Influence of Captopril and Enalapril on Regional Vascular Alpha-Adrenergic Receptor Reactivity in SHR

Christine Richer, Marie-Pascale Doussau, and Jean-François Giudicelli

SUMMARY The effects of short-term oral treatment with captopril and enalapril (two angiotensin-I-converting-enzyme inhibitors [ACEIs] that were administered in equipotent antihypertensive doses) on the systemic vasopressor response and on the renal, mesenteric, and hindlimb vascular responses to cirazoline and UK-14,304 (α₁- and α₂-adrenergic receptor-specific agonists, respectively) were investigated in adult pithed spontaneously hypertensive rats (SHR) of the Okamoto-Aoki strain. In the nonbephrectomized animal, captopril and enalapril reduced to the same extent the systemic blood pressure and renal and hindlimb vascular resistances. They also decreased to the same extent systemic pressor and regional vasoconstrictor responses to cirazoline and UK-14,304, especially in the renal and mesenteric vascular beds. Simultaneously, the effects of angiotensin I and angiotensin II on the pressor response were abolished and almost not modified. In the bephrectomized animals, captopril and enalapril no longer reduced the systemic blood pressure and regional vascular resistances, but whereas the sympathoinhibitory effect of captopril vs the systemic pressor and regional vasoconstrictor responses to cirazoline and UK-14,304 persisted, those of enalapril disappeared. It is concluded that 1) captopril and enalapril lower blood pressure in SHRs by mechanisms dependent on the presence of the kidneys; 2) there are functional α₁- and α₂-adrenergic receptors in the three investigated vascular territories; 3) the sympathoinhibitory effect of captopril and enalapril affects both types of postsynaptic α-adrenergic receptors; 4) the sympathoinhibitory effect of both ACEIs is not due to the reduction in basal arteriolar smooth muscle tone that they induce; and 5) the sympathoinhibitory effect of enalapril is dependent upon the presence of the kidneys while that of captopril is not, a difference possibly related to the chemical structures of the two ACEIs.

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KEY WORDS • captopril • enalapril • pithed spontaneously hypertensive rats • regional vascular reactivity • α₁-adrenergic receptor • α₂-adrenergic receptor • angiotensin

It is now well established that angiotensin I (ANG I)-converting-enzyme inhibitors (ACEIs) exert an inhibitory effect on postjunctional, α-adrenergic-receptor-mediated vasoconstrictor responses. Thus, in vitro, decreased vascular contractile or decreased vasopressor responses to norepinephrine (NE) have been reported.1-4 In vivo, acute or chronic ACEI treatment of rats has been shown to lower NE responses5-7 and/or to diminish the vasopressor responses to sympathetic nerve stimulation.7-9 We have recently reported that captopril and enalapril significantly reduced or even abolished the NE-induced increases in renal and mesenteric vascular resistances in the spontaneously hypertensive rat (SHR).10 Finally, it has been shown in humans that NE vasopressor responses were significantly decreased after a single oral dose of captopril.11 Although extensively investigated, the mechanism of this sympathoinhibitory effect of ACEIs has not yet been elucidated. Several questions remain: Does this effect of ACEIs affect both types of α-adrenergic receptors? Does it affect all different vascular beds in the same way? Does it develop pre- and/or postjunctionally? Is it a common property of all ACEIs? To answer some of these questions, we assessed by pulsed Doppler technique in the pithed SHR of the Okamoto-Aoki strain the effects of captopril and enalapril on the vascular responses of three different vascular beds after cirazoline and UK-14,304 administration (selective α₁- and α₂-adrenergic-receptor agonists, respectively) and the effects of bilateral nephrectomy thereupon.
Methods

We placed 20- to 22-week-old male SHRs (Charles River Laboratories, Saint Aubin les Elbeuf, France, Okamoto-Aoki strain) on a normal chow diet with water ad libitum and randomized them into three groups of 50 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 by the indirect tail-cuff method (Physiograph DMP, Narco Biosystems Inc., Houston, Texas) at 1.5 hours after the 7th day of oral drug administration, which was the time of the maximal antihypertensive effect.

