Altered Vascular Reactivity and Baroreflex Sensitivity Induced by Chronic Central Administration of Captopril in the Spontaneously Hypertensive Rat

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SUMMARY Previous studies from our laboratory have shown that chronic intracerebroventricular administration of captopril attenuates the development of hypertension in the spontaneously hypertensive rat of the Okamoto strain (SHR) without altering sodium and water balance, plasma renin, or sympathoadrenal activities. To determine whether the depressor effect of intracerebroventricular captopril was associated with an alteration in peripheral vascular reactivity and/or baroreflex sensitivity, vascular reactivity to phenylephrine and vasopressin was assessed in renal, mesenteric, and hindquarter vascular beds using pulsed Doppler flow probes. Captopril was infused into the jugular vein or lateral ventricle of male SHR and Wistar-Kyoto (WKY) rats for 4 weeks (osmotic mini pump, 1.25 µg/0.5 µl/hr). Control SHR or WKY received intracerebroventricular infusions of vehicle. Four weeks of captopril decreased arterial pressure in both SHR and WKY. In response to phenylephrine and vasopressin, SHR and WKY treated with intracerebroventricular captopril showed significantly attenuated increases in arterial pressure and vascular resistance in comparison to either vehicle-treated rats or rats receiving intravenous captopril. Reflex decreases in heart rate in response to phenylephrine were also greater in SHR and WKY treated with intracerebroventricular captopril than in the other rat groups. Neither vascular reactivity nor baroreflex sensitivity was altered in rats treated with intravenous captopril. We conclude that the depressor effect of captopril involves a blunting of vascular reactivity to vasoconstrictors and a potentiation of the baroreflex. (Hypertension 5:689-700, 1983)

KEY WORDS • captopril • SHR • baroreflex sensitivity • vascular reactivity

I t has generally been thought that the renin-angiotensin system does not play a role in the pathogenesis of hypertension in the spontaneously hypertensive rat of the Okamoto strain (SHR). Plasma renin activity in SHR is either no different from or lower than that seen in Wistar-Kyoto (WKY) control rats.1,2 Moreover, peripheral administration of a competitive inhibitor of angiotensin II3 or angiotensin II antibody4 has no effect on blood pressure in SHR. However, recent anatomical and functional studies have provided evidence that the brain renin-angiotensin system may play a role in the development and maintenance of hypertension in SHR. Increased renin activity5 and angiotensin-like immunoreactivity6 have been reported in the brain as well as increased levels of angiotensin-like material in the cerebrospinal fluid7 of SHR compared with WKY. SHR also show a supersensitivity to the pressor effects of central administration of angiotensin II (AII)8 and may have an increased number of AII receptors in the brain.9 Furthermore, acute or chronic intracerebroventricular administration of a competitive inhibitor of AII, saralasin,10,11 or of the converting enzyme inhibitor, captopril,12-13 was found to substantially lower blood pressure in chronically hypertensive SHR, suggesting that the brain renin-angiotensin system plays a role in the maintenance of hypertension in this model.

Recently, Okuno et al.14 showed that chronic intracerebroventricular administration of captopril attenuated the development of hypertension in young SHR. This antihypertensive effect of captopril was produced at doses that had no effect on blood pressure when
administered peripherally and was not related to inhibition of the peripheral renin-angiotensin system, peripheral sympathetic nervous system, vasopressin release, or alterations in water and sodium balance.\(^{14}\)

In this present study we examined two additional mechanisms that may underlie the depressor effect of chronic central administration of captopril to SHR. We tested the hypotheses that captopril may produce its antihypertensive effect by: 1) decreasing peripheral vascular reactivity to vasoconstrictors, and/or 2) increasing or preserving the sensitivity of the baroreceptor reflex to changes in arterial pressure. Recent studies have shown that captopril produces a decrease in vascular reactivity to norepinephrine and sympathetic stimulation.\(^{15-20}\) Mechanisms by which captopril may affect vascular reactivity include alterations in vascular renin\(^{21}\) and in passive sodium permeability in the vascular smooth muscle cell.\(^{15}\)

Captopril lowers blood pressure without increasing heart rate and plasma norepinephrine,\(^{22,23}\) suggesting that it may potentiate arterial baroreflexes. It has been reported that captopril potentiates reflex slowing of heart rate in response to norepinephrine and vasopressin.\(^{18}\) This potentiation could be due to depletion of brain-angiotensin II by captopril. Angiotensin II, through a central mechanism of action, has been shown to have an inhibitory effect on the baroreceptor reflex.\(^{24}\) Accordingly, captopril could produce its central depressor effect in SHR by increasing or preserving the sensitivity of the baroreceptor reflex to buffer the increase in arterial pressure seen in this model.

