Angiotensin-Induced Hypertension in the Rat
Sympathetic Nerve Activity and Prostaglandins

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To elucidate mechanisms of angiotensin II (Ang II)–related hypertension, we infused angiotensin (76 ng/min s.c.) into rats with minipumps for 10–14 days. Control rats received sham pumps. We measured blood pressure by tail-cuff, and the excretion of aldosterone and prostaglandins (PG) (PGE2, prostacyclin derivative 6kPGF1α, and thromboxane [Tx] derivative TxB2). Angiotensin II increased blood pressure by 20 mm Hg by day 2 and by 90 mm Hg by day 10. Aldosterone excretion increased from 10 to 70 ng/day in Ang II rats by day 7. Urine PGE2 did not increase in angiotensin rats; however, both 6kPGF1α and TxB2 excretion increased with angiotensin. Control rats had no changes in any of these parameters. A sympathetic component was tested in a separate group of angiotensin rats that received phenoxybenzamine (300 μg/kg/day) during angiotensin infusion; their increase in blood pressure of 40 mm Hg at 10 days was less than in those rats with angiotensin alone but more than in control rats. Phenoxybenzamine did not influence the angiotensin-induced increases in excretion of 6kPGF1α or TxB2. Additional groups of conscious angiotensin and control rats were equipped with splanchnic nerve electrodes on day 14 for recording of sympathetic nerve activity. Angiotensin rats had greater basal sympathetic nerve activity than the control rats. Incremental methoxamine injections demonstrated altered baroreceptor reflex function in rats receiving angiotensin. We conclude that increased blood pressure with chronic angiotensin infusion is accompanied by increased production of aldosterone and increased sympathetic tone. The latter may be modulated by PG. (Hypertension 1989;14:396–403)

Angiotensin II (Ang II) is intimately involved in the homeostatic regulation of blood pressure and body fluids, although the details of its mechanisms of action remain quite controversial.1 In addition to a well-characterized vasoconstrictor action, Ang II has also been proposed to increase peripheral vascular resistance indirectly through peripheral and central mechanisms that lead to an increased activity of the sympathetic nervous system.2–4 Further, Ang II causes sodium retention both by a direct action on the renal tubule,2 5 and through the stimulation of aldosterone release.5 Finally, Ang II administration influences the plasma concentration, renal excretion, and tissue generation of prostaglandins (PGs) that modulate the vasoconstriction.6 However, the relevance of some of these studies to the pathophysiological role of Ang II in hypertension is not clear, as many were conducted during short-term Ang II infusion in animals under anesthesia.

To further define mechanisms in the production of Ang II–related hypertension, we infused Ang II into conscious rats over a 14-day period. We measured sympathetic nervous system activity directly with bipolar electrodes implanted on their splanchnic nerves. We determined the excretion of aldosterone and PG (PGE2, 6kPGF1α, and thromboxane [Tx]B2) to further investigate the role of the sympathetic nervous system in this model of Ang II–dependent hypertension. We examined the effect of α-adrenergic receptor blockade on the development of hypertension and the excretion of PGs. We found evidence for increased sympathetic
nerve activity despite enhanced baroreceptor reflex surveillance of sympathetic tone, increased aldosterone release, and increased prostacyclin and Tx production. Since phenoxybenzamine moderated the hypertension without influencing PG or TxB2 excretion, our results indicate that, in addition to aldosterone, the sympathetic nervous system contributes to Ang II–dependent hypertension independent of effects on vasodilator or vasoconstrictor PG production by the kidneys.

Materials and Methods

Experiments were performed on male Sprague-Dawley rats with initial body weights of 170–220 g. The rats had free access to water and standard rat chow. Several sets of experiments were conducted during prolonged Ang II infusion in conscious rats. Some of these rats received phenoxybenzamine by peritoneal injection daily, and others were used for short-term measurements of sympathetic nerve activity after having received ongoing infusions of Ang II for 14 days.

