Brain Angiotensin II and Baroreceptor Reflex Function in Spontaneously Hypertensive Rats

Savio W.T. Cheng, Katharine A. Kirk, Joel D. Robertson, and Kathleen H. Berecek

We examined whether the increase in baroreceptor reflex function previously reported in lifetime-captopril-treated spontaneously hypertensive rats (SHR) was due to an inhibition of brain angiotensin II mechanisms. Pregnant and lactating SHR were given oral captopril (100 mg/kg/day). After weaning, pups were maintained on captopril (50 mg/kg/day) until the study (19–21 weeks). Control rats received tap water. One week before study captopril-treated and control SHR were given an intracerebroventricular infusion of angiotensin II (7.5 ng/hr, osmotic pump) or vehicle (artificial cerebrospinal fluid). Baroreceptor reflex control of heart rate was assessed by the slope of the relation between the change in mean arterial pressure (mm Hg) versus the change in pulse interval (msec beat⁻¹). Arterial pressure was raised or lowered by intravenous bolus injections of phenylephrine or nitroprusside, respectively. Central infusion of angiotensin II had no significant effect on mean arterial pressure in captopril or control SHR (captopril-angiotensin II 125±4 vs. captopril-vehicle 121±2; control-angiotensin II 169±5 vs. control-vehicle 173±7 mm Hg), but it produced a significant rise in basal heart rate (captopril-angiotensin II 371±10 vs. captopril-vehicle 323±8, p<0.0002; control-angiotensin II 338±7 vs. control-vehicle 312±8 beats/min, p<0.0183) and in daily water intake (captopril-angiotensin II 338±7 vs. captopril-vehicle 9.8±0.7, p<0.0426; control-angiotensin II 338±7 vs. control-vehicle 9.0±0.6 ml/100 g body wt, p<0.0001). Moreover, there was a significant decrease in the slope of the relation between the change in mean arterial pressure and the change in pulse interval for lifetime-captopril-treated SHR but only in response to an increase in mean arterial pressure (captopril-angiotensin II 0.88±0.06 vs. captopril-vehicle 2.76±0.49, p<0.0001; control-angiotensin II 0.62±0.08 vs. control-vehicle 0.50±0.07 mm Hg⁻¹). In response to a decrease in mean arterial pressure, the slopes were: captopril-angiotensin II 0.55±0.06, captopril-vehicle 0.80±0.11; control-angiotensin II 0.73±0.10, control-vehicle 0.79±0.15 mm Hg⁻¹. Our findings suggest that decreased brain angiotensin II activity induced by captopril underlies the increased baroreceptor reflex sensitivity in lifetime-captopril-treated SHR. (Hypertension 1989;14:274–281)

Previous studies have implicated brain angiotensin II (Ang II) in the pathogenesis of hypertension in spontaneously hypertensive rats (SHR). Compared with normotensive Wistar-Kyoto (WKY) rats, SHR have elevated renin activity1 and angiotensin-like immunoreactivity2 in the brain as well as increased levels of angiotensin-like material in the cerebrospinal fluid (CSF).3 Spontaneously hypertensive rats also show an enhanced pressor response to centrally administered Ang II and they may have an increased number of Ang II receptors in regions of the brain that are involved in cardiovascular regulation.4-6 Moreover, acute or chronic intracerebroventricular administration of either saralasin (a specific Ang II receptor antagonist) or captopril (an angiotensin I converting enzyme inhibitor), at doses that were not effective or much less effective when given intravenously, markedly reduced blood pressure in adult SHR and attenuated the development of hypertension in young SHR.7-13

