Effects of Captopril and Enalapril on Regional Vascular Resistance and Reactivity in Spontaneously Hypertensive Rats

CHRISTINE RICHER, PH.D., MARIE-PASCALE DOUSSAU, AND JEAN-FRANÇOIS GIUDICELLI, M.D., PH.D.

SUMMARY The present study compares the effects of short-term treatments with captopril and enalapril, administered in equipotent antihypertensive doses, on the regional vascular resistances and on the regional vascular responsiveness to vasopressor agents of adult spontaneously hypertensive rats (SHRs). Three groups of animals were treated by gavage with captopril (100 mg/kg), enalapril (25 mg/kg), or distilled water for 8 days. Arterial blood pressure (BP), heart rate (HR), plasma renin concentration (PRC), and plasma converting-enzyme activity (CEA) were measured. Cardiac index (CI), total peripheral resistance (PR), and organ flow distribution were determined using microspheres. Renal and mesenteric vascular responsiveness to vasopressor agents was evaluated by continuous measurement of renal and mesenteric blood flows with miniaturized pulsed Doppler flow probes. Data showed that in the anesthetized SHR the two drugs induced similar reductions in BP, PR, and HR, without affecting CI. They simultaneously produced a strong converting-enzyme inhibition as evidenced by the suppression of angiotensin I effects accompanied by a potentiation of angiotensin II responses, a reduction in CEA, and an increase in PRC. Organ flows were similarly and homogeneously increased, especially in the kidneys, in both treated groups. Norepinephrine (NE) vasoconstrictor responses were abolished in the mesenteric vascular bed by both drugs, but in the renal, NE responses although completely abolished by captopril were only partially reduced by enalapril. It thus appears that diminished vascular responsiveness to NE, especially in the case of captopril, is probably involved along with converting-enzyme inhibition in the antihypertensive action of converting enzyme inhibitors (CEI), the mechanism of the difference between captopril and enalapril remaining still speculative. (Hypertension 5: 312-320, 1983)

Key Words • vascular reactivity • vascular resistance • converting-enzyme inhibition • captopril • enalapril • spontaneously hypertensive rats • renal vessels • mesenteric vessels

ANGIOTENSIN I converting-enzyme inhibitors (CEI) are a new class of potent antihypertensive drugs.1-4 These drugs, e.g., captopril and enalapril, strongly reduce peripheral resistance and lower blood pressure but the precise mechanisms responsible for these effects are not yet clearly elucidated.

Although plasma converting-enzyme inhibition and hence plasma renin-angiotensin system inhibition have been postulated to be of primary importance, it has been shown that there is no correlation between the intensity and kinetics of the CEI antihypertensive effects and those of plasma converting-enzyme inhibition assessed either by direct measurement in the plasma from men5-6 or rats7 or by evaluation of the inhibition of the pressor response to angiotensin I in rats.8 This lack of correlation suggests that the CEI antihypertensive properties may result from converting-enzyme inhibition in some critical tissues rather than in plasma.9 In this respect, however, Cohen and Kurz10 have recently shown in SHRs that there were differences in the intensity and kinetics of converting
enzyme inhibition: 1) from one tissue to another with a given CEI; and 2) within a given tissue with different CEIs used in equipotent antihypertensive doses. These findings, together with the fact that angiotensin II receptors differ in number and sensitivity from one tissue to another, thus raise the possibility that CEI regional vasodilator properties may differ from one drug to another.