Prolonged Angiotensin II Infusion

The rats were anesthetized with ether. An incision was made in the midline in the lumbar region for insertion of osmotic minipumps (model 2002, ALZET Corp., Palo Alto, California; mean filling volume, 0.234 ml). The pumps generally were well tolerated, although a hematoma developed at the site of implantation in some rats; data from these rats were discarded. In earlier studies, we found that the growth of the rats was not impaired by pump implantation.7 Half the rats in each group (n=10) were given empty pumps, and the other half (n=10) were given pumps filled with Ang II (L-asparaginyl-5-L-valyl angiotensin octapeptide; CIBA-GEIGY Corp., Summit, New Jersey) in a concentration of 10 μg/μl. At the stated pump infusion rate of 10.32±0.72 μl/day, the pump would deliver 76 ng/min Ang II for approximately 21 days.

Rats were weighed daily, and systolic blood pressure was determined by tail-cuff measurements with a Doppler flowmeter (model 802A, Parks Electronics Laboratory, Beaverton, Oregon) or by a plethysmographic method. Rats infused with Ang II became hypertensive, and their blood pressure increased by more than 15 mm Hg within 3 to 7 days. Two additional groups of rats (n=8) were prepared identically. One group received Ang II and was simultaneously treated with bolus injections of phenoxybenzamine (300 μg/kg/day i.p.). The other group received only Ang II.

We performed preliminary experiments with phenoxybenzamine (300 μg/kg/day) according to methods previously used by others8–10 to determine the degree of adrenergic blockade and the effect on blood pressure at this dose in a group of six rats for 14 days. The doses of phenoxybenzamine were administered in the morning; blood pressure was also obtained in the mornings before that day’s phenoxybenzamine injections. With a single daily dose, we found that adrenergic blockade was highly effective. A 1 μg intravenous injection of norepinephrine, sufficient to increase blood pressure in control rats by 30 mm Hg, was attenuated to less than a 2–5 mm Hg change in blood pressure 24 hours after phenoxybenzamine was given. Systolic blood pressure was measured before treatment and every 2 days during the course of administration for 10 days in a group of rats with sham pumps. The mean systolic blood pressures of these rats at the termination of treatment was not significantly different from the sham-injected rats (114±7 mm Hg) reported in the present study.

Aldosterone and PG excretion were assessed by means of 24-hour urine collections. Sham-injected and Ang II rats were housed in metabolic cages. The rats were allowed to become accustomed to the cages for 5 days; urine was collected for 3 days before pump implantation and then daily for 9 additional days. Rats were removed from their cages only to have their blood pressures measured after minipump insertion and after surgical procedures. Fourteen days after pump emplacement, the rats were lightly anesthetized with ether and were equipped with femoral arterial and venous catheters, as well as with bipolar electrodes that were placed on the splanchnic nerve as described below.

Measurement of Nerve Activity

For measurements of efferent sympathetic nerve activity, chronic bipolar electrodes were implanted on the splanchnic nerve 1 or 2 days before recordings were taken. The operative procedures and the method of nerve recording were adapted from those described by Thoren and Ricksten.11 The rats were anesthetized with methohexital (Eli Lilly, Indianapolis, Indiana) (10 mg/kg i.v.). Repeated intravenous injections of methohexital were given during the operation as necessary. The area of the left splanchnic nerve, including the celiac ganglion, the renal artery, and kidney, was exposed retroperitoneally via a flank incision.

A splanchnic nerve branch between the celiac ganglion and the suprarenal plexus was dissected free of fat and connective tissue over a length of approximately 8–10 mm. The nerve was placed on a thin bipolar stainless steel electrode. When an optical signal was obtained, the nerve on the electrode was insulated and attached with a small amount of silicone rubber (Wacker Sil Gel 604, Munich, FRG). The transmission line to the amplifier was exteriorized via a miniature connector at the neck of the rat. The flank incision was then closed, and the rats were taken to their cages to recover from the procedure. During the operation, the rectal temperature of the rats was maintained constant with a servo-controlled heater.