Although evidence suggests that brain Ang II is involved in the development and maintenance of hypertension in SHR, the exact mechanisms by which Ang II causes such change are still unclear. One possible mechanism is that Ang II impairs the baroreceptor reflex.14,15 A decrease in baroreceptor reflex sensitivity in SHR has been reported by a
number of investigators. Accordingly, captopril may produce its antihypertensive effect by increasing the sensitivity of the baroreceptor reflex to modulate the rise in blood pressure observed in SHR. Recently, we have found that lifetime-captopril-treated SHR have an enhanced baroreceptor reflex control of heart rate and lumbar sympathetic nerve activity compared with untreated SHR. This effect of captopril was specific for SHR. Lifetime captopril treatment of WKY rats did not produce significant changes in baroreceptor reflex control of heart rate or lumbar sympathetic activity. These findings are consistent with the hypothesis that brain Ang II plays a role in the development and maintenance of hypertension in SHR, partially through an alteration in baroreceptor reflex sensitivity. However, the enhancement of baroreceptor reflex function in captopril-treated SHR could also be a consequence of lowering of blood pressure because lifetime captopril treatment prevented the development of hypertension in these rats. To examine whether the increase in baroreceptor reflex sensitivity in lifetime-captopril-treated SHR was due to an inhibition of brain Ang II mechanisms, we evaluated baroreceptor reflex control of heart rate in lifetime-captopril-treated SHR given an intracerebroventricular subpressor infusion of Ang II for 1 week. We also carried out the same experiments in untreated SHR to determine if intracerebroventricular Ang II infusion has any effect on baroreceptor reflex sensitivity in hypertensive SHR. We tested the effect of Ang II on control and captopril-treated SHR only because lifetime captopril treatment had no effect on baroreceptor reflex activity in WKY rats.

### Materials and Methods

Nineteen- to twenty-one-week-old male SHR and lifetime-captopril-treated SHR were used for studies of baroreceptor reflex control of heart rate. They were offspring of eight-week-old breeders from Charles River Breeding Laboratory (Raleigh, North Carolina). The female breeders were given captopril (100 mg/kg/day, Squibb Institute, Princeton, New Jersey) in their drinking water at the time of mating and captopril treatment was continued throughout pregnancy and lactation. After weaning, the dosage of captopril in the drinking water of the pups was lowered to 50 mg/kg/day and maintained until experimentation. Control female breeders and pups were given normal tap water. The animals were housed three to four per cage in a room with a constant temperature of 24° C, humidity of 60 ± 5%, and a 12-hour light/dark cycle. Standard laboratory rat chow was provided ad libitum.

One week before the baroreceptor reflex studies, rats were divided into four groups. Two groups were captopril-treated SHR that received intracerebroventricular infusion of Ang II (CAP-Ang II) or vehicle (artificial CSF) (CAP-Veh), respectively. Another two groups were SHR that received intracerebroventricular infusion of Ang II (CON-Ang II) and vehicle (CON-Veh), respectively. Ang II was administered at a dosage of 7.5 ng/hr by osmotic minipump (Alzet 2002, Alza Corp., Palo Alto, California) into the right lateral cerebral ventricle using a previously described method. Ang II and vehicle were placed in osmotic minipumps with a 14-day pumping duration. Rats were infused with Ang II for 7–9 days. All rats were catheterized on day 7 of infusion, and baroreceptor reflex studies were performed on day 8 or 9 of infusion. Ang II was dissolved in artificial CSF. Since the pH of the Ang II solution was 8.3, control rats received artificial CSF adjusted to a pH of 8.3 with 1N HCl. The dosage of Ang II chosen was similar to that used by Gronan and York and did not cause an increase in blood pressure. A subpressor dose of Ang II was selected to avoid possible confounding effects of changes in arterial pressure on baroreceptor reflex sensitivity.

Starting the second day after osmotic minipump implantation, we averaged 24-hour water intakes for 3–6 days. Since some rats were housed two to three per cage, water intakes were expressed in milliliters per 100 grams body weight.