Systemic and Regional Vascular Responsiveness to the Alpha-Adrenergic-Receptor Agonists Angiotensin I and Angiotensin II in Pithed SHRs

Experiment 1

In a first set of experiments, on the 8th day of treatment, 10 rats were randomly selected from each group and anesthetized with pentobarbital (50 mg/kg, i.p.) 0.5 hour after the last drug administration, pithed, artificially ventilated (Harvard 680 respirator, South Natick, Massachusetts), vagotomized, and then given i.v. atropine (1 mg/kg) and gallamine (20 mg/kg). Determination of the regional vascular reactivity was then performed by using the pulsed Doppler technique. Renal, mesenteric, and hindlimb vascular responses were evaluated simultaneously by continuous measurement of local flows with miniaturized pulsed Doppler flow probes placed around the vessels and connected to a pulsed Doppler flow instrument (545C directional pulsed Doppler, University of Iowa, Iowa City, Iowa). Changes in blood flow velocity measured as the Doppler shift in kHz and recorded on a Gould Model 6610-06 recorder (Gould Instruments, Ballainvilliers, France) have been shown to be directly and linearly proportional to volume flow. Simultaneously, arterial pressure was recorded from a P50 transducer connected to the carotid artery, and HR was recorded from the arterial pressure pulse with a tachometer (Biotach amplifier Model 1346-1566, Gould Instruments). After a 15-minute stabilization period, the basal values of all investigated parameters were determined. Systemic vasopressor responses and regional vascular reactivity (pulsed Doppler technique) of the mesenteric and hindlimb territories to $\alpha_1$- and $\alpha_2$-adrenergic-receptor agonists were then evaluated by the same protocol as described above in intact animals.

Experiment 2

In a second set of experiments, systemic vasopressor and regional vascular responses to intravenous injections of a single i.v. dose (3 $\mu$g/kg) of cirazoline were measured before and after an infusion of either saline (1.3 ml/kg over 5 minutes, Group A) or yohimbine (300 $\mu$g/kg over 5 minutes, Group B) or prazosin (30 $\mu$g/kg over 5 minutes, Group C).

Finally, in a last set of experiments, systemic vasopressor and regional vascular responses to intravenous injections of ANG I (400 ng/kg) and ANG II (3, 10, 30, 100 ng/kg) were measured on the 8th day of treatment in eight animals that had been randomly selected from each group and bilaterally nephrectomized 24 hours earlier, as previously described.

Selectivity of Cirazoline and UK-14,304 for Alpha$_1$- and Alpha$_2$-Adrenergic Receptors in Pithed SHRs

After 20- to 22-week-old male SHRs were randomized into six groups of eight each, they were anesthetized with pentobarbital (50 mg/kg, i.p.), pithed, artificially ventilated (Harvard Model 680 respirator), vagotomized, and given i.v. atropine (1 mg/kg) and gallamine (20 mg/kg). The systemic blood pressure and renal, mesenteric, and hindlimb vascular reactivity were determined by the pulsed Doppler technique, as described above. Before initiation of any experimental procedure, cardiovascular reactivity of the preparation was tested with 0.5 $\mu$g/kg of NE injected i.v. every 5 minutes until the peak responses to two successive administrations were similar.

In the first three groups of animals, the systemic and regional vascular effects of a single i.v. dose (3 $\mu$g/kg) of cirazoline were measured before and after an infusion of either saline (1.3 ml/kg over 5 minutes, Group A) or yohimbine (300 $\mu$g/kg over 5 minutes, Group B) or prazosin (30 $\mu$g/kg over 5 minutes, Group C).

In the last three groups of animals, systemic and regional vascular effects of a single i.v. dose (100 $\mu$g/kg) of UK-14,304 were measured before and after an infusion of either saline (1.3 ml/kg over 5 minutes, Group D) or yohimbine (300 $\mu$g/kg over 5 minutes, Group E), or prazosin (30 $\mu$g/kg over 5 minutes, Group F).
Measurement of Plasma Angiotensin-I-Converting-Enzyme Activity

On the 6th day of treatment, 10 rats were randomly selected from each group and 1.5 hours after drug administration, were given light ether anesthesia. A 0.8 ml blood sample was then taken from the jugular vein and centrifuged. Plasma was stored at −80° C. Converting-enzyme activity (CEA) was measured according to the method of Cushman and Cheung and expressed as nanomoles of hippuric acid generated per milliliter per minute (nmol/ml/min).

Drugs

Drugs used were ANG I (Beckman Instruments Bio-products/Microbics, Geneva Switzerland), ANG II (Hypertensin®, CIBA-Geigy, Basel, Switzerland), atropine sulphate (Sigma Chemical Company, St. Louis, Missouri), captopril (Squibb, Neully sur Seine, France), cirazoline hydrochloride (Synthélabo, Paris, France), enalapril (Merck Sharp & Dohme, Rahway, New Jersey), gallamine triiodide (Rhone Poulenc), pentobarbital sodium (Abbott, Saint Rémy sur Avze, France), prazosin base (Synthélabo), UK-14,304 tartrate (Pfizer, Orsay, France), and yohimbine hydrochloride (Sigma).

