Role of Brain Angiotensin II on Somatosensory-Induced Antinatriuresis in Hypertensive Rats

Chunlong Huang, Edward J. Johns

Abstract—The aim of this investigation was to compare the contribution of brain angiotensin II in mediating the transmission of a somatosensory stimulus within the brain to generate a renal sympathetic nerve–dependent antinatriuresis and antidiuresis in normotensive Wistar rats and stroke-prone spontaneously hypertensive rats (SHRSP). In anesthetized Wistar rats, stimulation of somatosensory receptors by subcutaneous capsaicin increased blood pressure by 9%, had no effect on renal hemodynamics, but decreased urinary flow and sodium excretion by 30% to 40%. These antidiuretic and antinatriuretic, but not blood pressure, responses were absent after intracerebroventricular losartan administration to block angiotensin II type 1 receptors. By contrast, in the SHRSP, although subcutaneous capsaicin raised blood pressure and renal blood flow, neither glomerular filtration rate, urinary flow, nor sodium excretion changed, and this pattern of responses was unaffected after intracerebroventricular losartan. However, an intracerebroventricular infusion of angiotensin II increased basal blood pressure and fluid output, and the capsaicin challenge elicited vasopressor, antidiuretic, and antinatriuretic responses similar in magnitude to those observed in the Wistar rats. The capsaicin challenge in the SHRSP also caused a slowly developing, long-lasting fall in blood pressure and fluid excretion. These findings show that angiotensin II is a necessary component in the somatorenal reflex in normotensive rats but that endogenous angiotensin II is unable to exert this role in SHRSP. (Hypertension. 2001;37:1369-1374.)

Key Words: angiotensin II ■ sympathetic nervous system, renal ■ sodium ■ brain

The sympathetic innervation of the kidney is very dense, with neuroeffector junctions present along most of the vascular and tubular elements.1 Their activation causes renin release, a stimulation of tubular epithelial cell reabsorption, and, at high levels of activation, marked reductions in renal hemodynamics.2 The level of renal sympathetic outflow is dependent on sensory input from a number of systems, the high- and low-pressure cardiovascular baroreceptors and the somatosensory and visceral systems. Reductions in pressure at the carotid sinus and aortic arch in anesthetized dogs and rats lead to an increase in renal sympathetic nerve activity and a renal nerve–dependent sodium retention,3,4 whereas stimulation of low-pressure cardiopulmonary receptors by phenylbiguanide or saline volume expansion has been shown to decrease renal sympathetic nerve activity and to cause a renal nerve–dependent increase in sodium excretion.3–7 In our own studies, we showed that activation of the somatosensory system in the rat by electrical stimulation of the brachial nerves8 or by administration of capsaicin to stimulate sensory receptors of the skin9 reflexly increased renal sympathetic nerve activity and caused a renal nerve–dependent antinatriuresis and antidiuresis. The ability of the somatosensory system to cause a neurally mediated antinatriuresis was found to be blocked after the administration of losartan into the lateral cerebral ventricles of the brain10 but was restored when angiotensin II (Ang II) was infused into the central nervous system.11 This suggested that Ang II was a necessary component within the central neural pathways transmitting sensory information from the soma and eliciting an autonomic response.

In further investigations, it became evident that stimulation of the somatosensory system in a genetic model of hypertension, the stroke-prone spontaneously hypertensive rat (SHRSP), elicited increases in renal sympathetic nerve activity but that renal nerve–dependent antidiuresis and antinatriuresis were markedly blunted compared with the response in normotensive Wistar control rats.9,12 The reasons underlying these attenuated excretory responses to the somatosensory stimulation were unclear, but it was apparent that the pattern of activity held within the renal nerve signal was different and changed in a less dynamic way compared with the that in Wistar control rats. This suggested that there was some change or defect in the central nervous system that might have been responsible. One possibility was that there might be a derangement in the levels of Ang II at specific loci within the neural pathway mediating the somatosensory-induced neural control of sodium and water excretion. This was investigated in the present study, in which the activity of the brain renin-angiotensin system in the SHRSP was either suppressed, by administering losartan to block Ang II type 1 (AT1) receptors, or was enhanced by infusing exogenous Ang II into the lateral cerebral ventricles.
Methods