Twenty-four to 48 hours before the baroreceptor reflex studies, rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and chronic catheters were placed into the descending aorta and inferior vena cava of each rat via the femoral artery and vein for the measurement of blood pressure and administration of drugs, respectively. After arterial and venous catheterization, rats were given 100,000 units penicillin G i.m. (Squibb Institute). Experiments of baroreceptor reflex control of heart rate were carried out in conscious, freely moving rats in their cages. Mean arterial pressure was monitored using a Century P23DB transducer (Century Technol. Co., Inc., Inglewood, California) and recorded on a Hewlett Packard polygraph (model 7758B, Hewlett-Packard Co., Palo Alto, California). Heart rate was monitored using a cardiometer (University of Alabama, Cardiovascular Research and Training Center, Electronics Shop, Birmingham, Alabama) triggered by the arterial pressure signal and recorded on the same polygraph. Experiments were commenced after blood pressure and heart rate had stabilized (30–40 minutes). Mean arterial pressure and heart rate responses to bolus injections of phenylephrine (phenylephrine HCl 0.15–30 μg/kg i.v., Sigma Chemical Co., St. Louis, Missouri) and nitroprusside (sodium nitroprusside 0.15–40 μg/kg i.v., Sigma Chemical Co.) were monitored. Drugs were dissolved in 0.9% NaCl, and the volume of injection ranged from 5 to 100 μl. A wide range of volumes (with one stock solution each of phenylephrine or nitroprusside) for injection was used because this method eliminated the necessity to frequently change injectors to keep the volume of injectate constant. In preliminary experiments using saline, the volume of injectate over the range we used did not have a significant
effect on heart rate. The order of administration of drugs (phenylephrine and nitroprusside) as well as doses were randomized. Blood pressure and heart rate were allowed to return to basal levels before the next dose was given. Peak increases or decreases in mean arterial pressure after phenylephrine or nitroprusside injections and the corresponding peak reflex changes in heart rate were recorded for each dose of drug. Heart rate was converted to pulse interval (msec) using the following formula: pulse interval=60,000/heart rate (beats/min). The slope (sensitivity) for baroreceptor control of heart rate was determined for each rat by fitting a regression line through points relating the changes in pulse interval (ΔPI) and the changes in mean arterial pressure (ΔMAP). Regression analyses were performed in the linear portion of the baroreceptor reflex changes and examined over the same pressure changes. Slopes from individual rats were averaged to obtain group means.

Rats were killed by decapitation 3-4 days after the baroreceptor reflex studies, and placement of the lateral cerebroventricular cannula was checked by injection of 10 μl 1% fast green dye into the cannula. Correct placement was verified by the presence of dye in the cerebroventricular system.

Statistical Analysis

Data are expressed as mean±SEM. Two-way analysis of variance was used to evaluate whether there were differences in mean arterial pressure, heart rate, body weight, and water intake among groups. Linear regressions relating ΔMAP to ΔPI were performed in each rat. At least 10 points were used in the linear regression calculation. The slopes of these relations among control SHR and lifetime-captopril-treated SHR with intracerebroventricular infusion of vehicle or Ang II were compared. This method of slope comparisons is preferred over standard analysis of covariance techniques in that fewer assumptions are made (e.g., homogeneity of slope from rat to rat within the same treatment-type of rat group is not required). Statistical significance was assumed when p<0.05.

Results

Table 1 shows the mean arterial pressure, heart rate, and body weight after 1 week of intracerebroventricular infusion of Ang II or vehicle in the four groups of rats used in the present studies. As expected, the CON-Veh group had significantly (p<0.001) higher mean arterial pressure (173±7 vs. 121±2 mm Hg) than the CAP-Veh group. However, there were no statistical differences in heart rate between these two groups of rats (CON-Veh 312±8 vs. CAP-Veh 323±8 beats/min). Captopril-treated SHR had significantly (p=0.0118) lower body weights than their age-matched controls (CAP-Veh 282±10 vs. CON-Veh 313±9 g).

Intracerebroventricular infusion of Ang II had no significant effect on mean arterial pressure (CAP-Ang II 263±7 vs. CAP-Veh 282±10; CON-Ang II 312±8 vs. CON-Veh 338±7 beats/min). Captopril-treated spontaneously hypertensive rats (SHR) that received intracerebroventricular (i.c.v.) infusion of angiotensin II (Ang II): CAP-Veh, captopril-treated SHR that received i.c.v. infusion of vehicle (artificial cerebrospinal fluid); CON-Ang II, control SHR that received i.c.v. infusion of vehicle; CON-Veh, control SHR that received i.c.v. infusion of vehicle.

