Pre- and Postjunctional Inhibition of Vascular Sympathetic Function by Captopril in SHR

Implication of Vascular Angiotensin II in Hypertension and Antihypertensive Actions of Captopril

MICHAEL J. ANTONACCIO, PH.D., AND LINDA KERWIN, M.S.

SUMMARY The present study was designed to examine the effects of treatment of SHR with captopril, teprotide, and saralasin on vascular and cardiac responses to sympathetic nerve stimulation and angiotensin I and II (AI, AII) and norepinephrine (NE). A single dose of captopril (10 mg/kg i.v. as well as 10 and 100 mg/kg p.o.) caused significant and marked inhibition of pressor responses to sympathetic nerve stimulation in pithed SHR but cardiac responses were unaffected. Pressor responses to AI were abolished but those to AII and NE were not significantly altered. Neither teprotide nor saralasin caused consistent inhibition of sympathetic responses despite total blockade of AI and AII responses respectively. Selective inhibition of pressor but not cardiac responses to sympathetic nerve stimulation was obtained after 2 weeks, 3 and 6 months of daily oral doses of captopril. In addition, postjunctional pressor responses to AI, AII, and NE were also significantly inhibited by chronic captopril treatment. Infusion of AII, bilateral nephrectomy, or pretreatment with indomethacin alone in pithed SHR receiving captopril had no effect on the inhibition of pressor responses to sympathetic stimulation. However, the combination of pretreatment of indomethacin and infusion of AII completely restored sympathetic function in SHR receiving captopril. These studies suggest that captopril has a selective inhibitory effect on vascular responses to sympathetic nerve stimulation but not on cardiac responses. Moreover, this effect may have a prejunctional component since, after acute treatment, there is no inhibitory effect on responses to AII or NE. Since, under appropriate conditions, the inhibition can be reversed by AII infusion but not nephrectomy, it is suggested that this inhibition occurs at the vascular level by inhibition of local AII formation by captopril, a site not accessible to teprotide or saralasin.

(Hypertension 3 (suppl I): I-54-I-62, 1981)

KEY WORDS • captopril • SHR • renin-angiotensin • prejunctional inhibition • sympathetic function • vascular renin • plasma renin activity

I is now clearly established that captopril (SQ 14, 225) is an effective antihypertensive agent in several animal models of hypertension including high and normal renal hypertension as well as normoreninemic spontaneously hypertensive rats (SHR). In addition, captopril decreases the blood pressure (BP) of essential as well as renovascular human hypertensive patients. While it is generally agreed that captopril is a potent and relatively specific inhibitor of angiotensin converting enzyme (ACE) and that its antihypertensive efficacy in high renin models of hypertension is related to this ability to inhibit ACE, its efficacy in normal renin models of hypertension remains unexplained. This latter efficacy of captopril is particularly perplexing when one considers that angiotensin II (AII) antagonists do not reduce BP in either chronic two-kidney renal hypertensive rats (RHR) or SHR, normal renin models in which captopril is very effective. We have been unable to demonstrate any pharmacological effects of captopril not related to ACE inhibition and, therefore, felt that its demonstrated ability to decrease BP was in some way related to its ability to inhibit ACE despite normal plasma renin activity (PRA) levels in some models. This led to the possibility that PRA levels may not be an accurate indicator of the functional status of the renin angiotensin system (RAS) in certain forms of hypertension, especially if extra-renal renin, for example in the vasculature, played any role in the maintenance of hypertension. Recently, levels of vascular renin or a renin-like enzyme (hereafter referred to as vascular renin for the sake of simplicity) have been shown to be elevated not only in the acute, high renin stage of two-clip RHR but also in the chronic normal renin...
Similarly, vascular renin levels have been demonstrated to be elevated in SHR, another normal renin model of hypertension. Furthermore, vascular renin levels are appropriately responsive to various manipulations since they increase with either captopril administration or salt depletion, and decrease with salt-loading. If the vascular renin angiotensin system were functional, it could contribute to hypertension development and/or maintenance in at least two ways: 1) by a direct vasoconstrictor action of AlI on vascular smooth muscle, and 2) facilitation of sympathetic function by increasing the release of norepinephrine (NE) in the vasculature. One might anticipate that, if the latter were true, a drug such as captopril might have an inhibitory effect on responses to sympathetic nerve stimulation and, further, that this inhibition would be preferentially prejunctional and specific for vascular sympathetic responses since the heart does not contain renin.