Renin-angiotensin system inhibition is most likely not the only mechanism by which CEI exert their antihypertensive effects. Other factors are also involved, e.g., potentiation of kinins, variations in prostaglandins production, and especially interaction with the sympathetic nervous system through the reduction in angiotensin II synthesis. Thus, increased as well as decreased or not modified vascular responses to adrenergic vasoactive agents have been reported in CEI-treated rats depending upon in vitro, ex vivo, or in vivo studies, the vascular region investigated, and the strain of rats used. In vitro, contractile or pressor responses to norepinephrine (NE) are usually not modified or reduced by captopril. Ex vivo, equivalent or enhanced contractile responses to NE have been described in aortic strips from captopril-treated SHR. In vivo, chronic CEI-treatment of rats has been reported to lower NE22, 23 and phenylephrine24 vasopressor responses, the same phenomenon being observed in humans with NE after a single oral dose of captopril. And it is likely that these CEI-induced modifications of responsiveness to adrenergic stimuli, which may be partially linked to the regional differences in tissue converting-enzyme inhibition, also play a role in the antihypertensive effects of CEI.

Captopril and enalapril are two orally active CEI, differing in their chemical structure and their tissue converting-enzyme inhibition profile but sharing well-documented antihypertensive effects in adult as well as in young SHR. Thus, the present studies were undertaken to determine whether these agents differentially affect regional vascular resistances at equipotent doses and whether any alterations in vascular reactivity associated with the antihypertensive action can be demonstrated.

**Methods**

Twenty to 22-week-old male SHR (Charles River, France, Okamoto strain), placed on a normal chow diet and receiving water ad libitum, were divided in three groups (n = 30 each). They were treated once daily for 8 days by gavage either with captopril (100 mg/kg, 1 ml/100 g), enalapril (25 mg/kg, 1 ml/100 g), or distilled water (1 ml/100 g). Systolic blood pressure (SBP) and heart rate (HR) were recorded in the conscious animals (Physiograph DMP, Narco Biosystems Inc.) twice, at 1.5 hours (i.e., at the time of the maximal antihypertensive effect) and at 24 hours after the 7th day of oral drug administration.

**Measurement of Cardiac Index and Regional Blood Flow by the Tracer Microsphere Method**

On their 8th day of treatment, 10 rats were randomly selected from each group and anesthetized with Dial (60 mg/kg, i.p., 0.06 ml/100 g) 1 hour after dosing with captopril, enalapril, or distilled water. The trachea was intubated but the animals breathed spontaneously. Body temperature was maintained at 36°C with a heating pad. Catheters were placed in the right femoral and in both carotid arteries (PE 50). The right carotid catheter was advanced into the left ventricle. The entire surgical procedure lasted approximately 20 minutes. Radioactive microspheres (141Ce, 15 ± 3 μm, specific activity = 9.96 mCi/g, NEN) were diluted in 10% dextran solution and ultrasonically shaken for 15 minutes. Then 0.02 ml (corresponding to 60,000–80,000 spheres) were injected in the left ventricle over 10 seconds and flushed with 0.2 ml saline, exactly 1.5 hours after the last captopril, enalapril, or distilled water administration. Starting 10 seconds before the injection, blood was withdrawn into a preweighed heparinized disposable syringe by a Harvard Pump (model 901) from the right femoral catheter at a constant rate of 0.7 ml/min for 90 sec. Arterial pressure was recorded from a P50 transducer connected to the left carotid catheter. The HR was obtained from the arterial pressure pulse using a tachometer (Biotach amplifier, model 1346–1566). These parameters were recorded on a multichannel Gould Brush polygraph (model 6610-06).

At the end of the experiments, the rats were killed, and the kidneys, spleen, liver, heart, and a sample of the hind limb muscle were immediately removed, cleaned of fat and fibrous tissues, blotted dry, and weighed. The tissue samples and the blood withdrawn from the femoral catheter were counted in a gamma counter (Compugamma LKB 1280).