**Methods**

**Experimental Animals**

Six-week-old male SHR and WKY (Charles River Breeding Laboratories, Wilmington, Massachusetts) were used for these studies. The animals were housed in groups of four per cage under identical conditions of temperature (24°C) humidity (60% ± 5%) and photo period (12 hours on, 12 hours off) and were allowed normal rat chow and water ad libitum. Following two determination of baseline blood pressure and heart rate, animals were divided into three groups: Group 1 received intracerebroventricular infusion of captopril; Group 2 received intracerebroventricular infusion of vehicle, and Group 3 received intravenous infusion of captopril.

**Intravenous and Intracerebroventricular Captopril Administration**

Rats were given an infusion of captopril for 4 weeks beginning at 7 weeks of age at a dose of 1.25 μg/hr into either the left lateral cerebral ventricle or jugular vein. This had been previously found to be the lowest dose of captopril that would attenuate the development of hypertension in SHR.\(^{14}\) Moreover, this dose of captopril administered into the left lateral cerebral ventricle was shown to block the pressor effect of intracerebroventricular injection of angiotensin I (50–800 ng) by 50% but not to alter the pressor response to centrally administered AII. Captopril was infused by osmotic mini pump (Alzet Model 2002, Alza Corporation, Palo Alto, California). The nominal reservoir volume and pumping rate were 200 μl and 0.5 μl/hr, respectively. Pumps were changed 2 weeks after initiation of the infusion. Captopril was dissolved in 0.9% sterile saline. Since the pH of the captopril solution was 3.0, control rats received a vehicle solution of 0.9% saline adjusted to pH 3.0 with 1N HCl. Osmolality of both the vehicle and captopril solutions was 294–296 mOsm/kg.\(^{14}\) Osmotic mini pumps used for intracerebroventricular infusion were tunneled under the skin between the scapulae; those used for intravenous infusion were tunneled under the skin and positioned over the upper abdomen.

Cannulation of the lateral ventricle was performed under ether anesthesia using a stereotaxic apparatus. Cannulas were made of polyethylene tubing (PE 10). A restraining hub was produced on each cannula by gentle heating. The ventricular catheter length from the bottom of the hub to its tip was 4 mm. Coordinates for the left lateral ventricle were: (with skull leveled between bregma and lambda) −1 mm posterior to bregma, −1.5 mm lateral from the midline and −4 mm ventral to the skull surface. Stainless steel jewelers screws and dental acrylic cement were used to secure the cannula in place. Correct placement of the cannula into the lateral cerebral ventricle was verified by injection of 10 μl of 0.5% methylene blue through the cannula just prior to sacrificing the animal. Brains were removed from the animals and frozen immediately on dry ice and then placed in a cryostat (Slee Inc., London, England) at −10°C; 40 μm sections were cut from the appropriate area. Correct placement of the catheters was verified by the presence of dye in the ventricular system.

Cannulation of the jugular vein was also accomplished under ether anesthesia. Intravenous catheters were constructed from microline tubing (Thermoplastics Scientifics, Warren, New Jersey) which had been pre-treated with graphite. These catheters were filled with heparinized saline (50 units/ml) prior to catheterization to keep them patent; whereas the intracerebroventricular catheters were filled with the captopril or vehicle solution. Following either central or peripheral catheterization, rats were given 100,000 units of penicillin G.

Systolic blood pressures were measured twice weekly using an indirect tail cuff method (Narco Biosystems Inc., Houston, Texas) in conscious, restrained rats prewarmed at 37°C for 5–10 minutes. The rats were conditioned to the restraining devices and cuff inflations prior to determination of baseline parameters.