When blood pressure was increased by phenylephrine, the slopes of the relation between ΔMAP and ΔPI were not significantly different between control SHR with intracerebroventricular infusion of Ang II or vehicle (CON-Ang II 0.63±0.08 msec mm Hg⁻¹, r=0.92±0.02 vs. CON-Veh 0.50±0.07 msec mm Hg⁻¹, r=0.96±0.01; Figure 1, Table 2). In contrast, there was a significant (p<0.001) decrease in the slope of the relation between ΔMAP and ΔPI for captopril-treated SHR with intracerebroventricular infusion of Ang II when compared with that for captopril-treated SHR with intracerebroventricular infusion of vehicle (CAP-Ang II 0.88±0.06 msec mm Hg⁻¹, r=0.96±0.01 vs. CAP-Veh 2.76±0.49 msec mm Hg⁻¹, r=0.91±0.02) (Figure 1, Table 2). The slope for the CAP-Ang II group was not significantly different from that for the CON-Veh group, whereas the slope for the CAP-Veh group was significantly (p<0.0001) greater than that for the CON-Veh group. When blood pressure was lowered by nitroprusside, there were no significant differences in the slopes between CON-Ang II and CON-Veh (0.73±0.10 msec mm Hg⁻¹, r=0.92±0.01 vs. 0.79±0.15 msec mm Hg⁻¹, r=0.93±0.02, respectively) (Figure 2, Table 2). The slopes for CAP-Ang II and CAP-Veh (0.55±0.06 msec mm Hg⁻¹, r=0.94±0.02 vs. 0.80±0.11 msec mm Hg⁻¹, r=0.93±0.02, respec-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>BW (g)</th>
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</thead>
<tbody>
<tr>
<td>CAP-Ang II</td>
<td>125±4</td>
<td>371±10*</td>
<td>263±7</td>
</tr>
<tr>
<td>(n=11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP-Veh</td>
<td>121±2</td>
<td>323±8</td>
<td>282±10</td>
</tr>
<tr>
<td>(n=11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON-Ang II</td>
<td>169±5</td>
<td>338±7†</td>
<td>298±64</td>
</tr>
<tr>
<td>(n=16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON-Veh</td>
<td>173±7§</td>
<td>312±8</td>
<td>313±9</td>
</tr>
<tr>
<td>(n=12)</td>
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Values are mean±SEM. MAP, mean arterial pressure; HR, heart rate; BW, body weight; CAP-Ang II, captopril-treated spontaneously hypertensive rats (SHR) that received intracerebroventricular (i.c.v.) infusion of angiotensin II (Ang II); CAP-Veh, captopril-treated SHR that received i.c.v. infusion of vehicle (artificial cerebrospinal fluid); CON-Ang II, control SHR that received i.c.v. infusion of Ang II; CON-Veh, control SHR that received i.c.v. infusion of vehicle. *p<0.0002 compared with CAP-Veh; †p<0.0032 compared with CAP-Ang II; §p<0.001 compared with CAP-Veh; ‡p<0.0118 compared with CAP-Veh.
FIGURE 1. Plot of relation between change in mean arterial pressure (ΔMAP) and change in pulse interval (ΔPI) in response to bolus injections of phenylephrine for control SHR (CON-SHR) and captopril-treated SHR (CAP-SHR) with intracerebroventricular infusion of angiotensin II or vehicle. Lines are based on average slope and intercept for each group.

Figures 1 and 2 respectively were not significantly different (Figure 2, Table 2).