Nerve potentials were amplified with a differential preamplifier and gated with a high-pass filter set at 10 Hz and a low-pass filter set at 3 kHz. These
signals were amplified further, then rectified, and quantitated by using a rate meter with a time constant of 5 seconds. The background level of nerve activity, which was defined from that measured 30 minutes after the rat was killed, was usually below 2 μV and was subtracted from the measured values in each rat. Mean rectified splanchnic nerve activity (SpNA), mean arterial pressure, and heart rate were displayed on a Gould (Gould-Statham, Oxnard, California) Brush 2400 recorder. Baseline values represent the average of 10 readings during a 60-second preinjection period. The analogue nerve signal was continuously monitored with an oscilloscope and an audio amplifier. Rats were then placed into their home cages and were allowed 24–36 hours to recover from the operation before experiments were performed. By that time, the rats had resumed their regular eating, drinking, and grooming habits and did not exhibit any signs of stress or pain. On alternate days and in random order, Ang II and sham-infused rats (n=8 each) were attached to the monitoring equipment and, after a basal state of 30 minutes, received bolus injections of methoxamine (10, 30, or 100 μg in random order). Thirty-minute recovery periods were allowed between each separate injection. The recordings of nerve activity, heart rate, and splanchnic nerve activity were taken simultaneously at the maximum change in the blood pressure. The changes in heart rate and nerve activity were concordant with those in blood pressure.

Urinary aldosterone was measured by a previously described radioimmunoassay. Urine for PG analysis was stored deep frozen at -40°C. Aliquots (0.5 ml) were purified by organic extraction followed by thin-layer chromatography. These extracts were analyzed by radioimmunoassay with very highly specific antisera to PGE₂, 6kPGF₁α, and TxB₂. The details of the purification and assay methods used, the performance characteristics of the assay, and the validation procedures have been published. The sensitivity of the PG method used was 2–5 pg/sample for TxB₂ and 5–10 pg/sample for 6kPGF₁α and PGE₂. The interassay coefficient of variation (n=31) for TxB₂ was 7.6%, for 6kPGF₁α was 8.3%, and for PGE₂ was 9.2%. The accuracy was assessed each week by addition of 1,000 pg TxB₂ and 6kPGF₁α to 1 ml rat urine. The results were +975±22 pg/ml (n=23) for 6kPGF₁α and 1,001±26 pg/ml (n=26) for TxB₂. In the present study, a 0.5 ml aliquot from each 24-hour urine specimen was extracted, purified, and analyzed for PGs. Each sample was individually spiked with approximately 1,000 cpm [³H]TxB₂ as a tracer to assess the individual recovery. This recovery averaged 55–60%. The concentrations of TxB₂ in urine averaged 900 pg/ml (range 200–2,000 pg/ml), whereas those for 6kPGF₁α and PGE₂ were approximately twofold to fourfold greater. Thus, the concentrations measured in urine were one to two orders of magnitude above the assay sensitivity.

Statistical comparisons were made with two-way analysis of variance, repeated-measures analysis of variance, and linear regression analysis using a standard, computerized program (SPPSx). The slopes of regressions were compared. The 95% limits of probability were accepted as significant. Data are expressed as mean±SD.

Results

Figure 1 shows systolic blood pressure of rats receiving the various regimens; the rats with sham minipumps had no changes through time in their blood pressure. The blood pressure of rats with pumps containing Ang II rose progressively from the second day of infusion. The blood pressure of the rats that received Ang II and daily intraperitoneal injections of phenoxybenzamine clearly increased, but the rise in blood pressure was delayed and the final level of blood pressure was reduced by about 50%. The three groups were distinguishable from each other by analysis of variance (p<0.05).

Figure 2 (Panel A) shows the effect of Ang II infusion on the excretion of PGE₂, 6kPGF₁α, and TxB₂. Ang II infusion had no consistent effect on the excretion of PGE₂. However, it significantly increased the excretion of 6kPGF₁α and TxB₂. Further, the daily administration of phenoxybenzamine did not influence the excretion of either 6kPGF₁α or of TxB₂ (Figure 2, Panel B). Analysis of variance indicated that the effect of Ang II on prostaglandin excretion was not significantly influenced by the administration of phenoxybenzamine.