**Measurement of Regional Vascular Reactivity by the Pulsed Doppler Technique**

In a first set of experiments, 10 other animals were randomly selected from each group for evaluation of regional vascular reactivity to vasopressor agents. They were anesthetized as previously described 30 minutes after the 8th day of drug administration; the trachea was intubated but the animals breathed spontaneously. Catheters were inserted into the left carotid artery (PE50) and the right femoral vein (PE10). Then a midline laparotomy was performed. After carefully isolating the superior mesenteric artery and the left renal artery, small pulsed Doppler flow-probes were placed on each of these vessels. A complete description of these flow-probes and their construction has been published by Haywood et al.31 The flow-probes were connected to a pulsed Doppler flow instrument (545 C directional pulsed Doppler, Bioengineering Department of the University of Iowa). The changes in blood flow velocity, measured as the Doppler shift in kHz and recorded on a Gould recorder (model 6610-06), have been shown to be directly and linearly pro-
portional to volume flow. Simultaneously, arterial pressure was recorded from a P50 transducer connected to the carotid catheter, and HR was recorded from the arterial pressure pulse using a tachometer (Biotach amplifier, model 1346-1566). Responses to intravenous injections of norepinephrine (NE) (0.1, 0.3, 1, 3 \( \mu \)g/kg), angiotensin II (3, 10, 30 ng/kg), angiotensin I (400 ng/kg), and phenylephrine (3 \( \mu \)g/kg) were then recorded, thus starting 1.5 hours after the last captopril, enalapril, or distilled water administration.

In a second set of experiments, the remaining 10 animals from each group were used to investigate the changes in cardiac output and systemic peripheral resistance induced by the same vasopressor agents, 1.5 hours after the last captopril, enalapril, or distilled water administration. The SHRs were anesthetized as previously described 30 minutes after the 8th day of drug administration, the trachea was intubated for artificial ventilation (Harvard Apparatus, model 680). Catheters were inserted into one of the carotid arteries for arterial blood pressure and HR recordings and into the right femoral vein for injections. An electromagnetic Statham flow-probe (2 mm in diameter) was then placed around the ascending aorta for continuous measurement of ascending aorta flow before and during injections of the vasopressor agents.

Measurement of Plasma Renin Concentration and Angiotensin Converting-Enzyme Activity

On the 6th day of treatment, 10 rats were randomly selected from each group. At 1.5 hours after the last drug administration, two blood samples of 0.8 ml each were taken from the jugular vein under light ether anesthesia in order to measure plasma renin concentration (PRC) and angiotensin converting-enzyme activity (CEA). PRC was evaluated by the radioimmunoassay technique and expressed in ng of angiotensin I generated per milliliter (ml) of plasma per 2 hours of incubation. Angiotensin I and antiserum (CEA-Sorin) were used according to the method described by Ménard and Catt. Angiotensin converting-enzyme activity (CEA) was evaluated according to the method of Cushman and Cheung and expressed in nmoles of hippuric acid generated per ml per minute.

Drugs

Captopril (Squibb) and enalapril (Merck, Sharp & Dohme) were used in doses previously shown to be equipotent in inhibiting pressor effects of angiotensin I, in reducing established hypertension in SHRs, and in preventing development of genetic hypertension in young SHRs. The following other drugs were used: alobarbital (Dial, Ciba-Geigy), norepinephrine bitartrate (Levophed R, Winthrop), angiotensin II (Hypertensin R, Ciba), angiotensin I (Sigma), phenylephrine hydrochloride (Sigma).

Calculations and Analysis of Data

Calculation of Cardiac Index, Regional Blood Flows, and Systemic and Regional Vascular Resistances

Cardiac index (CI) was calculated as:

\[
(CI) \ (ml/min/kg) = \frac{reference \ blood \ sample \ withdrawal \ rate \times \ total \ radioactivity \ injected}{reference \ blood \ sample \ radioactive \ \times \ body \ weight}
\]

Regional blood flows were calculated as:

\[
Organ \ blood \ flow = \frac{organ \ radioactivity \times 100 \times \ cardiac \ output}{total \ radioactivity \ injected \times \ organ \ weight}
\]

Total peripheral resistance and relative organ resistance are expressed in arbitrary units and were obtained by dividing the mean aortic arterial pressure either by CI or by the organ blood flow respectively.