All surgical techniques were carried out under the UK Government Project License PPL 40/1367 and Personal Investigator Licenses PIL 40003711 (to E.J.J.) and PIL 4002632 (to C.H.). Male Wistar rats (312±26 g) and SHRSP (325±5 g) were anesthetized with halothane/O2/N2O, the femoral vein was immediately cannulated, and chloralose and urethane were given intravenously at 12 and 180 mg·kg−1·min−1, respectively, over 45 minutes, followed by supplementary doses every 30 minutes. The depth of anesthesia was checked regularly by ensuring a lack of pedal reflex when the toe was pinched. Cannulas were put in the carotid and femoral arteries to measure systemic blood pressure and renal perfusion pressure (RPP). The left kidney was exposed through a flank incision, and its artery was cleared and fitted with an electromagnetic flowmeter probe (Carolina Medical Electronic). The left ureter was cannulated for urine sample collection. A thread was placed around the aorta above the renal artery to enable RPP to be maintained constant in the face of increasing arterial pressure. Saline (150 mmol/L NaCl) was infused at 3 mL·h−1 immediately after the femoral vein had been cannulated. After the surgery had been completed, a 2 mL bolus of inulin (15 mg·mL−1) in saline was given intravenously as a primer, which was followed by an infusion of saline containing 15 mg·mL−1 inulin at 3 mL·h−1 throughout the rest of the experiment. The animals were allowed 2 hours to stabilize before the experimental procedures were begun.

Intracerebroventricular administration of drugs was performed by injection into the right lateral cerebral ventricle with use of a guide cannula placed at a site 1.0 mm posterior to the bregma, 2.5 mm lateral to the midline, and 2.55 mm ventral to the surface of the dura. Another stainless-steel tube, connected to a Hamilton syringe on a Macintosh) as appropriate. Significance was assumed at P<0.05.

Results

In group I (Table 1), the administration of capsaicin elicited a significant (P<0.01) increase (∼9%) in blood pressure, which had returned to control levels in the period after capsaicin and was still at this level during the recovery period. During the entirety of the study, RPP was regulated at a value close to that obtained in the control period (Table 1). The capsaicin challenge had no effect on either renal blood flow or the glomerular filtration rate, but urinary flow and absolute and fractional sodium excretions were significantly (P<0.01, P<0.05, and P<0.01, respectively) reduced by

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
 & MAP, mm Hg & RPP, mm Hg & RBF, mL·kg−1·min−1 & GFR, mL·kg−1·min−1 & UV, µL·kg−1·min−1 & UoV, µmol·kg−1·min−1 & FE\text{\scriptsize{UNa}} \text{%} \\
\hline
Capsaicin injection (n=7) & & & & & & & \\
\hline
Control & 114±2 & 107±2 & 29.2±2.8 & 4.2±0.5 & 48.0±5.3 & 8.7±1.3 & 1.3±0.1 \\
During capsaicin & 124±2\* & 106±2 & 29.1±2.6 & 4.2±0.5 & 35.1±4.9\* & 5.3±0.7\† & 0.8±0.1\† \\
After capsaicin & 116±1 & 105±2 & 31.5±2.8 & 4.3±0.4 & 43.7±7.7 & 6.9±0.9 & 1.1±0.1 \\
Recovery & 112±3 & 101±4 & 33.4±2.7 & 3.9±0.3 & 46.3±6.2 & 8.9±0.6 & 1.4±0.1 \\
Capsaicin injection after losartan at 15 µg·7.5 µg·h−1 ICV (n=6) & & & & & & & \\
Baseline & 114±4 & 107±4 & 31.6±2.5 & 3.9±0.4 & 48.6±4.3 & 7.4±0.6 & 1.5±0.3 \\
Control-losartan & 114±4 & 108±4 & 30.7±2.1 & 3.8±0.2 & 51.5±2.8 & 7.3±0.7 & 1.3±0.2 \\
During capsaicin & 125±4\* & 109±4 & 31.0±2.1 & 3.8±0.2 & 50.4±2.9 & 7.4±0.5 & 1.4±0.1 \\
After capsaicin & 116±4 & 108±3 & 33.4±2.4 & 4.2±0.2 & 53.9±4.0 & 7.7±0.5 & 1.3±0.1 \\
Recovery & 110±3 & 102±3 & 32.9±2.3 & 3.7±0.3 & 51.8±3.4 & 8.1±0.7 & 1.6±0.2 \\
\hline
\end{tabular}
\caption{Blood Pressure and Renal Responses to Capsaicin Injection in Wistar Rats}
\end{table}