Calculations and Analysis of Data

Calculation of Changes in Vascular Resistance of the Different 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. Absolute change in local resistance before and after drug administration was then calculated.

Statistical Analysis

Data are expressed as means ± SEM. Comparisons between captopril- and enalapril-treated SHRs and untreated SHRs were performed by using analysis of variance followed by comparison of means by Student’s t test. In the selectivity experiments, statistical analysis was performed by Student’s paired t test that compared pre- and posttreatment values.

Results

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

Table 1 indicates the systolic blood pressure and heart rate measured in the conscious state in the three experimental groups. Both ACEIs in the doses used induced strong and equipotent decreases in systolic blood pressure at 1.5 hours after administration, but heart rate was not significantly affected.

Effects of Captopril and Enalapril on Angiotensin-Converting-Enzyme Activity

Plasma CEA was significantly inhibited by both drugs (Table 1).

Systemic and Regional Hemodynamic Effects of Captopril and Enalapril in Nonbiphenectomized and in Biphenectomized, Anesthetized, Pithed SHRs

In nonbiphenectomized pithed SHRs (Experiments 1 and 2), captopril and enalapril induced significant and almost identical reductions in blood pressure without affecting heart rate (Table 2). Vascular resistances in the kidney and the hindlimb were significantly reduced to the same extent by both drugs, whereas mesenteric resistance was not significantly modified (Table 2). There were no differences between the values of all investigated parameters in Experiments 1 and 2.

In biphenectomized pithed SHRs (Experiment 3), the basal blood pressure value of the control animals was not different from that observed in control nonbiphenectomized animals (Experiments 1 and 2). In contrast, basal heart rate and mesenteric and hindlimb resistance values in control animals from Experiment 3 were significantly lower than in control animals from Experiments 1 and 2 (Table 2).

In the biphenectomized pithed animals, captopril and enalapril had no effects on blood pressure, heart rate, and mesenteric and hindlimb vascular resistances (Table 2).

Selectivity of Cirazoline and UK-14,304 for Alpha,- and Alpha,-Adrenergic Receptors in Pithed SHRs

Increments in systemic vasopressor and regional vasoconstrictor responses induced by cirazoline and UK-
14,304 in pithed SHRs before and after saline or yohimbine or prazosin infusions are shown in Table 3. Prazosin pretreatment significantly reduced or even abolished the cirazoline-induced increases in systemic blood pressure and in regional vasoconstrictor responses in the three different vascular beds investigated, whereas the effects of UK-14,304 were not affected. In contrast, yohimbine significantly reduced UK-14,304 systemic vasopressor and regional vasoconstrictor responses but did not attenuate the effects of cirazoline.

Effects of Captopril and Enalapril on Regional Vascular Responsiveness to Vasopressor Agents in Nonbinephrectomized Pithed SHRs

Figure 1 shows that captopril and enalapril significantly reduced or even abolished the renal, mesenteric, and hindlimb vasopressor and the renal, mesenteric, and hindlimb vasoconstrictor responses to ANG I. In contrast, both ACEIs had no effects on systemic vasopressor and hindlimb vasoconstrictor responses and slightly potentiated the renal vasoconstrictor responses to ANG II. Only mesenteric vasoconstrictor responses to ANG II were significantly reduced by captopril and enalapril.

Figure 2 shows that captopril or enalapril significantly reduced the systemic pressor effects of increasing doses of cirazoline. Simultaneously, cirazoline-induced renal, mesenteric, and hindlimb vasoconstrictor effects were significantly decreased by both drugs.