Calculation of Changes in Vascular Resistance of the Renal and Mesenteric Vascular Beds

Zero flow can be accurately measured by determining baseline with the ultrasound signal turned off. Doppler shift is directly proportional to volume flow, so resistance can be arbitrarily calculated as the mean arterial pressure/mean Doppler shift ratio. Percentage change in local resistance before and after drug administration is then calculated.

Calculation of systemic peripheral resistance was performed by dividing mean arterial pressure by aortic blood flow.

Data are expressed as means ± SEM and comparisons between captopril- and enalapril-treated SHRs and untreated SHRs have been performed using analysis of variance followed by comparison of means by Student’s t test.

Results

Effects of Captopril and Enalapril on Body Weight, Systolic Blood Pressure and Heart Rate in Conscious SHRs

Table 1 indicates the values for body weight, systolic blood pressure (SBP), and heart rate (HR) measured in the conscious state in the three experimental groups. Both CEIs induced strong and equipotent decreases in SBP 1.5 hours after administration, and this effect was long-lasting since after 24 hours SBP values were only 9.2 (captopril) and 10.1 (enalapril) mm Hg higher (p < 0.05) than at the time of the peak effect. Heart rate was reduced by both drugs 1.5 and 24 hours after administration, but only the captopril-induced bradycardia was significant.

Effects of Captopril and Enalapril on Plasma Renin Concentration and Angiotensin Converting-Enzyme Activity

Plasma renin concentration (PRC) was considerably increased by both drugs and significantly more by ena-
TABLE 1. Effects of Captopril and Enalapril on Body Weight, Systolic Blood Pressure, Heart Rate, Plasma Renin Concentration, and Converting Enzyme Activity in Conscious SHRs

<table>
<thead>
<tr>
<th>Time after drug administration (hr)</th>
<th>Control SHRs</th>
<th>Captopril-treated SHRs</th>
<th>Enalapril-treated SHRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>194.2±4.6</td>
<td>155.0±3.2†</td>
<td>150.0±3.2‡</td>
</tr>
<tr>
<td>24</td>
<td>196.1±3.1</td>
<td>164.2±2.8‡</td>
<td>160.1±2.8§</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>500.0±10.4</td>
<td>460.0±14.9*</td>
<td>486.0±14.9</td>
</tr>
<tr>
<td>24</td>
<td>495.0±9.7</td>
<td>453.8±11.2†</td>
<td>479.6±8.0</td>
</tr>
<tr>
<td>Plasma renin concentration (ng/ml/2 hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>73.0±13.2</td>
<td>252.7±24.9‡</td>
<td>318.7±24.4¶</td>
</tr>
<tr>
<td>Converting enzyme activity (nmol/ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>29.2±5.3</td>
<td>3.8±3.7†</td>
<td>0.9±0.2‡</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>300.0±2.6</td>
<td>295.0±3.5</td>
<td>299.5±2.6</td>
</tr>
</tbody>
</table>

* p < 0.05; † p < 0.01; ‡ p < 0.001, values significantly different from corresponding control values.
§ p < 0.05, significantly different from corresponding 1.5-hour value.
¶ p < 0.05, significantly different from corresponding captopril group value.

lapril than by captopril ( p < 0.05) (table 1). Plasma converting-enzyme activity (CEA) was significantly inhibited by both drugs.

Hemodynamic Effects of Captopril and Enalapril in Anesthetized SHRs

Table 2 indicates the values of the parameters measured in the three groups of anesthetized animals after 8 days of treatment. There were no significant differences between the two treated groups. As expected, SBP and HR were significantly decreased and to the same extent by both treatments. Captopril and enalapril tended to slightly increase cardiac index while peripheral resistance was significantly decreased.