There were no significant differences in 24-hour water intakes between CAP-Veh and CON-Veh (9.8±0.7 vs. 9.0±0.6 ml/100 g body wt, respectively). Central infusion of Ang II resulted in a significant increase in water intake in both captopril-treated and control SHR (CAP-Ang II 20.7±2.2 and CON-Ang II 33.1±3.8 ml/100 g body wt, p<0.0001). However, the dipsogenic effects of intracerebroventricular infusion of Ang II were significantly greater in control SHR compared with captopril-treated SHR (Table 3).

TABLE 2. Slopes of Relation of Change in Mean Arterial Pressure Versus Change in Pulse Interval for Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PE</th>
<th>NP</th>
</tr>
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<tbody>
<tr>
<td>CAP-Ang II (n=11)</td>
<td>0.88±0.06*</td>
<td>0.55±0.06</td>
</tr>
<tr>
<td>CAP-Veh (n=11)</td>
<td>2.76±0.49†</td>
<td>0.80±0.11</td>
</tr>
<tr>
<td>CON-Ang II (n=16)</td>
<td>0.63±0.08</td>
<td>0.73±0.10</td>
</tr>
<tr>
<td>CON-Veh (n=12)</td>
<td>0.50±0.07</td>
<td>0.79±0.15</td>
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Values are mean±SEM of slopes (msec mm Hg⁻¹). PE, phenylephrine; NP, nitroprusside; CAP-Ang II, captopril-treated spontaneously hypertensive rats (SHR) that received intracerebroventricular (i.c.v.) infusion of angiotensin II (Ang II); CAP-Veh, captopril-treated SHR that received i.c.v. infusion of vehicle (artificial cerebrospinal fluid); CON-Ang II, control SHR that received i.c.v. infusion of Ang II; CON-Veh, control SHR that received i.c.v. infusion of vehicle.

* p<0.0001 compared with CAP-Veh.
† p<0.0001 compared with CON-Veh.

TABLE 3. Averaged 24-Hour Water Intake for Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>24-hour water intake (ml/100 g body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP-Ang II (6)</td>
<td>20.7±2.2*</td>
</tr>
<tr>
<td>CAP-Veh (6)</td>
<td>9.8±0.7</td>
</tr>
<tr>
<td>CON-Ang II (7)</td>
<td>33.1±3.8†</td>
</tr>
<tr>
<td>CON-Veh (7)</td>
<td>9.0±0.6</td>
</tr>
</tbody>
</table>

The number of cages for each group is shown in parentheses and the number of rats in each of the four groups were 11, 11, 16, and 12, respectively. Values are mean±SEM. CAP-Ang II, captopril-treated spontaneously hypertensive rats (SHR) that received intracerebroventricular (i.c.v.) infusion of angiotensin II (Ang II); CAP-Veh, captopril-treated SHR that received i.c.v. infusion of vehicle (artificial cerebrospinal fluid); CON-Ang II, control SHR that received i.c.v. infusion of Ang II; CON-Veh, control SHR that received i.c.v. infusion of vehicle.

* p<0.0426 compared with CAP-Veh.
† p<0.0026 compared with CAP-Veh.
‡ p<0.0001 compared with CON-Veh.