Figure 3 shows the effect of chronic Ang II infusion on the excretion of aldosterone. Urinary aldosterone excretion increased progressively (p<0.05) in rats receiving a chronic infusion of Ang.
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Panel A: Changes from baseline in excretion of prostaglandins (PG) and their derivatives PGE₂, prostacyclin 6kPGF₁α, and thromboxane (Tx) TxB₂ in rats receiving Ang II infusion and controls. 6kPGF₁α and TxB₂ increased progressively during Ang II infusion, but PGE₂ excretion was not affected. Panel B: Excretion of 6kPGF₁α and TxB₂ in rats receiving Ang II and concomitant phenoxybenzamine. Excretion of PG was not affected by phenoxybenzamine.

Figure 4 shows the effect of nitroprusside (Panel A) 10 μg i.v. in a representative (sham-injected) rat that had bipolar electrodes implanted on a splanchnic nerve to measure SpNA. In these animals blood pressure and heart rate were measured continuously and directly. Panel B in Figure 4 shows the same response to 10 μg methoxamine. Nitroprusside caused an abrupt decrease in blood pressure, increase in heart rate, and increase in SpNA. Methoxamine caused an abrupt increase in blood pressure, decrease in heart rate, and decrease in SpNA. These maneuvers were used to select rats that had measurable and physiologically responsive records of SpNA. Only rats exhibiting these responses in blood pressure, heart rate, and SpNA were used in the studies shown on Table 1.

Table 1 shows blood pressure, heart rate, and SpNA in rats with Ang II pumps or sham pumps. The change in these variables from baseline is also given. The measurements were obtained in conscious rats in a resting state. After 30 minutes of baseline observation before and between injections, doses of methoxamine were given as intravenous bolus in random order. By intragroup analysis of
variance, none of the three baseline periods could be distinguished within the Ang II or sham groups. This finding suggested that steady resting levels in blood pressure, heart rate, and SpNA had been achieved. Blood pressure in Ang II rats was significantly greater than in sham rats at all periods of observation. Heart rate, on the other hand, was not significantly different. SpNA in rats receiving Ang II was significantly greater than in sham rats. The change in blood pressure, heart rate, and SpNA with methoxamine was also examined by repeated-measures analysis of variance. The changes in blood pressure with methoxamine in the Ang II group and sham group were not different. There was a trend for heart rate to decrease more in the sham group with methoxamine than in the Ang II group ($p=0.057$). SpNA decreased more in the Ang II group with methoxamine administration than in the sham group ($p<0.05$).

To compare the baroreceptor control of rats receiving Ang II to those of sham-injected rats further, we conducted linear regression analyses, with blood pressure as the manipulated variable. Significant relations were identified in both groups for the expression: $\delta HR = a + b (\delta BP)$, where $\delta HR$ equals the change in heart rate and $\delta BP$ equals the change in blood pressure.

For 24 observations in rats receiving Ang II ($r=0.89$, $p<0.001$) the slope $b$ was $-2.49\pm0.27$. For 24 observations in sham-injected rats ($r=0.71$, $p<0.001$), the slope $b$ was $-2.77\pm0.62$. These slopes were not significantly different by the $F$ test. Significant relations were also identified in both groups for the expression: $\delta SpNA = a + b (\delta BP)$, where $\delta SpNA$ was greater than in sham-injected group ($p<0.05$).

### TABLE I. Responses in Blood Pressure, Heart Rate, and Splanchnic Nerve Activity After Bolus Injections of Methoxamine