**Vascular Reactivity Studies**

Acute hemodynamic studies were performed in the 4th week of captopril/vehicle administration under Dial-urethane (0.06 ml/100 g, CIBA-Geigy, Wehr/ Baden, West Germany) anesthesia. The trachea was intubated to insure a patent airway, and the right femoral artery and vein were cannulated for arterial pres-
ure measurement and drug administration, respectively. Renal, mesenteric, and hindquarter blood flows were monitored using miniaturized Doppler flow probes and an ultrasonic pulsed Doppler flow meter (University of Iowa, Bioengineering Resource Facility, Iowa City, Iowa). The flow meter is a modified version of the instrument designed by Hartley and Cole (1974). The techniques for construction and use of the probes and application of the flow meter have been described in detail. Detection of flow with the pulsed Doppler system is dependent on changes in the emitted ultrasound frequency produced by the reflection of the signal off moving blood cells. The change in frequency (Doppler shift) is proportional to the velocity of blood cells in a vessel. This velocity shift is directly proportional to volume flow in the vessels to which the probes are attached. Data are therefore expressed as percent changes in vascular resistance. The percentage change in resistance was calculated by using the following formulas:

\[
\text{Doppler pressure} = \text{resistance} (R, \text{ arbitrary units});
\]

\[
\frac{\text{baseline } R - \text{R at peak response}}{\text{baseline } R} = \% \Delta \text{ in resistance.}
\]

The right renal artery, mesenteric artery, and abdominal aorta were gently dissected free. On exposure of the renal artery, care was taken to avoid tearing or occluding the adrenal branch. The abdominal aorta was dissected just above the iliac bifurcation, and the tail and deep mesenteric branches were ligated. After filling the lumen of the probes with coupling gel (Ultrasound Gel, Tucker Labs), probes were placed around the blood vessels and loosely sutured closed with 6-0 ophthalmic suture. Arterial pressure and Doppler signals off moving blood cells. The change in frequency (ultrasound frequency produced by the reflection of the signal off moving blood cells) is proportional to the velocity of blood cells in a vessel. This velocity shift is directly proportional to volume flow in the vessels to which the probes are attached. Data are therefore expressed as percent changes in vascular resistance. The percentage change in resistance was calculated by using the following formulas:

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\]

The right renal artery, mesenteric artery, and abdominal aorta were gently dissected free. On exposure of the renal artery, care was taken to avoid tearing or occluding the adrenal branch. The abdominal aorta was dissected just above the iliac bifurcation, and the tail and deep mesenteric branches were ligated. After filling the lumen of the probes with coupling gel (Ultrasound Gel, Tucker Labs), probes were placed around the blood vessels and loosely sutured closed with 6-0 ophthalmic suture. Arterial pressure and Doppler flow velocity signals (kHz shift) were recorded continuously on a Hewlett Packard 7758B System recorder. After stabilization of arterial pressure and blood flow responses (approximately 30 minutes), reactivity studies were begun. Arterial pressure, heart rate, and regional flow responses to graded doses of phenylephrine (L-Phenylephrine HCl, 1.25–40 μg/kg, Sigma Chemical Company, St. Louis, Missouri), nitroglycerine (Nitrostat, 5-320 μg/kg, Parke Davis, Morris Plains, New Jersey) and vasopressin (Pitressin, 5-250 μg/kg, Parke Davis) were monitored. The same Pitressin preparation was used for all reactivity studies. All drug doses were calculated as free base. Drugs were dissolved in 0.9% NaCl and freshly prepared each day. They were administered as bolus injections (maximum injection volume = 40 μl) into the femoral venous catheter. The order of administration was phenylephrine, nitroglycerine, and vasopressin.

Baroreceptor Reflex Sensitivity

Baroreceptor reflex sensitivity was evaluated concurrently with the reactivity studies. Peak increases in mean arterial pressure (MAP) to phenylephrine and the associated peak reflex decreases in heart rate were recorded for each drug dose. Heart rate was converted to pulse interval (PI, in msec) by the formula: PI = 60,000/heart rate.

The slope (gain) for baroreceptor control of heart rate (ΔPI/ΔMAP) was determined for each rat by fitting a regression line through points ΔPI vs ΔMAP.