Discussion

As found in our previous studies,19,22 lifetime oral captopril treatment prevented the development of hypertension in SHR. The antihypertensive action of captopril may be related to its ability to increase baroreceptor reflex sensitivity via an alteration in brain Ang II mechanisms. Although earlier studies reported that captopril does not cross the blood-brain barrier,23-25 numerous investigators have indicated that captopril can cross the blood-brain barrier particularly with chronic oral administration. Indirect evidence for tissue converting enzyme inhibition after systemic administration of converting enzyme inhibitor was first presented by Assad and ...
Antonacci and Ungar et al. Chronic oral antihypertensive treatment of SHR and stroke prone SHR (SHRSP) with captopril increased renin concentrations in the wall of the aorta and in certain parts of the brain, and this elevation could be dissociated with increased plasma renin of renal origin. Direct evidence subsequently presented for inhibition of converting enzyme in brain after oral therapy was provided by Cohen and Kurz. These investigators showed that in SHR a single dose of captopril or enalapril was able to decrease converting enzyme activity not only in serum and lung but also in the aortic wall, kidney, and brain. Using high-performance liquid chromatography–radioimmunoassay for angiotensin peptides in tissues, these same investigators were able to demonstrate a reduction in tissue Ang II concentration in brain after oral administration of converting enzyme inhibitors. Studies of Schelling and Felix showed that when SHRSP were treated daily with captopril (given orally) during the lifespan beginning with treatment of pregnant females, blood pressure remained at normotensive levels, and the Ang II–evoked neuronal responses in the septum were similar to Ang II–related neuronal sensitivity found in WKY rats. This is in contrast to higher sensitivity to Ang II in neurons from untreated SHRSP as compared with WKY rats. In addition, the extended discharge beyond application of Ang II seen in SHRSP was markedly reduced in captopril-treated SHRSP. In contrast, no differences were found in WKY rats and captopril-treated WKY rats. Furthermore, a change in chemosensitivity after captopril treatment was only observed in response to Ang II. These studies demonstrate that oral treatment with converting enzyme inhibitors can inhibit tissue converting enzyme and decrease Ang II levels in the brain.

Although we have not measured Ang I and Ang II levels in the brains of our rats we have presented evidence that angiotensin mechanisms in the brain are altered after captopril treatment. We reported that drinking responses to intracerebroventricular (10 ng) and subcutaneous (100 μg/kg) administration of Ang I and Ang II were significantly reduced in captopril-treated SHR in comparison with control SHR. The drinking response to Ang II has been identified as a specific centrally mediated effect. The reduced drinking responsiveness to Ang I observed in this study suggested that the conversion of Ang I to Ang II was inhibited by captopril. In addition, the observation that the drinking response to Ang II was also depressed suggested that decreased responsiveness may be related to a reduction in Ang II receptors in the brain. This was our finding in Ang II binding studies in the hypothalamus of captopril-treated SHR as compared with control rats and is consistent with findings of Schelling and Felix, who reported that captopril treatment decreased Ang II receptor sensitivity to iontophoretically applied Ang II. In contrast to the central effects, peripheral responsiveness to Ang II and receptor binding kinetics of the peptide were significantly enhanced as a result of lifetime captopril treatment. The vascular response to Ang II and peripheral vascular Ang II binding was significantly enhanced in lifetime–captopril-treated SHR as compared with controls. In the present study, central administration of Ang II resulted in an increase in water intake in both captopril-treated and control SHR. However, the dipsogenic response was not as great in captopril-treated as control rats. In addition to these findings, we have been conducting preliminary studies with immunocytochemical localization of Ang II in brains of lifetime–captopril-treated SHR versus control SHR using the Ang II antibody “Denise” from Dr. D. Ganten, Department of Pharmacology, University of Heidelberg, Heidelberg, FRG. Preliminary results from these studies show significant labeling similar to Ang II in the hypothalamus and amygdala in SHR. However, in over 50% of the captopril-treated SHR, this Ang II staining was found to be virtually eliminated. These studies give evidence for a disturbance in central Ang II mechanisms in response to lifetime oral captopril administration.