Figure 3 shows that the dose-pressor curve in response to UK-14,304 was significantly shifted to the right and to a similar extent by both captopril and enalapril. The renal and mesenteric vasoconstriction induced by UK-14,304 was completely abolished by both drugs. Vasoconstrictor responses in the hindlimb

<table>
<thead>
<tr>
<th>Table 2. Basal Values of Mean Arterial Blood Pressure, Heart Rate, and Renal, Mesenteric, and Hindlimb Vascular Resistances in Nonbinephrectomized (Experiments 1 and 2) and in Binephrectomized (Experiment 3) Anesthetized, Pithed SHRs Treated Either with Captopril, or with Enalapril or with Distilled Water (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td><strong>Nonbinephrectomized (Experiment 1)</strong></td>
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<tr>
<td>Controls</td>
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<tr>
<td>Captopril</td>
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<tr>
<td>Enalapril</td>
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<tr>
<td><strong>Nonbinephrectomized (Experiment 2)</strong></td>
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<td>Controls</td>
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<tr>
<td>Captopril</td>
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<tr>
<td>Enalapril</td>
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<td><strong>Binephrectomized (Experiment 3)</strong></td>
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<td>Controls</td>
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<tr>
<td>Captopril</td>
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<td>Enalapril</td>
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</tbody>
</table>

Values are means ± SEM. AU = arbitrary units.

*p < 0.01, †p < 0.001, significantly different from corresponding control values.

Table 3. Increments in Mean Arterial Blood Pressure and in Renal, Mesenteric, and Hindlimb Vascular Responses Induced in Pithed SHRs by Cirazoline (3 μg/kg, i.v., Groups A, B, and C) or UK-14,304 (100 μg/kg, i.v., Groups D, E, and F) Before and After 5-Minute Infusions of Either Saline (Groups A and D) or Yohimbine (300 μg/kg, Groups B and E) or Prazosin (30 μg/kg, Groups C and F)

<table>
<thead>
<tr>
<th>Pretreatment (Group)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Renal vascular resistance (AU)</th>
<th>Mesenteric vascular resistance (AU)</th>
<th>Hindlimb vascular resistance (AU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
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<tr>
<td>Cirazoline</td>
<td></td>
<td></td>
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<tr>
<td>Saline (A)</td>
<td>110.2 ± 14.2</td>
<td>115.8 ± 16.2</td>
<td>800.4 ± 202.0</td>
<td>1132.0 ± 233.4</td>
</tr>
<tr>
<td>Yohimbine (B)</td>
<td>109.2 ± 8.0</td>
<td>103.8 ± 19.2</td>
<td>671.2 ± 195.6</td>
<td>858.8 ± 216.8</td>
</tr>
<tr>
<td>Prazosin (C)</td>
<td>113.5 ± 13.4</td>
<td>17.0 ± 4.0†</td>
<td>759.7 ± 165.4</td>
<td>6.4 ± 13.6†</td>
</tr>
<tr>
<td>UK-14,304</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Saline (D)</td>
<td>36.0 ± 5.5</td>
<td>32.2 ± 5.0</td>
<td>41.7 ± 5.6</td>
<td>36.1 ± 5.7</td>
</tr>
<tr>
<td>Yohimbine (E)</td>
<td>33.6 ± 5.0</td>
<td>16.7 ± 2.5†</td>
<td>58.6 ± 11.0</td>
<td>25.1 ± 10.7*</td>
</tr>
<tr>
<td>Prazosin (F)</td>
<td>38.8 ± 3.9</td>
<td>32.3 ± 2.6</td>
<td>50.4 ± 7.8</td>
<td>47.8 ± 11.3</td>
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</tbody>
</table>

Values are means ± SEM. AU = arbitrary units.

*p < 0.05, †p < 0.01, ‡p < 0.001, significantly different from corresponding before pretreatment values.
Effects of Captopril and Enalapril on Regional Vascular Responsiveness to Vasopressor Agents in Binephrectomized Pithed SHRs

The effects of captopril and enalapril on the systemic vasopressor and on the mesenteric and hindlimb vasoconstrictor responses to ANG I and ANG II in binephrectomized SHRs were qualitatively and quantitatively identical to those observed in nonbinephrectomized rats (data not shown).

Figure 4 shows that the attenuating effect of enalapril on systemic and hindlimb vasopressor responses in binephrectomized SHRs was completely abolished, while that on the mesentery was only diminished. Simultaneously, the attenuating effect of captopril in all vascular beds entirely persisted. Figure 4 also shows that systemic vasopressor responses to cirazoline in the control binephrectomized SHRs did not differ significantly from those observed in the control nonbinephrectomized SHRs (Figures 2 and 4). However, the control mesenteric and hindlimb responses to the highest dose of cirazoline were significantly reduced in the binephrectomized as compared to the nonbinephrectomized animals (Figures 2 and 4).