Statistics

Data are expressed as means ± SE. Analysis of variance was used to evaluate weekly measurements of arterial pressure, heart rates and body weights and arterial pressure, heart rate and body weight of the rats at the time of acute experimentation. Comparisons of the cardiovascular effects of phenylephrine, nitroglycerine, and vasopressin and of baroreflex sensitivity between the SHR and WKY groups were also evaluated by analysis of variance. In all cases of these multiple comparisons, when a significant (p < 0.05) F ratio was obtained, the Newman-Keul's test was used to determine which of the comparisons was significantly different. Cardiovascular responses among the various groups of rats were compared at each dose of drug given. In addition slopes of the linear portion of the dose response curve was determined for each animal by the least squares method. Calculation of slopes was determined from responses obtained at 5, 10, 20, and 40 μg/kg; phenylephrine, at 10, 50, 160 μg/kg for nitroglycerine and at 10, 50, 250 μg/kg for vasopressin. These same dose ratios were used for all rats. Individual slopes and correlation coefficients were averaged for each group of rats and compared among the groups by analysis of variance and the Newman-Keul's test. Determination and comparison of the slopes was done in an attempt to determine the magnitude of the changes in vascular responsiveness.

Results

Effects of Captopril Treatment on the Development of Hypertension in SHR

Table 1 shows the effect of chronic intracerebroventricular and intravenous administration of captopril on the development of hypertension in SHR. At the age of 7 weeks, prior to captopril treatment, SHR groups showed no difference in systolic arterial pressure, and, further, no significant difference from the systolic arterial pressure of age-matched WKY rats. A rise in arterial pressure occurred in all SHR groups over the next 4 weeks. However, this rise was significantly attenuated in SHR treated with intracerebroventricular captopril, whereas the same dose of captopril infused intravenously did not alter the development of hypertension.

Table 2 shows that at the time of the acute experiment (within the 4th week of captopril administration) there were no differences in body weight or heart rate among SHR groups. Mean arterial pressure, measured by direct arterial cannulation in anesthetized rats, was significantly (p < 0.01) less in SHR treated with intracerebroventricular captopril than in rats treated with intracerebroventricular vehicle or with intravenous captopril.
Table 1. Effect of Chronic Intracerebroventricular (i.c.v.) and Intravenous (i.v.) Administration of Captopril on Systolic Arterial Pressure in SHR and WKY Rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Pretreatment</th>
<th>1st week</th>
<th>2nd week</th>
<th>3rd week</th>
<th>4th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>i.c.v. captopril (n = 17)</td>
<td>131.7 ± 2.3</td>
<td>132.5 ± 2.5*</td>
<td>138.5 ± 2.7†</td>
<td>151.5 ± 3.0†</td>
<td>152.1 ± 2.0†</td>
</tr>
<tr>
<td>i.c.v. vehicle (n = 12)</td>
<td>128.0 ± 2.9</td>
<td>140.8 ± 3.0</td>
<td>154.1 ± 2.5</td>
<td>170.0 ± 2.9</td>
<td>175.2 ± 3.1</td>
</tr>
<tr>
<td>i.v. captopril (n = 13)</td>
<td>130.7 ± 2.1</td>
<td>144.7 ± 3.7</td>
<td>147.5 ± 4.1</td>
<td>167.3 ± 4.2</td>
<td>179.2 ± 4.9</td>
</tr>
<tr>
<td>WKY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.c.v. captopril (n = 9)</td>
<td>131.9 ± 3.0</td>
<td>126.5 ± 3.8</td>
<td>130.4 ± 3.3</td>
<td>123.0 ± 3.3</td>
<td>122.7 ± 2.9‡</td>
</tr>
<tr>
<td>i.c.v. vehicle (n = 11)</td>
<td>127.0 ± 3.3</td>
<td>127.0 ± 3.9</td>
<td>128.6 ± 3.6</td>
<td>135.0 ± 3.0</td>
<td>134.0 ± 5.6</td>
</tr>
<tr>
<td>i.v. captopril (n = 11)</td>
<td>128.1 ± 3.4</td>
<td>125.0 ± 3.3</td>
<td>127.4 ± 3.7</td>
<td>131.6 ± 2.6</td>
<td>134.0 ± 3.4</td>
</tr>
</tbody>
</table>

Arterial pressure measured by indirect tail-cuff method in conscious, restrained rats. Statistical analysis was by analysis of variance plus Newman-Keul’s test.