Captopril and enalapril (MK-421) have been shown to enhance baroreceptor reflex sensitivity. Berecek et al. showed that chronic central administration of captopril increased baroreceptor reflex control of heart rate in response to an increase in blood pressure in SHR. It has also been shown that captopril augmented baroreceptor reflex control of heart rate in response to a decrease in blood pressure in hypertensive patients. In the latter study, baroreceptor reflex sensitivity to an increase in blood pressure was enhanced in normotensive men given a single oral dose of enalapril. It has also been shown that captopril augmented baroreceptor reflex control of heart rate in response to a decrease in blood pressure but unaltered in response to an increase in blood pressure in hypertensive patients. In the present study, baroreceptor reflex control of heart rate in response to a rise in blood pressure in the CAP-Veh group was enhanced compared with that of the CON-Veh group. Our findings that the CAP-Veh group showed improved baroreceptor reflex control of heart rate in response to a rise in blood pressure but not to a fall in blood pressure compared with the CON-Veh group are consistent with those of Guo and Abboud, who showed that angiotensin attenuated the baroreceptor reflex response to an increase in
pressure but not to a decrease in pressure. Campagnole-Santos et al also reported that administration of saralasin into the nucleus tractus solitarius (NTS) of rats facilitated the baroreceptor reflex but only for increases in blood pressure. Moreover, this improved baroreceptor reflex function in the CAP-Veh group was reversed in the CAP-Ang II group of rats. It is of interest that the slopes of the relation between ΔPI and ΔMAP during an increase in blood pressure were similar in the CAP-Ang II and the CON-Veh groups. This indicated that centrally administered Ang II exerted an inhibitory influence on baroreceptor reflex function in lifetime-captopril-treated SHR, resulting in a reduced baroreceptor reflex sensitivity similar to that of control SHR. Although the slope of the relation between ΔPI and ΔMAP in response to a decrease in blood pressure was smaller in the CAP-Ang II group compared with that of the CAP-Veh group, the difference was not statistically significant. These observations suggest that the enhanced baroreceptor reflex function in lifetime-captopril-treated SHR is due to an inhibition of brain Ang II mechanisms. This hypothesis is supported by previous findings that Ang II has an inhibitory influence on baroreceptor reflex sensitivity in sheep, rabbits, dogs, and humans. Furthermore, it has been reported that angiotensinlike immunoreactive fibers and renin content were increased in SHR in the region of the NTS, the first synapse of the baroreceptor reflex arc. Recent studies have provided evidence that the NTS may be a site where Ang II exerts its influence on baroreceptor reflex sensitivity. Campagnole-Santos et al found that bilateral injections of an Ang II antagonist into the NTS enhanced the baroreceptor reflex control of heart rate. Casto and Phillips showed that microinjections of Ang II into the NTS attenuated the baroreceptor reflex control of heart rate.

Converting enzyme inhibitors interfere with the metabolism of other peptides known to affect blood pressure such as bradykinin, the opioid peptides, and substance P. The effects of captopril on these peptides may contribute to its blood pressure-lowering action and effect on the baroreceptor reflex. Angiotensin converting enzyme is identical to kininase II, a bradykinin degrading enzyme. In the periphery, captopril produces a potentiation of the depressor action of kinins by inhibiting kininase II. Captopril also potentiates the central effects of bradykinin but unlike its action in the periphery bradykinin produces a pressor response when injected into the brain. The effect of bradykinin on the baroreceptor reflex function is not known; however, Casto and Phillips have reported that injection of bradykinin into the NTS had no effect on heart rate or blood pressure. Converting enzyme has properties in common with an enkephalin degrading dipeptidyl carboxypeptidase, although a more specific enkephalinase is not identical with converting enzyme. It is unclear what the precise role of opioid peptides is in cardiovascular regulation as analysis of this role is complicated by the presence of multiple opioid receptors and a variety of different peptides and by evidence that specific opioid receptors may not mediate the same responses in different regions of the brain. It has been demonstrated in vitro that captopril inhibits both converting enzyme activity and enkephalinase activity for mouse and rat brain preparations; however, captopril had a thousandfold higher inhibitor potency against converting enzyme. Few studies have explored the possible role of opioids in the actions of captopril and the results have been inconclusive. Substance P is a potent vasodilator substance when injected intravenously but has marked pressor effects on administration into brain ventricles. The role of substance P in baroreceptor reflex function is uncertain. Application of this peptide into the NTS has elicited hypertension and tachycardia as well as hypotension and bradycardia. Talman and Reis, using very small volumes and controlled rates of injection, found no change in heart rate, blood pressure, or the baroreceptor reflex when substance P was injected into the NTS. Whether these peptides contribute to the effects of captopril on baroreceptor reflex activity will require further investigation as it is uncertain whether these peptides affect baroreceptor reflex function. The ability of central administration of Ang II to reverse the enhanced baroreceptor reflex sensitivity for control of heart rate in captopril-treated rats strongly suggests that the action of captopril on the baroreceptor reflex is due to a disturbance in brain Ang II mechanisms. Furthermore, the effect of Ang II on baroreceptor reflex activity is due to a central mechanism and not due to leakage of Ang II into the periphery. Gronan and York, using a larger dose (10 ng/hr) than the one used in this study (7.5 ng/hr), found that subcutaneous administration of this dose was without effect. This is in contrast to intracerebroventricular administration, which had no effect on blood pressure but produced a marked elevation in water intake.