Figure 5 shows that in binephrectomized SHRs enalapril no longer reduced systemic and regional vasopressor responses to UK-14,304, while the attenuating effect of captopril persisted. It also shows that systemic vasopressor responses to UK-14,304 in the control binephrectomized SHRs did not differ significantly from those observed in the control nonbinephrectomized SHRs (Figures 3 and 5). However, the control mesenteric and hindlimb vasoconstrictor re-
responses to UK-14,304 were significantly less in binephrectomized than in nonbephectomized SHRs (Figures 3 and 5).

**Discussion**

This study investigated the effects of captopril and enalapril on the systemic vasopressor and regional vasoconstrictor responses to α-adrenergic-receptor agonists. The two drugs were administered over a 1-week period to allow them to reach the renal-angiotensin system outside the circulation, especially within the vascular wall, and to prevent the consequences of the renin secretion stimulation induced by pithing the SHRs. Moreover, both ACEI doses were chosen to induce similar reductions in blood pressure at the time of their maximal effects. Our results show that this goal was achieved in the conscious as well as in the anesthetized nonbephectomized animals. Simultaneously, both drugs produced a strong inhibition of ANG I-converting enzyme, as evidenced by the suppression of ANG I systemic and regional vasopressor effects and the significant reduction in plasma CEA. Simultaneously, ANG II renal responses were slightly potentiated, but systemic and hindlimb responses were not modified. Finally, for an unknown reason, the mesenteric responses were unexpectedly abolished by both ACEIs. Our experiments in anesthetized pithed SHRs with intact kidneys show that captopril and enalapril lower blood pressure and strongly reduce the systemic vasopressor and renal, mesenteric, and hindlimb vasoconstrictor responses to cirazoline and UK-14,304, two drugs that have been shown to be α₁- and α₂-adrenergic receptor agonists, respectively. It also appears that in binephrectomized pithed SHRs the blood-pressure-lowering effect of captopril and enalapril-
pril no longer develops and that, while the sympathoinhibitory effect of enalapril vs cirazoline and UK-14,304 disappears in almost all the investigated vascular beds, that of captopril is maintained.

With regard to systemic blood pressure, comparison of our data in binephrectomized and nonbinephrectomized animals supports the conclusion, which remains disputed, however, that captopril and enalapril lower blood pressure in SHRs by a renal-dependent mechanism. This mechanism could be either a reduction by ACEIs of the synthesis or release of a vasodepressor material (such as prostaglandins), or a combination of these two effects. The first possibility is clearly not operative since, if it were, bilateral nephrectomy would per se have mimicked the action of ACEIs and induced a fall in blood pressure. This was not the case. On the contrary, our data strongly support the view that in nonbinephrectomized animals, ACEIs lower blood pressure by releasing a renal vasodepressor substance. When bilateral nephrectomy was performed, the blood pressure rose back to its predrug level, a value identical to that observed in the control nephrectomized and nonbinephrectomized animals. Finally, the third possibility, a combined effect of ACEIs on both a vasopressor and a vasodepressor substance, can probably also be excluded, since bilateral nephrectomy alone would have reduced blood pressure but to a lesser extent than ACEIs, which was not the case.

Regarding the mechanism of the sympathoinhibitory effect of captopril and enalapril, our data indicate a major difference between the two drugs. After bilateral nephrectomy, the sympathoinhibitory effect of enalapril disappeared while that of captopril persisted.

Timmermans et al. have recently postulated that in pithed normotensive rats ANG II has a modulating role at the level of the postsynaptic α2-adrenergic receptors, as evidenced by the fact that hypertensive responses to BHT-920, an α2-adrenergic-receptor agonist, are reduced by captopril and binephrectomy.

In our study, a vasopressor response was similarly observed with the structurally distinct α2-adrenergic-receptor antagonist UK-14,304. Moreover, in our experiments with captopril and enalapril, the renal, mesenteric, and hindlimb vascular responses to UK-14,304 were significantly reduced and, indeed, almost abolished by both ACEIs. Also, the mesenteric and hindlimb vascular responses to UK-14,304 were reduced by binephrectomy, which tends to confirm the postulated modulatory role of ANG II on postsynaptic α2-adrenergic receptors. However, it must be pointed out that in our experiments the systemic vasopressor responses to UK-14,304 were not affected by binephrectomy, whereas those responses to BHT-920 have been reported to be reduced. The fact that BHT-920 stimulates not only α2-adrenergic but also dopaminergic receptors might possibly explain the discrepancy between our experiments and those of Timmermans et al. It must also be pointed out that the former were performed in SHRs and the latter in normotensive rats.