Table 3 shows the flow velocities and calculated vascular resistances in the SHR groups at the time of acute experimentation. Flow velocities in the renal, mesenteric, and hindquarter vascular beds were similar in the three SHR groups; however, calculated vascular resistances were significantly less in SHR treated with intracerebroventricular captopril than in rats treated with intracerebroventricular vehicle or intravenous captopril.

Changes in Vascular Reactivity

Phenylephrine

Intravenous injection of phenylephrine produced the expected dose-dependent increase in renal, mesenteric, and hindquarter vascular resistances accompanied by an increase in mean arterial pressure and a reflex decrease in heart rate. In contrast to SHR treated with intravenous captopril or intracerebroventricular vehicle, SHR treated with intracerebroventricular captopril showed significantly lesser increases in arterial pressure, greater decreases in heart rate (fig. 1) and lesser increases in renal, mesenteric, and hindquarter vascular resistance (fig. 2) in response to phenylephrine. Intravenous infusion of the same dose of captopril as that used for central infusions failed to alter vascular reactivity to phenylephrine in SHR. Dose-response curves for percent increases in arterial pressure and vascular resistances in response to phenylephrine in SHR given intracerebroventricular captopril were shifted to the right and had significantly lesser slopes as compared to the other SHR groups. In contrast, the slope of the response curve for percent decrease in heart rate in response to phenylephrine in SHR given intracerebroventricular captopril was significantly greater (p < 0.001) than that for SHR given intracerebroventricular vehicle and that for SHR given intravenous captopril.

Vasopressin

As with phenylephrine, SHR treated with intracerebroventricular captopril showed significantly lesser increases in arterial pressure (fig. 3) and vascular resistances (fig. 4) in response to intravenous injections of vasopressin. Dose-response curves for percent increases in arterial pressure and vascular resistances in response to vasopressin in SHR receiving intracerebro-
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**TABLE 3. Organ Flow Velocities and Vascular Resistances at the Time of Acute Experimentation**

<table>
<thead>
<tr>
<th></th>
<th>Flow velocities</th>
<th>Vascular resistances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renal</td>
<td>Mesenteric</td>
</tr>
<tr>
<td>SHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.c.v. captopril (n = 17)</td>
<td>3.3±0.2</td>
<td>6.5±0.3</td>
</tr>
<tr>
<td>i.c.v. vehicle (n = 12)</td>
<td>3.0±0.2</td>
<td>6.0±0.25</td>
</tr>
<tr>
<td>i.v. captopril (n = 13)</td>
<td>2.8±0.3</td>
<td>6.7±0.4</td>
</tr>
<tr>
<td>WKY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.c.v. captopril (n = 9)</td>
<td>4.2±0.5</td>
<td>6.2±0.35</td>
</tr>
<tr>
<td>i.c.v. vehicle (n = 11)</td>
<td>4.4±0.6</td>
<td>6.6±0.4</td>
</tr>
<tr>
<td>i.v. captopril (n = 11)</td>
<td>4.3±0.6</td>
<td>7.2±0.5</td>
</tr>
</tbody>
</table>

Flow velocities were measured by miniaturized ultrasonic pulsed Doppler flow probes; Doppler shift (kHz). Vascular resistance was measured as arterial mean pressure/Doppler shift = resistance (arbitrary units). Statistical analysis was done by analysis of variance and the Newman-Keul's test.

* p < 0.05 different from SHR i.c.v. vehicle and SHR i.v. captopril.
† p < 0.05 different from SHR i.v. captopril.
‡ p < 0.01 different from SHR i.c.v. vehicle.

Ventricular captopril were shifted to the right and had significantly lesser slopes as compared to the other SHR groups. Intravenous infusion of captopril in SHR had little effect on reactivity to vasopressin with the exception that there was a lesser increase in hindquarter vascular resistance in response to 25, 50, and 100 m units/kg of vasopressin in these rats compared with vehicle-treated SHR. However, the slope of the response curve of SHR treated with intravenous captopril did not differ significantly from that of vehicle-treated SHR (fig. 4).