Values are mean±SEM. MAP indicates mean arterial pressure; RBF, renal blood flow; GFR, left glomerular filtration rate; UV, urinary flow; UoV, absolute sodium excretion; and FE\text{\scriptsize{UNa}}, fractional sodium excretion.

\*P<0.01, †P<0.05, and ‡P<0.001 vs control (control-losartan).

Groups of Rats

Six groups of rats (2 groups of Wistar rats and 4 groups of SHRSP) were studied: In group I (n=7), a series of six 15-minute clearance periods, as described above, were undertaken in Wistar rats. In group II (n=6), a series of eight 15-minute clearance periods was performed in Wistar rats. Two hours after the surgery, 2 clearances were taken before the nonpeptide AT1-specific receptor antagonist, losartan, was given intracerebroventricularly as a 15 µg initial bolus (in 2 µL saline), followed by an infusion of 7.5 µg·h−1 (in 1 µL saline). Twenty minutes later, 6 further clearances were collected in a pattern that was identical to that in group I. Group III (n=6) and group IV (n=6) were SHRSP in which the experimental protocols were identical to those performed in group I and group II, respectively. In group V (n=6), SHRSP were subjected to the same procedure as group II, except that Ang II, instead of losartan, was given intracerebroventricularly as an initial bolus of 100 ng (in 2 µL saline), followed by an infusion of 50 µg·h−1 (in 1 µL saline). In group VI (n=8), SHRSP were subjected to the same protocol as group V, except that the capsaicin challenge was not given. This represented an Ang II intracerebroventricular time control.

Statistical Analysis

All data represent the average values calculated from individual rats and are expressed as mean±SEM. The effect of capsaicin was taken as the difference between the values obtained during the capsaicin injection and the average value of the 2 control (or control-drug) clearances. The influence of the drug intracerebroventricularly was taken as the difference between the average values of the 2 clearances obtained immediately before and 20 minutes after the administration. Comparisons were undertaken by using a Student’s paired t test or a 2-way ANOVA (Super ANOVA software for Macintosh) as appropriate. Significance was assumed at P<0.05.
The group III SHRSP (Table 2) had control blood pressures and renal blood flows that were higher than those in the Wistar rats (Table 1) and urinary flows and absolute and fractional sodium excretions (Table 2) that were lower than those in the Wistar rats (Table 1). When capsaicin was given, systemic blood pressure was increased significantly (by \( \approx 13\% \), \( P<0.001 \)), but thereafter, it fell slightly below control levels in the period after capsaicin and fell even further during the recovery period (by \( \approx 8\% \), \( P<0.05 \)). RPP was held at an unchanged level during and after the capsaicin injections, but in the recovery period, RPP had fallen to a level significantly (\( P<0.05 \)) below the control level (Table 2). Capsaicin administration was associated with an increase in renal blood flow, but neither glomerular filtration rate, urinary flow, nor sodium excretion changed during the course of the experiment. These excretory responses to the subcutaneous capsaicin are compared with those obtained in Wistar rats in the Figure.