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Ang II</th>
<th>$\delta$</th>
<th>Sham</th>
<th>$\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure (mm Hg)</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>154±15</td>
<td>...</td>
<td>106±11</td>
<td>...</td>
</tr>
<tr>
<td>Baseline</td>
<td>149±11</td>
<td>...</td>
<td>106±11</td>
<td>...</td>
</tr>
<tr>
<td>Baseline</td>
<td>148±16</td>
<td>...</td>
<td>104±13</td>
<td>...</td>
</tr>
<tr>
<td>Methoxamine (1 µg)</td>
<td>163±16</td>
<td>+9±5</td>
<td>120±10</td>
<td>+14±5</td>
</tr>
<tr>
<td>Methoxamine (3 µg)</td>
<td>173±16</td>
<td>+24±6</td>
<td>139±12</td>
<td>+33±4</td>
</tr>
<tr>
<td>Methoxamine (10 µg)</td>
<td>201±18</td>
<td>+53±10</td>
<td>157±14</td>
<td>+53±11</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>534±73</td>
<td>...</td>
<td>496±91</td>
<td>...</td>
</tr>
<tr>
<td>Baseline</td>
<td>536±58</td>
<td>...</td>
<td>502±91</td>
<td>...</td>
</tr>
<tr>
<td>Baseline</td>
<td>535±71</td>
<td>...</td>
<td>511±81</td>
<td>...</td>
</tr>
<tr>
<td>Methoxamine (1 µg)</td>
<td>522±69</td>
<td>-12±16</td>
<td>467±84</td>
<td>-29±18</td>
</tr>
<tr>
<td>Methoxamine (3 µg)</td>
<td>479±62</td>
<td>-57±27</td>
<td>418±65</td>
<td>-84±44</td>
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<tr>
<td>Methoxamine (10 µg)</td>
<td>408±40</td>
<td>-127±41</td>
<td>344±51</td>
<td>-167±47</td>
</tr>
<tr>
<td><strong>SpNA (µV)</strong>‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.5±5.5</td>
<td>...</td>
<td>7.6±4.5</td>
<td>...</td>
</tr>
<tr>
<td>Baseline</td>
<td>13.4±4.9</td>
<td>...</td>
<td>7.7±5.4</td>
<td>...</td>
</tr>
<tr>
<td>Baseline</td>
<td>12.5±3.9</td>
<td>...</td>
<td>7.7±5.4</td>
<td>...</td>
</tr>
<tr>
<td>Methoxamine (1 µg)</td>
<td>11.8±5.0</td>
<td>-1.7±3.5</td>
<td>6.8±4.3</td>
<td>-0.8±1.0</td>
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<tr>
<td>Methoxamine (3 µg)</td>
<td>8.5±2.8</td>
<td>-3.6±3.4</td>
<td>4.8±3.1</td>
<td>-2.9±2.0</td>
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<tr>
<td>Methoxamine (10 µg)</td>
<td>6.4±1.1</td>
<td>-6.1±3.6</td>
<td>4.1±2.6</td>
<td>-3.6±2.9</td>
</tr>
</tbody>
</table>

Values are mean±SD. $\delta$, change (mean) in variable compared with corresponding baseline.

*Blood pressure in angiotensin II (Ang II) group was greater than that in sham-injected group ($p<0.05$), but the change in blood pressure was not significantly different.
†Change in heart rate between Ang II group and sham-injected group, $p=0.057$.
‡Change in splanchnic nerve activity (SpNA) in Ang II group was greater than sham-injected group ($p<0.05$).
equals the change in splanchnic nerve activity and \(\Delta BP\) equals the change in blood pressure. For 21 observations in rats receiving Ang II (\(r=0.53, p<0.01\)), the slope \(b\) was \(-0.102\pm0.04\). For the sham-injected rats (\(r=0.47, p<0.03\)), the slope \(b\) was \(-0.062\pm0.03\). These slopes were significantly different by the \(F\) test (\(p<0.01\)), indicating that the rate of fall of SpNA with increasing blood pressure was greater for rats receiving Ang II than in control rats.

Discussion

Renal hemodynamics, plasma aldosterone concentrations, and body fluid and electrolyte homeostasis have been examined during the onset and progression of chronic Ang II hypertension in various conscious animal models. Hall et al\(^5\) performed both acute and chronic infusions of Ang II into dogs and concluded that both renal hemodynamic effects of Ang II and aldosterone release contributed to sodium and water retention and increased blood pressure. Bean et al\(^{16}\) observed that Ang II infusion in dogs increased plasma aldosterone values only transiently. We measured urinary aldosterone excretion rate rather than plasma values and confirmed an early rise in aldosterone excretion by the second day of Ang II infusion, but this persisted until the measurements were terminated after 9 days. In an earlier report, we observed that rats receiving Ang II infusions retained sodium and that the sodium retention was mediated by calcium-dependent mechanisms.\(^7\) However, Textor et al\(^{10}\) could identify no significant sodium retention in rats after the chronic administration of Ang II. The reasons for these differences are not clear but may be related to methodology. Rats reestablish sodium balance within hours of receiving mineralocorticoids,\(^{16}\) which makes it particularly difficult to document sodium retention in this species. The development of hypertension cannot be attributed solely to the retention of salt. For instance, in the case of deoxycorticosterone acetate-salt–treated rats,\(^{17}\) the hypertension is mediated in part by central mechanisms that are expressed through increased sympathetic nervous system activity.