**Nitroglycerine**

Intravenous injections of nitroglycerine were found to produce a dose-dependent decrease in arterial pressure (fig. 5) and a decrease in renal, mesenteric, and hindquarter vascular resistances (fig. 6). Nitroglycerine had no effect on the heart rate of anesthetized rats. In contrast to the findings of depressed reactivity to vasoconstrictors in SHR treated with intracerebroventricular captopril, there was no alteration in the vascular response to the vasodilator nitroglycerine.

**FIGURE 1.** Average percent changes in mean arterial pressure and heart rate in response to phenylephrine in SHR treated with intracerebroventricular (icv) captopril, intracerebroventricular (icv) vehicle, and intravenous (iv) captopril. Responses are expressed as group means ± se. Slopes of the dose-response curves were derived by linear regression and were compared using analysis of variance and the Newman Keul's ranking test.
Baroreflex Sensitivity

We tested the heart rate response to stimulation of the baroreceptor reflex by injecting phenylephrine to raise arterial pressure (fig. 7). SHR treated with intracerebroventricular captopril showed significantly greater reflex changes in heart rate in response to increases in arterial pressure induced by phenylephrine than did the other SHR groups. The points in figure 7 represent the average change in arterial pressure and pulse interval. The lines represent the least squares regression equation fit through the points. It can be seen that SHR treated with intracerebroventricular captopril showed a nonparallel shift to the left of the function relating pulse interval to arterial pressure and a significant (p < 0.01) increase in the slope (sensitivity) for baroreceptor control of pulse interval. The sensitivity of the reflex for SHR treated with intracerebroventricular captopril (1.67 ± 0.5, r = 0.94) was approximately 4 times greater than that for vehicle-treated SHR (0.45 ± 0.02, r = 0.93) or SHR treated with intravenous captopril (0.49 ± 0.03, r = 0.93). Again, peripheral administration of captopril at the same dose that was used centrally failed to alter the baroreflex.

Changes in Vascular Reactivity and Baroreflex Sensitivity in Normotensive WKY Treated with Captopril

We extended our studies of the effects of captopril on vascular reactivity and baroreflex function to normotensive WKY rats in order to determine whether the results observed in SHR were attributable to the lower arterial pressure per se. Chronic intracerebroventricular administration of captopril was found to produce a small but significant (p < 0.05) decrease (approximately 10 mm Hg) in systolic arterial pressure in WKY rats during the 4th week of treatment (table 1). At the time of acute experimentation, direct mean arterial pressure was also 10 mm Hg less (p < 0.01) in rats treated with intracerebroventricular captopril than in vehicle-treated or intravenous-captopril-treated rats (table 2). Although arterial pressure was slightly lower in WKY treated with intracerebroventricular captopril, there were no significant differences found among the WKY rat groups in flow velocities or vascular resistances (table 3).
Similar to the findings in SHR, WKY rats treated with centrally administered captopril showed significantly lesser increases in mean arterial pressure, a greater decrease in heart rate, and lesser increases in vascular resistances in response to the vasoconstrictors phenylephrine (figs. 8 and 9) and vasopressin (figs. 10 and 11) than did control groups. Response curves from WKY treated with intracerebroventricular captopril were shifted to the right and the slopes of the curves were less than those seen for vehicle-treated and intravenous-captopril-treated rats. An exception was the response curve for percent decrease in heart rate in response to phenylephrine, which was shifted to the left and had a significantly greater slope. As in the case of the SHR groups, no differences were seen among the WKY groups in the cardiovascular responses to nitroglycerine.

WKY treated with intracerebroventricular captopril also showed an increase in the sensitivity of baroreflex control of heart rate (fig. 12). The slope of the function relating pulse interval to arterial pressure was twice as great ($p < 0.01$) in WKY treated with intracerebroventricular captopril ($3.6 \pm 0.4, r = 0.93$) as in vehicle-treated ($1.83 \pm 0.16, r = 0.96$) or intravenous-captopril-treated WKY ($1.52 \pm 0.08, r = 0.94$).