Regarding regional blood flows and vascular resistances, both captopril and enalapril induced similar variations in the distribution of cardiac output. Fra-

TABLE 2. Systemic and Regional Hemodynamic Effects of Captopril and Enalapril in Anesthetized SHRs ( n = 10)

<table>
<thead>
<tr>
<th></th>
<th>Control SHRs</th>
<th>Captopril-treated</th>
<th>Enalapril-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>167.0±5.4</td>
<td>128.3±11.9†</td>
<td>123.5±8.0‡</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>475.4±9.0</td>
<td>412.2±14.7†</td>
<td>418.0±10.6‡</td>
</tr>
<tr>
<td>Cardiac index (ml/min/kg)</td>
<td>190.7±21.3</td>
<td>201.3±30.5</td>
<td>233.3±25.4</td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg/ml/min/kg)</td>
<td>0.80±0.08</td>
<td>0.56±0.09*</td>
<td>0.48±0.07†</td>
</tr>
<tr>
<td>Blood flow (ml/min/g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>7.4±0.6</td>
<td>11.5±1.8</td>
<td>11.1±2.0</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.66±0.10</td>
<td>0.69±0.13</td>
<td>0.73±0.12</td>
</tr>
<tr>
<td>Liver</td>
<td>0.12±0.02</td>
<td>0.24±0.05*</td>
<td>0.23±0.05*</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.09±0.02</td>
<td>0.08±0.01</td>
<td>0.10±0.02</td>
</tr>
<tr>
<td>Vascular resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg/ml/min/g)</td>
<td>19.8±2.0</td>
<td>10.4±1.9†</td>
<td>11.9±2.6*</td>
</tr>
<tr>
<td>Kidney</td>
<td>336.1±106.2</td>
<td>206.4±56.3</td>
<td>159.4±20.9</td>
</tr>
<tr>
<td>Spleen</td>
<td>14440.6±254.3</td>
<td>630.2±203.7*</td>
<td>708.3±233.1*</td>
</tr>
<tr>
<td>Liver</td>
<td>2080.2±258.7</td>
<td>1589.3±346.0</td>
<td>1374.6±249.6</td>
</tr>
<tr>
<td>Heart weight/body weight</td>
<td>3.83±0.05</td>
<td>3.65±0.03</td>
<td>3.63±0.06</td>
</tr>
</tbody>
</table>

* p < 0.05; † p < 0.01; ‡ p < 0.001; values significantly different from corresponding control values.
Effects of Captopril and Enalapril on Renal and Mesenteric Vascular Reactivity to Vasopressor Agents in Anesthetized SHRs

Figure 1 shows that the pressor response to angiotensin I was strongly reduced by the two treatments and significantly more by enalapril than by captopril. Furthermore, captopril and enalapril almost completely abolished angiotensin I-induced increases in renal and mesenteric resistances.

Captopril and enalapril slightly but not always significantly potentiated angiotensin II pressor responses and total peripheral resistance increases (fig. 2). Angiotensin II-induced renal vasoconstriction was also significantly potentiated, while mesenteric response to angiotensin II was not affected by captopril and enalapril (fig. 1).

Figures 3 and 4 illustrate the vascular responses to increasing doses of NE. Blood pressure and total peripheral resistance increases were slightly but not significantly enhanced by captopril and enalapril as compared to control animals. In contrast, renal and mesenteric vascular responses to all doses of norepinephrine (NE) were almost completely abolished in captopril-treated SHRs. In enalapril-treated animals, mesenteric vascular responses to all doses of NE were also completely abolished, but in the renal vascular bed only the vasoconspctor response to the highest NE dose was significantly reduced (fig. 3).

Captopril and enalapril tended to enhance the systemic blood pressure increase induced by phenylephrine whereas they reduced its renal and mesenteric vasoconstrictor effects. There was no statistical difference between these effects of the two drugs.
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Discussion

In the present study, which compares the effects of captopril and enalapril on local flows and resistances in specific vascular beds and on the responses of some of these beds to vasopressor agents, the two drugs were administered over a 1-week period in order to allow them to reach the renin-angiotensin system outside the circulation, especially within the vascular wall. Moreover, both CEIs were used in doses chosen to induce similar reductions in blood pressure at the time of their maximal effects. Our results show that this goal was achieved. Simultaneously, both drugs produced a strong inhibition of converting enzyme, as evidenced by: 1) the suppression of angiotensin I systemic and regional vasopressor effects, which was accompanied by a potentiation of angiotensin II effects on blood pressure, and on total peripheral and renal resistances; 2) a significant reduction in plasma converting-enzyme activity; and 3) a significant increase in plasma renin concentration.