Although morphology was not performed after Ang II infusion in the present study, we believe that the causes for the elevation in blood pressure were functional rather than structural. Semiquantitative histological examinations of kidneys from our earlier report\(^2\) did not indicate the presence of severe renal damage after 14 days of Ang II infusion (Huelsmann et al, unpublished observations). Further, in our earlier report,\(^7\) the glomerular filtration rate of rats receiving chronic Ang II infusion was actually increased above baseline values during the concurrent administration of a calcium entry blocking drug. Thus, we feel that the presence of an intrinsic limitation on functional capacity of the kidney produced by a 10–14-day period of Ang II–induced hypertension is highly unlikely.

Previous investigations suggest that Ang II impairs the baroreceptor reflex control of heart rate.\(^{18,19}\) In the present study, the change in heart rate tended to be less in the Ang II group than the sham-injected group with a relatively small number of rats (\(p=0.057\)). Cheng et al\(^{20}\) recently studied the baroreceptor reflex function in spontaneously hypertensive rats (SHR) treated with captopril for a lifetime. They found that untreated SHR exhibited a decrease in baroreceptor reflex control of heart rate, which is in accord with our previous observations in stroke-prone SHR\(^{21}\) and in rats receiving Ang II in the present study. Cheng et al\(^{20}\) measured lumbar sympathetic nerve activity in their rats under anesthesia, and noted that SHR appeared to have an impaired sensitivity for baroreceptor reflex control of lumbar sympathetic nerve activity. In both our earlier study in stroke-prone SHR\(^{21}\) and in the present study, the control of SpNA appeared to be increased in the hypertensive rats, even though baroreceptor control of heart rate was decreased compared with normotensive rats. These results are consistent with those of Guo and Thames,\(^{22}\) who found that baroreceptor reflex control of sympathetic nerve activity was preserved in hypertensive rabbits despite an impaired control of heart rate. However, the conclusion that Ang II enhanced or preserved the baroreceptor reflex control of SpNA may not be reasonable because baseline blood pressure was different in the Ang II and sham-injected rats. This difference may be important, as the baroreceptor reflex is nonlinear. Further, baseline SpNA was also different in the Ang II and sham-injected rats. This difference might have influenced the sympathetic nerve response to a given stimulus independent of specific effects of Ang II on the baroreceptor reflex.

Previous studies have established that the sympathetic nervous system is involved in the pressor response to Ang II. Faber and Brody\(^{23}\) concluded that the sympathetic nervous system mediated 40–50% of the rise in blood pressure in the Ang II–dependent model of constriction of a renal artery. Our studies have implicated the sympathetic nervous system more directly since we identified an increase in basal sympathetic nervous system activity during prolonged Ang II infusion. This increase occurred in the face of a progressive rise in blood pressure, which should normally reduce SpNA. Nerve activity in conscious animals is subject to sufficient variability to prevent finding consistent differences between SHR compared with Wistar-Kyoto rats.\(^{21,24–27}\) The results are consistent with a central mechanism that modifies baroreceptor reflex regulation. Cowley and DeClue\(^{28}\) also observed that chronic Ang II infusion in the dog modified the baroreceptor response. They concluded that this effect could account for 35% of the rise in blood pressure they observed.