Our data also demonstrate that there are functional α1- as well as α2-adrenergic receptors in the three vascular beds investigated and that the sympathoinhibitory effect of captopril and enalapril applies not only to postsynaptic α2-adrenergic receptors, but also to postsynaptic α1-adrenergic receptors, since the systemic vasopressor and the renal, mesenteric, and hindlimb vasoconstrictor responses to both cirazoline and UK-14,304 were significantly reduced by both drugs. It should be noted that the α2-mediated responses seem to be slightly more reduced by ACEIs than the α1-mediated ones. Finally, although sympathoinhibition appears to develop in all the vascular beds investigated, it is more marked at the renal level, where the density of the α2-adrenergic receptors is threefold that of the α1-adrenergic receptors, and at the mesenteric level, than in the hindlimb, where the dose response curves are almost similar to those for mean blood pressure. Thus, ACEI-induced sympathoinhibition appears to develop mainly in the resistance vessels.

The mechanism of the ACEI-induced sympathoinhibition is not yet fully understood. Redleaf and Tobian...
have postulated that a reduction in the cross-sectional area of the resistance-determining precapillary arterioles will always result in an increased responsiveness to vasopressor stimuli. Conversely, Johnson et al. and more recently De Jonge et al. have claimed that the ACEI-induced reduction in basal arteriolar smooth muscle tone is responsible for the reduced postjunctional adrenergic vasopressor responses, and, in fact, these responses can be restored when the reduction in basal diastolic pressure is prevented by vasopressin infusion. Thus, the postjunctional sympathoinhibitory effect of captopril would be apparent rather than real. However, if this were true, the systemic vasopressor and regional vasconstrictor responses to ANG II would also be reduced. This was not the case in our experiments, except in the mesenteric bed. Also, in binephrectomized animals, in which basal diastolic blood pressure is not different from that observed in nonbinephrectomized SHR rats and in which captopril and enalapril no longer reduce diastolic blood pressure, the sympathoinhibitory effects of both drugs should have been abolished, which was not the case with captopril. Thus, this persistent sympathoinhibitory effect of captopril in binephrectomized animals, already mentioned by some but not all investigators, is not due to a reduced basal arteriolar smooth muscle tone and is not dependent upon postjunctional effects of renal ANG II. It also seems unlikely to be related to a presynaptic mechanism, since the reduction in neural NE release induced by the lack of ANG II formation should not affect postjunctional vasoconstrictor effects of cirazoline and UK-14,304. However, our data obviously do not rule out a presynaptic effect of ACEIs on neuronal release of NE.

Finally, since ANG II increases postsynaptic α-adrenergic-receptor sensitivity to NE, it might be argued that ACEI-induced ANG II deprivation is responsible for the reduced adrenergic-responses. Although the reduced control regional vasoconstrictor responses to cirazoline and UK-14,304 in binephrectomized vs nonbinephrectomized rats tend to support this hypothesis, the fact that captopril further reduces these responses in SHRs without kidneys indicates that postsynaptic α-adrenergic-receptor desensitization by ACEIs is at least not the only mechanism involved. Thus, the sympathoinhibitory effect of captopril is clearly different from that of enalapril, which requires the presence of the kidneys and could result from the induced reduction either in ANG II levels or in renal prostaglandins release.

Thus, there are differences between the various ACEIs as to their sympathoinhibitory effects. Recently, we have investigated the effects of another ACEI, 1-[(2S) 2-[(1S)-carbethoxybutyl- amino] 1-oxopropl] (2S, 3aS, 7aS) perhydroindole 2-carboxylic acid, which is twice as potent as enalapril and which, like enalapril, is a monoacid monoester drug that has to be converted in vivo into the active diacid metabolite. The fact that this drug, like enalapril, no longer exhibits sympathoinhibitory effects in binephrectomized animals suggests that the differences between ACEIs as to sympathoinhibition might be related to their chemical structures. Finally, it must be stressed that, in pithed SHRs, captopril-induced sympathoinhibitory effects are not likely to be of major importance in the development of the drug’s antihypertensive action since, in binephrectomized animals, these effects persist while the blood pressure is not lowered.

In conclusion, it appears that ACEI-induced sympathoinhibition in the anesthetized pithed SHR affects both types of postsynaptic α-adrenergic receptors and mainly develops in the renal and mesenteric vascular beds. The mechanism of this sympathoinhibition, which remains to be elucidated, is neither unequivocal nor common to captopril and enalapril; the differences may possibly be related to the chemical structures of ACEIs.

Acknowledgments

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