In group IV SHRSP (Table 2), after control measurements were taken, the administration of intracerebroventricular losartan had no effect on the basal levels of any of the measured variables. Capsaicin administration (Table 2) significantly (\( P<0.001 \)) increased blood pressure by \( \approx 10\% \), but in the period after capsaicin and in the recovery period, it was significantly lower (\( P<0.01 \) and \( P<0.05 \), respectively) than control levels. Consequently, although RPP was held constant during the period of capsaicin administration, it was significantly less after capsaicin and in the recovery period (\( P<0.01 \) and \( P<0.05 \), respectively). The capsaicin injection had no measurable effect on either renal blood flow, glomerular filtration rate, urinary flow, or absolute or fractional sodium excretion during, after, or in the recovery phase (Table 2), and responses are compared with those of the other groups in the Figure.

Infusion of intracerebroventricular Ang II in group V (Table 3) significantly increased both blood pressure and RPP (both \( P<0.01 \)) by \( \approx 24 \) to \( 28 \) mm Hg, and although neither renal blood flow nor glomerular filtration rate was altered, there were marked 2- to 3-fold increases in urinary flow and absolute and fractional sodium excretions (all \( P<0.001 \)). Under these conditions, capsaicin significantly (\( P<0.01 \)) increased blood pressure while it was being given. It fell to control levels in the period after capsaicin but decreased significantly (\( P<0.05 \)) below control values during the recovery phase (Table 3). RPP (Table 3) was held at a value not different from control levels both during and after the capsaicin injection but fell below control levels in the recovery period (\( P<0.05 \)). Renal blood flow did not change either during or after capsaicin administration but was significantly (\( P<0.05 \)) lower during the recovery phase, by \( \approx 8\% \) (Table 3). The administration of capsaicin caused the glomerular filtration rate to decrease significantly (\( P<0.05 \) to \( P<0.01 \)) while it was given and also in the clearance period immediately after the challenge, by \( \approx 10\% \) to \( 15\% \), but it returned to control levels during the recovery phase (Table 3). Urinary flow and absolute and fractional sodium excretions were all significantly (\( P<0.01 \) to \( P<0.001 \)) reduced during the capsaicin administration, by \( \approx 35\% \), \( \approx 40\% \), and \( \approx 42\% \), respectively (all \( P<0.01 \)), decreased further in the period.

27\%, 39\%, and 38\%, respectively, during the period of capsaicin administration. In the subsequent period, all 3 variables rose toward control levels, which were completely attained during the recovery period (Table 1).

The administration of intracerebroventricular losartan in group II Wistar rats had no meaningful effect on the basal values of blood pressure or any renal hemodynamic or excretory variable (Table 1). The capsaicin challenge elicited an \( \approx 10 \) mm Hg increase in mean blood pressure (\( P<0.01 \)), whereas RPP was maintained at the control value. However, neither renal blood flow, glomerular filtration rate, urinary flow, nor absolute or fractional sodium excretion was altered during or after the capsaicin administration and remained at these levels during the recovery period (Table 1). Comparisons of the excretory responses caused by capsaicin are given in the Figure.
immediately after the capsaicin administration, and continued to decline in the recovery period (Table 3). Comparisons of the immediate renal excretory responses to the capsaicin in this group of rats with the other groups are given in the Figure.

The group VI SHRSP were a control group, in that Ang II was infused but capsaicin was not administered (Table 3). Administration of the Ang II intracerebroventricularly increased both systemic blood pressure and renal perfusion, had no effect on either renal blood flow or glomerular filtration rate, but caused significant (P<0.01 to P<0.001) increases in urinary flow and absolute and fractional sodium excretions of 2- to 3-fold (Table 3). Thereafter, all variables remained at a constant level for the remainder of the experimental protocol.