Along with the reduction in blood pressure and probably because of the resulting decrease in afterload, the cardiac index (despite the decrease in heart rate) tended after 8 days of treatment to increase with both drugs, confirming previous results with captopril and enalapril. It is well known that during the development of genetic hypertension in SHRs, the progressive increase of peripheral resistance with age is not accompanied by any redistribution of blood flow and it has been shown that captopril decreases blood pressure by homogeneously reducing all local vascular resistances. Our results confirm these data for captopril and show that enalapril exerts qualitatively and quantitatively similar effects in the investigated vascular beds. Hence, despite their differences in chemical structure and in tissue converting-enzyme inhibition profile, there was no difference between the two drugs regarding their effects on regional vascular resistances in the investigated territories. Fur-
thermore, both drugs appear to increase renal blood flow despite the reduction in systemic blood pressure.

Regarding vascular responsiveness to vasopressor agents, our results show that angiotensin II-induced increases in mean arterial pressure and total peripheral and renal resistances were slightly, although not always, significantly enhanced by captopril and enalapril. This result, which confirms previous data, could at least partially be accounted for by a CEI-induced increased sensitivity to angiotensin II. However, this potentiation was not observed in the mesenteric vascular bed, which is known to be less sensitive than the renal bed to the vasoconstrictor effects of angiotensin II.

In the three groups of animals NE induced dose-dependent increases in blood pressure, which were generally more marked in the two CEI-treated groups, confirming our previous data with enalapril. Total peripheral resistance was also augmented but there was no significant difference between the increases of this parameter observed in the three groups of animals. Simultaneously, both CEIs abolished the NE-induced increase in mesenteric vascular resistance; captopril abolished, while enalapril only reduced, the NE-induced increase in renal vascular resistance. These results are in agreement with previous in vitro data showing a captopril-induced reduction in NE vasoconstrictor responses in respectively isolated mesenteric arteries and isolated perfused kidney. Since total peripheral resistance is augmented by NE in both CEI-treated groups, failure of renal and mesenteric vascular resistances to simultaneously increase implies that a strong vasoconstriction must occur in other territories, e.g., muscle and skin.

Khairallah et al. have shown that perfusion of isolated organs with angiotensin II potentiates their vasoconstrictor response to exogenous NE by reduction of the uptake phenomenon. Thus, in CEI-treated animals, prolonged converting-enzyme blockade and hence prolonged decrease in angiotensin II formation may result in a reduced vasoconstrictor response to exogenous NE. This cannot, however, be the sole explanation for the reduced responses to NE, since enalapril was less effective than captopril in reducing NE vasoconstrictor responses in the renal vascular bed, despite being slightly more effective in blocking plasma converting enzyme and markedly more effective in inhibiting renal converting enzyme and for a longer period of time than captopril.

Theoretically, pressor and vascular responsiveness might depend partially on the level of baseline blood pressure or vascular resistance. Thus, a possible influence of blood pressure or vascular resistance per se on responsiveness to vasopressor agents would be nonspecific and should affect equally the sensitivity to NE and angiotensin II. However, this was not the case in our experiments.