Much of the rise in blood pressure produced by blood-borne Ang II is mediated by central brain...
mechanisms.\textsuperscript{29} Braun-Menendez et al\textsuperscript{30} found that Ang II augments the release of catecholamines by the adrenal medulla. Sympathectomy moderates the development of vasoconstriction with Ang II injection,\textsuperscript{31} whereas injection of Ang II into the central circulation increases sympathetic vasoconstrictor discharge.\textsuperscript{32} The central administration of Ang II increases blood pressure, thirst, salt appetite, and enhances secretion of pituitary hormones, particularly arginine vasopressin. In short-term experiments, we found that the intracerebroventricular administration of Ang II resulted in decreased sympathetic tone despite an increase in blood pressure.\textsuperscript{33}

The pressor response and inhibition of SpNA may have been related to release of arginine vasopressin. Likewise, short-term intravenous infusion of Ang II can attenuate sympathetic nervous system tone, perhaps because of a predominant effect of baroreceptor activation by the rise in blood pressure.\textsuperscript{34}

Circulating Ang II has access to the central nervous system at various sites in which the bloodbrain barrier is relatively permeable.\textsuperscript{35–38} The site at which Ang II acted to increase SpNA was not defined by our studies. However, Ferrario and colleagues\textsuperscript{39–43} have concluded that the area postrema is accessible to blood-borne Ang II and that the area contains an Ang II–sensitive pressor mechanism. Our finding that phenoxybenzamine blunted the increase in blood pressure during Ang II infusion supports the hypothesis that the increase in blood pressure was in part sympathetically mediated. On the other hand, the dose of phenoxybenzamine was high, and yet the blood pressure was not reduced to control values. This observation clearly demonstrates that other factors in addition to \( \alpha \)-receptor stimulation mediate the rise in blood pressure. As indicated previously, we believe that one of these factors was sodium retention, related to aldosterone. Sympathetic discharge via the renal nerves may greatly influence sodium retention (see Reference 44 for review). However, a recent report by Mizelle et al.\textsuperscript{45} suggests that the renal nerves do not play a major role in mediating the sodium-retaining effects of Ang II, at least not under the condition of sodium restriction.

Short-term Ang II infusion releases vasodilator PGs, which attenuate the renal and systemic vasoconstriction.\textsuperscript{46} Prolonged Ang II infusions also augment PGI\(_2\) production, but PGE\(_2\) generation, as reflected in plasma measurements or release from renal cortical slices, is unaffected by Ang II.\textsuperscript{6} Our data support these conclusions. Another link between Ang II–dependent hypertension and arachidonate metabolites is suggested by our findings of an increase in the excretion of TxB\(_2\). Thromboxane is a potent vasoconstrictor\textsuperscript{47} and could contribute to salt retention and vasoconstriction by potentiation of the tubuloglomerular feedback mechanism.\textsuperscript{13} Moreover, the inhibition of thromboxane synthesis attenuates vascular responses to sympathetic nerve stimulation.\textsuperscript{48} Increased TxB\(_2\) synthesis stimulated by Ang II may have increased the release of, or responsiveness to, sympathetic neurotransmitters and thereby facilitated the development of hypertension. Thromboxane synthesis or receptor antagonists have been shown to reduce the systemic and renal vasoconstriction produced by short-term Ang II infusions\textsuperscript{49} and to reduce the blood pressure of conscious rats receiving prolonged Ang II infusions.\textsuperscript{50} The sympathetic nervous system itself may promote the release of PGs; however, the release of PGs during prolonged Ang II administration would appear to be independent of \( \alpha \)-receptor activation, as the administration of phenoxycarbamyl had no effect on 6kPGFla or TxB\(_2\) excretion. Effects of converting enzyme inhibitors on PGs may explain some of their antihypertensive actions that are independent of Ang II.\textsuperscript{31}

In summary, this study underscores the complexity of the mechanisms that mediate the pressor response to prolonged Ang II infusion. Our data suggest that these infusions not only result in a sustained release of aldosterone, but also augment the basal sympathetic tone in the face of increasing blood pressure. The ensuing increase in sympathetic nervous system activity and \( \alpha \)-receptor activation could mediate up to half of the rise in blood pressure. TxB\(_2\) production promoted by Ang II infusion may subsequently enhance the response to the increase in sympathetic nervous system activity.

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