Discussion

There is accumulating evidence that Ang II, generated in the brain itself via a local renin-angiotensin system, may be involved in modulating the degree of sympathetic outflow in response to sensory input. In our previous studies, we had shown that Ang II in the brain was necessary to allow a somatosensory-induced renal nerve-dependent antidiuresis and antinatriuresis to take place. Indeed, this would be consistent with the observations of Sasaki and Dampney and Hirooka and Dampney, who showed that Ang II elicited an excitatory action at the rostral ventrolateral medulla, an important nucleus involved in determining sympathetic outflow, and appeared to have a facilitatory role in allowing somatosensory stimulation to elicit an increase in sympathetic outflow to the periphery. However, it was also evident that this somatosensory-mediated reflex neural control of sodium excretion was blunted in the SHRSP, but whether this was due to a deficit within the brain or at the neuroeffector sites within the kidney was not clear. The issue addressed in the present investigation was whether there was a deficiency in the role of Ang II within the brain of the SHRSP in modulating the somatosensory-mediated antidiuresis and antinatriuresis.

TABLE 2. Blood Pressure and Renal Responses to Capsaicin Injection in SHRSP

<table>
<thead>
<tr>
<th>Clearance</th>
<th>MAP, mm Hg</th>
<th>RPP, mm Hg</th>
<th>RBF, mL·kg⁻¹·min⁻¹</th>
<th>GFR, mL·kg⁻¹·min⁻¹</th>
<th>UV, µL·kg⁻¹·min⁻¹</th>
<th>U₆NaV, µmol·kg⁻¹·min⁻¹</th>
<th>FE₆Na, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin injection (n=6)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>170±4</td>
<td>164±6</td>
<td>48.5±3.6</td>
<td>6.0±0.4</td>
<td>31.6±7.4</td>
<td>4.0±1.3</td>
<td>0.5±0.2</td>
</tr>
<tr>
<td>During capsaicin</td>
<td>192±5‡</td>
<td>167±5</td>
<td>52.8±3.1*</td>
<td>5.0±0.4</td>
<td>29.7±8.1</td>
<td>3.9±1.9</td>
<td>0.5±0.2</td>
</tr>
<tr>
<td>After capsaicin</td>
<td>165±8</td>
<td>154±5</td>
<td>51.3±2.5</td>
<td>4.2±0.5</td>
<td>27.7±10</td>
<td>4.2±2.1</td>
<td>0.6±0.3</td>
</tr>
<tr>
<td>Recovery</td>
<td>156±8‡</td>
<td>149±7†</td>
<td>51.7±3.2</td>
<td>5.7±0.7</td>
<td>34.6±11.3</td>
<td>4.8±1.7</td>
<td>0.6±0.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*P<0.01, †P<0.05, and ‡P<0.001 vs control (control-losartan).