The vascular structural changes, i.e., thickening of the vascular wall, which accompany genetic hypertension development in the SHR's contribute to the vascular hyperreactivity of these animals to vasopressor agents. The CEIs, by reducing arterial blood pressure, could also reduce vascular wall thickness and hence vascular hyperreactivity to vasopressor agents, but as previously mentioned, only NE and not angiotensin II vasoconstrictor responses were reduced. Furthermore, the duration of treatment (8 days) is probably too short to induce significant reductions in vascular wall thickness. In fact, at the cardiac level, left ventricular hypertrophy was only slightly but not significantly reduced after 8 days of CEI treatment, although it has been shown to be strongly and significantly reduced after longer periods of treatment.

Attenuation of NE vasoconstrictor effects by both CEIs can also result from a decrease in postsynaptic \( \alpha \)-adrenoceptors responsiveness. Our results, as well as those of many others, clearly indicate that CEIs interfere with the \( \alpha \)-adrenergic responses, reducing or abolishing them, but the mechanism of this interaction is not clear. In our experiments, phenylephrine vasoconstrictor responses were reduced by captopril and enalapril in both mesenteric and renal vascular beds but to a much smaller extent than NE responses. Hence, the interaction between CEI and \( \alpha \)-adrenergic agonists could possibly develop at levels other than that of postsynaptic \( \alpha \)-adrenoceptors. For instance, captopril and enalapril might exert differential effects at the level of postsynaptic \( \alpha \)-adrenoceptors, which are activated by exogenous NE but almost not at all by endogenous NE. This hypothesis is supported by the recent findings of Timmermans et al. who showed in pithed rats that angiotensin II has a modulatory role at the level of postsynaptic \( \alpha \)-adrenoceptors. As evidenced by the fact that hypertensive responses to BHT 920, an \( \alpha \)-(adrenoceptor agonist, are reduced by captopril. However, in this study, enalapril was not investigated. Furthermore, at the mesenteric and renal levels, no experiments of this type have yet been performed, and hence no definite conclusion can be drawn.

Whatever the exact mechanism of the interaction, it must be stressed that both CEIs abolished the vasoconstrictor responses to NE in the mesenteric vascular bed, a finding that does not support the hypothesis of Antonaccio et al. that the sulphydryl moiety in the captopril molecule might be responsible for the attenuation of NE responses. Furthermore, our data show that this attenuation, at least in the mesenteric vascular bed, is not, as has been postulated, a specific effect of captopril since it also applies to enalapril.

In the renal vascular bed, however, captopril and enalapril induced significantly different modifications of NE responses. Thus, while in captopril-treated SHR's NE vasoconstrictor effects were almost abolished at all doses, in enalapril-treated rats only the effects of the highest NE dose were significantly reduced. This difference is paradoxical since, at the renal level, enalapril is a more potent and a more lasting CEI than captopril. Imai et al. have recently postulated that captopril attenuates NE pressor responses through endogenous angiotensin II depletion, a hypothesis disputed by Saruta et al. with two other
CEIs, i.e., teprotide and SA 446. Our data also contest this possibility since, if it were true, NE vasoconstrictor responses would have been abolished by enalapril not only at the mesenteric but also at the renal level. It thus appears that, if both CEIs reduce blood pressure and increase renal blood flow to approximately the same extent in adult SHRs, only captopril affords the renal vascular bed an almost complete protection against NE vasoconstrictor effects.

In summary, short-term treatment with captopril and enalapril, administered orally in equipotent antihypertensive doses to adult SHRs, strongly inhibited plasma converting enzyme and significantly reduced blood pressure, peripheral resistance, and heart rate without affecting cardiac output. Local vascular resistances were homogeneously decreased by both drugs, and the renal blood flow augmented. Norepinephrine vasoconstrictor responses were abolished in the mesenteric vascular bed by both drugs, independent of their chemical structure. In the renal vascular bed, NE vasoconstrictor responses were completely abolished by captopril but only reduced by enalapril. We conclude that the hemodynamic effects of the two CEIs are similar, except for the depression of renal vascular reactivity to NE. Reduction of vascular responsiveness to the sympathetic neurotransmitter, especially in the mesenteric vascular bed, may well contribute to the antihypertensive action of CEIs.

Acknowledgments

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