The present studies were performed to examine the effects of captopril and other agents on sympathetic function in SHR during acute and chronic therapy with captopril.

Methods
Ten to 14-week-old male spontaneously hypertensive rats (SHR) of the Okamoto and Aoki strain were obtained from Taconic Farms, Germantown, New York, and were placed on a normal rat chow diet and water ad libitum. The rats were randomly assigned to cages and treated as described below.

Rats from each group were randomly selected after either 2 weeks, 3 or 6 months of daily dosage for the measurement of mean arterial blood pressure (MAP), heart rate, and responses to various agents in pithed rats. The SHR were anesthetized (sodium pentobarbital, 35 mg/kg i.p.) at an appropriate time after dosing (1 to 1 1/2 hours) so that responses were obtained 2 hours after initial gavage. The BP was measured from a carotid artery and drugs administered through a jugular vein catheter. Heart rate was measured with a cardiostimulator triggered by the systolic BP pulse. All measurements were recorded on a Beckman dynograph.

Responses to sympathetic nerve stimulation (80 Hz, 10 V for 20 sec) were obtained in SHR by stimulating the complete sympathetic outflow from the spinal cord of pithed rats as described by Gillespie and Muir.

Responses to other agents were determined after pithing. A paired or unpaired Student's t-test was used to determine statistical significance.

Results
Effects of Captopril, Teprotide and Saralasin on Responses to Sympathetic Nerve Stimulation, Norepinephrine, Angiotensins I and II in Pithed Intact SHR

A single dose of captopril administered either intravenously (10 mg/kg) or orally (10 and 100 mg/kg) caused significant reductions in the pressor responses to stimulation of the entire sympathetic outflow in pithed SHR (fig. 1). However, positive chronotropic responses to the same stimulation were not altered (fig. 1). Although pressor responses to AlI were similarly inhibited in all three groups of treated rats, pressor responses to NE and AlII were not significantly reduced (table 1). Heart rate responses followed the pressor responses in a totally analogous manner (not shown).

In SHR treated daily with captopril (100 mg/kg, p.o.) for 2 weeks, 3 or 6 months and subsequently pithed, the pressor responses to sympathetic stimulation were also inhibited to comparable degrees in comparison with SHR receiving only a single dose of captopril (fig. 2). As in the SHR receiving only a single

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**Table 1. Effects of Captopril Treatment on Pressor Responses (Δ Mean Blood Pressure, mm Hg) to Norepinephrine, Angiotensins I and II in Pithed SHR**

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Dose (mg/kg p.o.)</th>
<th>n</th>
<th>Norepinephrine (1 μg/kg)</th>
<th>Angiotensin II (1 μg/kg)</th>
<th>Angiotensin I (1 μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>12</td>
<td>45.0 ± 4.2</td>
<td>60.1 ± 5.2</td>
<td>46.6 ± 2.2</td>
</tr>
<tr>
<td>2 hrs</td>
<td>10 (i.v.)</td>
<td>6</td>
<td>33.3 ± 1.9</td>
<td>58.3 ± 3.8</td>
<td>7.5 ± 0.4</td>
</tr>
<tr>
<td>2 hrs</td>
<td>10</td>
<td>6</td>
<td>42.0 ± 6.7</td>
<td>60.2 ± 5.7</td>
<td>7.7 ± 0.8</td>
</tr>
<tr>
<td>2 hrs</td>
<td>100</td>
<td>6</td>
<td>32.3 ± 2.5</td>
<td>49.0 ± 4.1</td>
<td>5.3 ± 1.4</td>
</tr>
<tr>
<td>2 wks</td>
<td>100</td>
<td>7</td>
<td>23.9 ± 1.6</td>
<td>32.7 ± 1.9</td>
<td>4.4 ± 0.8</td>
</tr>
<tr>
<td>3 mos</td>
<td>100</td>
<td>8</td>
<td>26.8 ± 2.7</td>
<td>42.5 ± 5.5</td>
<td>5.0 ± 1.1</td>
</tr>
<tr>
<td>6 mos</td>
<td>100</td>
<td>7</td>
<td>25.6 ± 3.2</td>
<td>45.4 ± 4.4</td>
<td>7.1 ± 0.9</td>
</tr>
</tbody>
</table>

