg, Folkow, and colleagues. The kidneys are perfused at maximal vasodilatation with a solution isosmotic to plasma through a series of increasing pressure steps. Pressure-flow and pressure-GFR relations are thus determined. We found that 25 days of Ang II infusion had a small, but statistically significant, effect on the pressure-flow relation, indicating a small dose-dependent reduction in the vessel lumen diameter of the maximally dilated kidney. The relation between pressure and GFR was shifted significantly to the right with the effect being related to the dose of Ang II infused during the previous 25 days. Taken together with the pressure-flow data, this is interpreted as indicating an increase in the ratio of preglomerular to postglomerular resistance, with increased preglomerular resistance; that is, there appears to have been a dose-dependent rise in preglomerular resistance, with a small rise in total renal resistance, resulting in a lower GFR at any given pressure in the Ang II–infused kidneys. These conclusions are further supported by our observations that the lowest perfusion pressure at which urine was recorded to flow increased progressively with the dose of Ang II infused for 25 days; that is, a perfusion pressure of 71.8±2.7 mm Hg was required in the kidneys infused with Ang II at 4.5 ng $\cdot$ kg $^{-1} \cdot$ min $^{-1}$ to overcome the oncotic pressure of the artificial plasma, compared with only 51.5±4.3 mm Hg in the vehicle-infused kidneys. In addition, the slope of the relation between arterial distending pressure and
GFR was reduced with Ang II infusion. This suggests that the Ang II infusion may have reduced the filtration surface area, which is another prohypertensive mechanism by which GFR could be lowered in the Ang II–treated kidneys. Morphological studies are now required to determine whether the observed reduction in GFR at any given pressure is due to Ang II–induced increases in preglomerular resistance and/or reduction in filtration surface area.

Shifts to the right in the pressure-GFR relation have been seen in other forms of hypertension with this technique, including renal artery clip hypertension (the consequent renal artery narrowing exerts a substantial preglomerular resistance) and SHR hypertension, where increased preglomerular resistance or decreased vessel lumen dimensions have been observed. Recently, we showed that chronic ACE inhibition of SHR (perindopril for 6 weeks) resulted in a left shift in the pressure-GFR relation.

Intrarenal Ang II infusion resulted in dose-related hypertension that was evident as early as 8 to 11 days (awake direct measurement and telemetry). The cause of the rise in arterial pressure remains to be determined. It did not appear to be due to simple spillover of Ang II into the systemic circulation that led to systemic vasoconstriction, because acute losartan administration had similar effects on arterial pressure between rats infused with the highest dose of Ang II and vehicle-infused rats. Studies on the extent of Ang II metabolism during passage through the rat kidney indicates almost complete (93%) destruction of the peptide. Intraportal administration of the same doses of Ang II for 25 days had no effects on arterial pressure. Previous experiments in dogs showed that the intravenous administration of Ang II had less effect on arterial pressure than intrarenal infusion at the same dose. The hypertension could also have been due to Ang II–mediated release of a vasodilator substance (eg, an arachidonate metabolite or medullipin).

The apparent effects of the chronic Ang II infusion on the renal preglomerular vasculature are compatible with the hypothesis that the infused Ang II may have produced a form of renovascular hypertension by inducing structural changes in the renal vasculature that resulted in a reduction of lumen diameter in resistance vessels. The possibility that structural changes that narrow the lumen of the preglomerular vasculature may cause renovascular hypertension has been the subject of speculation ever since Goldblatt pointed out that his landmark experiments of producing hypertension from renal artery stenosis were based on the "assumption that, if the hypertension be the result of the intrarenal arterial and arteriosclerosis, then the real cause of the elevated blood pressure might be the functional disturbance of renal hemodynamics produced by the stenosing vascular disease in the kidney." Although stenosis of the type Goldblatt envisaged does not seem to occur in renal vessels in human hypertension, wall hypertrophy with lumen encroachment and remodeling around a smaller lumen would be predicted to cause similar disturbances to renal hemodynamics. However, confirmation of structural narrowing of these vessels is now required, with unbiased stereologic approaches.

The contralateral kidney was removed in some experiments to avoid confounding any prohypertensive effects in the infused kidney with antihypertensive effects of the non-infused kidney. We performed the nephrectomy both simultaneously with commencement of the Ang II infusions into the right kidney and 1 month before the commencement of the infusion to the right kidney, but we found similar elevations in mean arterial pressure (≈25 mm Hg). We also studied an additional group of rats in which the contralateral kidney was not removed. In these rats, hypertension still occurred, although the difference between mean arterial pressure in vehicle- and Ang II– (4.5 ng/kg·min−1) infused rats was slightly smaller (≈18 mm Hg on day 14). This mirrors the situation in renal artery clip hypertension, with a greater rise in arterial pressure seen in 1-kidney, 1-clip rats than with a stenosis of the same dimensions in 2-kidney, 1-clip rats.

The infusion of Ang II into the renal artery did not appear to affect kidney weight, nor were there obvious effects on gross renal morphology. The increase in left ventricular weight is consistent with the rises in arterial pressure in the various Ang II–infused groups. In conclusion, the results are compatible with the hypothesis that the Ang II infusion for up to 25 days caused a remodeling of the preglomerular resistance vessels around a narrower lumen. This is suggested by the significant, dose-related right shift of the relation between arterial distending pressure and GFR in the maximally dilated kidney, indicating that the lumen diameters of the preglomerular resistance vessels were significantly reduced structurally by the Ang II infusion. These results now must be confirmed with stereologic techniques. The intrarenal infusion of Ang II in doses apparently confined to the kidney also resulted in dose-related increases in arterial pressure that occurred regardless of whether the kidney was removed at the time of commencement of or 1 month before the Ang II infusion or was not removed.

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References


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