<p>| TABLE 3. Blood Pressure and Renal Responses in SHRSP After Ang II |
|-------------------------|---------------------|-------------------|-------------------|-------------------|------------------------|--------|</p>
<table>
<thead>
<tr>
<th>Clearance</th>
<th>MAP, mm Hg</th>
<th>RPP, mm Hg</th>
<th>RBF, mL·kg⁻¹·min⁻¹</th>
<th>GFR, mL·kg⁻¹·min⁻¹</th>
<th>UV, µL·kg⁻¹·min⁻¹</th>
<th>U₆NaV, µmol·kg⁻¹·min⁻¹</th>
<th>FE₆Na, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin after Ang II at 100 ng·50 ng · h⁻¹ IVC (n=6)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>172±7</td>
<td>165±7</td>
<td>47.5±2.9</td>
<td>5.9±0.9</td>
<td>26.3±3.8</td>
<td>3.7±0.8</td>
<td>0.5±0.1</td>
</tr>
<tr>
<td>Control–Ang II</td>
<td>196±10*</td>
<td>193±10*</td>
<td>47.5±2.7</td>
<td>4.4±0.2</td>
<td>54.5±4.99</td>
<td>10.5±1.2§</td>
<td>1.7±0.2*</td>
</tr>
<tr>
<td>During capsaicin</td>
<td>209±9†</td>
<td>192±10</td>
<td>48.6±2.2</td>
<td>3.9±0.2†</td>
<td>35.3±4.41</td>
<td>6.3±1.3†</td>
<td>1.1±0.2‡</td>
</tr>
<tr>
<td>After capsaicin</td>
<td>188±7</td>
<td>180±7</td>
<td>44.2±3.2</td>
<td>2.8±0.6‡</td>
<td>21.9±6.6€</td>
<td>3.6±1.4€</td>
<td>0.8±0.2‡</td>
</tr>
<tr>
<td>Recovery</td>
<td>152±5†</td>
<td>145±6†</td>
<td>41.0±4.0†</td>
<td>5.1±1.2</td>
<td>18.8±4.6€</td>
<td>2.0±1.0‡</td>
<td>0.3±0.2‡</td>
</tr>
<tr>
<td>Ang II at 100 ng·50 ng · h⁻¹ IVC but no capsaicin (n=8)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>167±4</td>
<td>162±4</td>
<td>38.6±1.8</td>
<td>4.5±0.3</td>
<td>23.5±3.0</td>
<td>2.9±0.6</td>
<td>0.5±0.1</td>
</tr>
<tr>
<td>Control–Ang II</td>
<td>195±5*</td>
<td>191±4*</td>
<td>42.8±1.4</td>
<td>5.0±0.3</td>
<td>48.9±4.4§</td>
<td>8.6±1.5§</td>
<td>1.2±0.2*</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*P<0.01 and §P<0.001 vs baseline; †P<0.05, ‡P<0.01, and †P<0.001 vs control–Ang II.
The first set of studies in the normotensive Wistar rats with saline infused intracerebroventricularly showed that subcutaneous administration of capsaicin elicited a transient increase in blood pressure, and although RPP and renal hemodynamics were unchanged, there was a short-lived fall in urinary flow and sodium excretion. We have previously reported that in this situation the capsaicin acts to depolarize the subcutaneous nociceptors, giving rise to a somatosensory input, thus causing a reflex increase in renal sympathetic nerve activity and a renal nerve–mediated antidiuresis and antinatriuresis. The present study supports this view in that the somatorenal reflex was intact in the Wistar rats. It was also clear that this somatosensory-mediated reflex neural control of urinary flow and sodium excretion was dependent on Ang II in the brain, as following blockade of its receptors with intracerebroventricular losartan, the excretory responses were prevented. Indeed, these observations support our previous study, which reported that if endogenous production of brain Ang II was blocked by captopril, exogenous Ang II administration into the brain could restore the excretory responses to subcutaneous capsaicin administration.

The situation in the SHRSP given saline intracerebroventricularly was very different, in that although the subcutaneous capsaicin produced a prompt and short-lived increase in blood pressure, there were small insignificant changes in urinary flow and sodium excretion. Again, these findings support our earlier observations that somatosensory activation, by electrically stimulating the brachial nerves by upper airway tract stimulation or subcutaneous capsaicin, resulted in a blunted excretory response compared with that in the normotensive Wistar rats. This occurred even though basal rates of renal hemodynamics were slightly higher and urinary flow and sodium excretion were lower in the SHRSP compared with the Wistar rats. However, the issue to be explored was whether these blunted excretory responses were a consequence of overactivity or underactivity of Ang II within the brain of the SHRSP.

Blockade of AT1 receptors in the brain of the SHRSP was without effect on the basal blood pressure in this group of rats and had no consistent action on either renal hemodynamics or the rate of urinary flow or sodium excretion. During the period of capsaicin administration, there was a significant vasopressor action but no meaningful changes in renal hemodynamics, urinary flow, or sodium excretion, which was a pattern of responses very similar to that obtained in the SHRSP in which saline was given intracerebroventricularly. This would suggest that the blunted antidiuretic and antinatriuretic responses were not due to an overactivity of Ang II in the brain, exerting a tonic inhibitory action, but rather due to a deficit in its action or ability to exert a normal effect at important points along the pathway that integrated the somatosensory input with an appropriate response in renal sympathetic outflow.