**Discussion**

Chronic intracerebroventricular administration of captopril to young SHR has been found to attenuate the development of hypertension. The mechanism by which captopril produces this effect is unknown, but does appear to be central, as the same dose of drug infused intravenously had no effect on the development of hypertension in SHR. The current study shows that the depressor effect of chronic intracerebroventricular captopril administration in SHR is associated with marked depression in vascular reactivity and enhancement of baroreflex sensitivity. These effects of captopril are due to a central mechanism of action, as chronic peripheral administration of captopril at the same dose as that given centrally did not alter vascular reactivity or baroreflex sensitivity in SHR. Moreover, central administration of captopril to normotensive WKY rats produced a small but significant decrease in arterial pressure associated with a significant depression in vascular reactivity and an enhancement in baroreflex sensitivity.

The finding of a similar pattern of vascular and reflex changes in normotensive rats with chronic central administration of captopril suggests that the changes in SHR are not secondary to decreases in arterial pressure or initial vascular resistance per se, but are rather part of the antihypertensive mechanism.
of action of captopril. Studies from several laboratories have demonstrated that the magnitude of a pressor or vasoconstrictor response is inversely proportional to the initial arterial pressure or vascular resistance, while the magnitude of a depressor or vasodilator response is directly proportional to the initial pressure and resistance. Thus, a decrease in the initial resistance in SHR treated with intracerebroventricular captopril should lead to a greater response to vasoconstrictors and a lesser response to vasodilators if the vascular response were solely dependent upon initial resistance. We found a decrease in the magnitude of vasoconstrictor responses and no alteration in the response to the vasodilator nitroglycerine in SHR treated with intracerebroventricular captopril. Moreover, we found an attenuation in pressor responsiveness in WKY treated with intracerebroventricular captopril in spite of the fact that the initial vascular resistance in this group was not different from that in the other WKY groups. These results suggest that the alterations in vascular responsiveness seen in rats treated with intracerebroventricular captopril were not simply due to lower baseline vascular resistance.

Vascular reactivity to vasoconstrictor stimuli has been reported to be elevated in perfused vascular beds of SHR in both the prehypertensive and chronic stages of hypertension, and this change has been implicated in the pathogenesis of hypertension in this model. Changes in both the structure of the arteriolar wall (medial hypertrophy) and the sensitivity of vascular smooth muscle cells within the wall to vasoconstrictor

**FIGURE 6.** Average percent change in renal, mesenteric, and hindquarter vascular resistance in response to nitroglycerine in the same groups as indicated in figure 1. Responses are expressed as group means ± se. Slopes and statistical comparison as in figure 1.
agents appear to contribute to increased vascular reactivity in SHR.\textsuperscript{31,32} There is evidence that such structural alterations are secondary to increased arterial pressure,\textsuperscript{33} whereas functional changes in vascular smooth muscle cells are not. Part of the depressant effect of centrally administered captopril on vascular reactivity observed in our study may be attributable to the ability of captopril to attenuate the development of structural vascular changes. Captopril may also prevent the increase in sensitivity of vascular smooth muscle cells to vasoconstrictor agents that has been reported in SHR.\textsuperscript{31,33} The finding of changes in vascular responsiveness in normotensive WKY that are qualitatively similar to those in SHR, despite the major differences in magnitude and duration of the blood pressure lowering effect, suggests that the vascular changes in SHR given intracerebroventricular captopril were not secondary to its antihypertensive effect. Rather, it appears that the effect of captopril on vascular responsiveness may underlie its antihypertensive action.

It has recently been shown that acute or chronic peripheral administration of captopril in doses much higher than those used in this study produces an inhibitory effect on vascular reactivity to vasoconstrictor agents and sympathetic nerve stimulation in both hypertensive animals and humans.\textsuperscript{15-20} In the current study, chronic intravenous administration of captopril at a dose of 1.25 \(\mu\)g/hr had no effect on arterial pressure or vascular responsiveness in either hypertensive

**Figure 8.** Average percent change in mean arterial pressure and heart rate in response to phenylephrine in WKY treated with intracerebroventricular (icv) captopril, icv vehicle, and intravenous (iv) captopril. Responses are expressed as group means \(\pm\ SE\). Slopes of the dose-response curves were derived by linear regression and were compared using analysis of variance and the Newman-Keul’s ranking test.