It is possible that the enhanced baroreceptor reflex function in the CAP-Veh group compared with that of the CON-Veh group could be a consequence of the lowering of blood pressure per se. However, our findings in the CAP-Veh and CAP-Ang II groups argued against a blood pressure effect on baroreceptor reflex function. The depressed baroreceptor reflex control of heart rate in CAP-Ang II SHR compared with CAP-Veh SHR was not associated with any significant changes in mean arterial pressure. Thus, the differences in baroreceptor reflex sensitivity observed between these two groups cannot be attributed to changes in basal mean arterial pressure. The findings of Imai and coworkers that the enhanced baroreceptor reflex control of heart rate seen in captopril-treated humans was not accompanied by any changes in mean arterial pressure also suggest that blood pressure is
not responsible for the enhanced baroreceptor reflex function. Furthermore, it has recently been reported that the effects of captopril on baroreceptor reflex control of lumbar sympathetic nerve activity are also independent of a change in mean arterial pressure.46 Our findings suggest that impairment of the baroreceptor reflex due to a hyperactive brain renin-angiotensin system may contribute to hypertension and not merely be a consequence of the hypertension. It should be noted that despite reduced baroreceptor reflex sensitivity for 7–9 days, blood pressure did not rise in captopril-treated SHR given intracerebroventricular infusion of Ang II. It is possible that hypertension might develop if Ang II was infused for a longer period of time or reduced baroreceptor reflex sensitivity was maintained for a longer period of time. In the current study, intracerebroventricular infusion of Ang II did not further lower baroreceptor reflex sensitivity in control SHR. This might be because the baroreceptor reflex function in control SHR is already markedly impaired. Recent studies by Hayashi et al47 showed that intracerebroventricular administration of Ang II did not attenuate the reflex responses to aortic depressor nerve stimulation in SHR.

Our data suggest that lifetime oral captopril treatment potentiates baroreceptor reflex control of heart rate with a concomitant antihypertensive effect by altering the angiotensinergic system in the brain. This enhancing effect of captopril on baroreflex function is reversed by central administration of Ang II. The notion of a centrally mediated effect of Ang II on baroreceptor reflex sensitivity is corroborated by our data on water intakes after intracerebroventricular infusion of Ang II. The dipsogenic response by Ang II has been shown to be centrally mediated.48,49 In the present study, central administration of Ang II resulted in an increase in water intake in both captopril-treated and control SHR. However, the dipsogenic response was significantly less in captopril-treated SHR compared with control SHR. These findings are in agreement with our previous observations,22 which also showed that lifetime–captopril-treated SHR had decreased brain Ang II binding, suggesting a depressed angiotensinergic system in the brain. Our results are also consistent with those of Schelling and Felix,32 who showed a decrease in the sensitivity of Ang II receptors to iontophoretically applied Ang II in septal neurons of SHRSP with lifetime captopril treatment.32

In summary, lifetime oral captopril treatment prevented the development of hypertension in spontaneously hypertensive rats. The antihypertensive effect of captopril appeared to be due to its ability to augment baroreceptor reflex function. In addition, the enhanced baroreceptor reflex sensitivity in lifetime–captopril-treated SHR was likely due to an inhibition or decrease in brain Ang II activity because chronic intracerebroventricular infusion of the neuropeptide reversed the potentiating effect of captopril on baroreceptor reflex function.

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