A further study was performed with the use of SHRSP in which exogenous Ang II was infused intracerebroventricularly with a view to replacing the peptide at functionally important areas. It was evident that the Ang II increased blood pressure even further in these hypertensive animals and was accompanied by a diuretic and natriuretic response. Once the new basal levels had been achieved, the administration of capsaicin caused a further small transient pressor response, and although renal blood flow remained constant with a small fall in glomerular filtration rate, there were marked reductions in urinary flow and absolute and fractional sodium excretions. Thus, it was apparent that during this initial period of stimulation of the somatorenal system, there was an antidiuresis/antinatriuresis, the magnitude of which was significantly larger than that obtained in the SHRSP simply given a saline vehicle intracerebroventricularly but very comparable to that obtained in the normotensive Wistar rats given saline intracerebroventricularly. These observations were consistent with the suggestion that in some way Ang II was unable to exert its normal facilitatory action on the somatorenal reflex in the SHRSP. Whether this was due to a reduced generation of Ang II at important loci or to a fall in AT1 receptor density in specific regions is not clear and could not be determined by the experimental approaches used in these studies.

Over the course of the studies using SHRSP, a further important finding became apparent: when capsaicin was being given subcutaneously, there was a prompt pressure response, but in the subsequent clearance period, blood pressure fell to or more often below the various control values in the animals receiving saline, losartan, or Ang II intracerebroventricularly. Thereafter, in the recovery periods, blood pressure fell even further to a relatively low level. This progressive fall in pressure was not evident in the Wistar rats and appeared to be a feature of the SHRSP. One further consequence of the gradual reduction in blood pressure was that although renal hemodynamics were generally well maintained, urinary flow and sodium excretion progressively decreased. It is most likely that the reduced fluid output could be attributed in part to the pressure fall, because it is generally accepted that the level of blood pressure, via renal interstitial hydrostatic pressure, directly determines the level of tubular fluid reabsorption. However, an alternative possibility might be that there was a generalized decrease in sympathetic outflow, leading to dilation in a range of vascular beds. Although this may have resulted in a raised fluid excretion from the kidney as a result of withdrawal of sympathetic tone, this may have been confounded by the pressure-dependent mechanisms determining fluid output.

The cause of this fall in pressure after capsaicin administration was not immediately apparent. One possibility could be that the depressor response was a consequence of a long-lasting stimulation of the sensory receptors within the skin. Indeed, there have been reports that somatosensory stimulation can cause a long-lasting reduction in blood pressure, and it may be that by using this experimental approach in the SHRSP, this feature was more evident. The alternative possibility was that the fall in pressure in the later part of the experiments could have been due to Ang II within the central nervous system or could even be time-related. To explore this possibility, a final group of SHRSP were used. In that group, after the control measurements, Ang II was infused intracerebroventricularly throughout the study, but capsaicin was not given. The findings were clear-cut; ie, after the initial vasopressor, diuretic, and natriuretic effects of the
Ang II infusion, blood pressure and fluid excretion remained unchanged for the duration of the experiment. These observations indicated that Ang II was not involved and provided further support for the view that it was subcutaneous capsaicin that was responsible for the long-term vasodepressor, antidiuretic, and antinatriuretic events.

These studies have shown that somatosensory stimulation using subcutaneous capsaicin increased blood pressure and caused an antinatriuresis and antiuriresis in normotensive Wistar rats that was dependent on Ang II in the brain. By contrast, in the SHRSP, although the capsaicin-induced vasopressor response was intact, antidiuresis and antinatriuresis were not evident. In the SHRSP, blockade of AT1 receptors had no effect on the somatosensory-induced pressure or excretory responses, but when Ang II was given intracerebroventricularly, the capsaicin-induced antidiuretic and antinatriuretic responses were comparable to those obtained in Wistar rats. These findings suggest that in the SHRSP, there is a defect in the ability of Ang II in the brain to facilitate the signals from the somatosensory system to elicit response in the renal sympathetic nerves, leading to a fluid retention. It was evident that in the SHRSP, capsaicin elicited not only a short-term pressure response but also a longer-term depression of blood pressure and fluid output. The mechanisms underlying these responses require further investigation.

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