**Figure 9.** Average percent change in renal, mesenteric, and hindquarter vascular resistance in response to phenylephrine in the same groups as indicated in figure 8. Responses are expressed as group means \(\pm\ SE\). Slopes and statistical comparison as in figure 8.
or normotensive rats. It is therefore unlikely that the antihypertensive effects of intracerebroventricular captopril were due to leakage of drug into the periphery and a direct or indirect peripheral action on the vascular smooth muscle cell.

The ability of intracerebroventricular captopril to increase baroreflex sensitivity in hypertensive animals may also contribute to its antihypertensive effect. The fact that increased baroreflex sensitivity was also observed in WKY treated with intracerebroventricular captopril suggests that the change in reflex sensitivity are attributable to an effect of captopril rather than to an alteration in arterial pressure per se. Captopril has been shown to lower blood pressure without a concomitant increase in heart rate or plasma norepinephrine. This suggests that captopril may potentiate baroreceptor-mediated inhibition of autonomic nerve activity. In support of this hypothesis, Imai and co-workers reported that captopril potentiated reflex slowing of heart rate in response to exogenous norepinephrine and vasopressin even though it attenuated the pressor responses to these vasoconstrictors.

Our data suggest that intracerebroventricular captopril produces its antihypertensive effects and attendant decrease in vascular reactivity and potentiation of baroreflex sensitivity in SHR by a central mechanism; perhaps by altering brain angiotensin II. Neuroanatomical and biochemical studies show that angiotensin-like immunoreactive fibers and renin content are increased in SHR in the region of the nucleus tractus solitarii, the first (afferent) neuron of the baroreceptor reflex arc. Functional studies show that angiotensin II inhibits vagal tone through a central mechanism. Taken together, these data suggest that captopril might potentiate the baroreflex in SHR by decreasing endogenous brain angiotensin II. Angiotensin II is also known to stimulate the release of ACTH and vasopressin from the pituitary. Injection of renin into the brain ventricles produces a large rise in plasma corticosterone mediated by angiotensin II-induced stimulation of ACTH release. The increase in corticosterone is of particular interest in that glucocorticoids are known to increase the sensitivity of vascular smooth muscle to catecholamines and vasopressin. Moreover, plasma corticosterone has been reported to be increased in SHR as compared to WKY. Vasopressin is also known to potentiate the response of the vascular smooth muscle cell to catecholamines and nerve stimulation and has also been reported to be increased in SHR. Thus, it can be speculated that captopril alters vascular reactivity and baroreflex sen-

![Figure 10](https://hyper.ahajournals.org/)

**Figure 10.** Average percent change in mean arterial pressure in response to vasopressin in the same groups as indicated as in figure 8. Responses are expressed as group means ± se. Slopes and statistical comparison as in figure 8.

![Figure 11](https://hyper.ahajournals.org/)

**Figure 11.** Average percent change in renal, mesenteric, and hindquarter vascular resistance in response to vasopressin indicated as in figure 8. Responses expressed as group means ± se. Slopes and statistical comparison as in figure 8.
sitivity by inhibiting the brain renin-angiotensin system and central functions of angiotensin II. In addition, captopril may modify other brain peptides such as substance P and enkephalins. Sub P is a competitive substrate for converting enzyme, and converting enzyme has properties in common with an enkephalin-degrading dipeptidyl-carboxypeptidase. There is increasing evidence that these peptides may participate in blood pressure regulation and that captopril may produce its central antihypertensive effect by interfering with their degradation.

In summary, we have shown that chronic intracerebroventricular administration of captopril in both SHR and WKY lowers blood pressure, decreases vascular reactivity to vasoconstrictors such as phenylephrine and vasopressin, and increases baroreflex sensitivity. We have also shown that these effects of captopril are centrally mediated in that they do not occur in animals given equal doses of intravenous captopril. The occurrence of these responses in the normotensive rat suggests that they are not attributable to the reduction in arterial pressure per se but rather are part of the central antihypertensive action of captopril.

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