Values are mean ± SE; p refers to significant changes from untreated SHR.
FIGURE 1. Effects of captopril, single dose, on changes in blood pressure and heart rate to sympathetic stimulation in pithed SHR. Open symbol indicates significant difference (p < 0.05) from saline-treated animals. Values shown are mean ± SE of at least six rats per group.

FIGURE 2. Effects of captopril treatment (100 mg/kg p.o. daily) on changes in blood pressure and heart rate to sympathetic stimulation in pithed SHR. See figure 1 for details.
dose of captopril, positive chronotropic responses to sympathetic stimulation were unaltered despite the duration of captopril treatment.

Although pressor responses to AI were similarly inhibited by captopril in all the treated groups, pressor responses to NE were consistently and significantly reduced in comparison to untreated SHR (table 1). Similarly, pressor responses to All were also reduced by chronic captopril therapy, significantly so in the groups treated for 2 weeks or 3 months.

In SHR treated with teprotide (30 mg/kg s.c.), pressor and positive chronotropic responses to sympathetic stimulation in subsequently pithed animals were not consistently different from saline controls (fig. 3). Pressor responses to AI were markedly reduced by teprotide treatment whereas those to NE and All were not (table 2).

In pithed SHR receiving an intravenous infusion of salalasin (20 μg/kg/min), pressor responses to sympathetic stimulation at the lower frequencies were significantly enhanced and no change was observed in the highest frequency (fig. 3). Positive chronotropic responses were unaltered by salalasin. Pressor responses to AI and All were abolished by salalasin in these rats and to NE were significantly reduced (table 2).

**Effects of Oral Indomethacin and All Infusion Alone and in Combination on Pressor Responses to Sympathetic Stimulation, Norepinephrine, AI and All in Pithed SHR Treated with Captopril**

Pretreatment of SHR with indomethacin (5 mg/kg p.o.) 1 hour after captopril (100 mg/kg p.o.) had no

**TABLE 2. Effects of Teprotide or Saralasin Treatment in Pressor Responses to Norepinephrine, Angiotensins I and II in Pithed SHR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Norepinephrine (1 μg/kg)</th>
<th>Angiotensin II (1 μg/kg)</th>
<th>Angiotensin I (1 μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>45.0 ± 4.2</td>
<td>60.1 ± 5.2</td>
<td>48.6 ± 2.2</td>
</tr>
<tr>
<td>Teprotide (30 mg/kg s.c.)</td>
<td>34.2 ± 2.1</td>
<td>55.3 ± 3.2</td>
<td>6.2 ± 1.0</td>
</tr>
<tr>
<td>Saralasin (20 μg/kg/min)</td>
<td>26.0 ± 2.4</td>
<td>1.8 ± 0.3</td>
<td>1.0 ± 0.4</td>
</tr>
</tbody>
</table>

![Figure 3](http://hyper.ahajournals.org/) Effects of teprotide and Sar^1-Ala^8-All on changes in blood pressure and heart rate to sympathetic stimulation in pithed SHR. See figure 1 for details.

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significant effect on the inhibition of pressor responses to sympathetic stimulation in pithed rats normally observed after captopril alone (fig. 4, compare fig. 1). Moreover, indomethacin had no significant effect on the pressor responses to AI, AII, and NE typically observed after captopril (table 3). Similarly, AII infusion (200 ng/kg/min) in captopril treated SHR at a dose sufficient to raise BP from 42.2 ± 1.7 mm Hg to 71.5 ± 4.2 mm Hg (p < 0.02) had no effect on pressor responses to sympathetic stimulation normally observed after captopril (fig. 4). However, the AII infusion had a significant inhibitory effect on pressor responses to AI and AII but not on NE in captopril treated pithed SHR (table 3).

In contrast, in SHR treated with captopril (100 mg/kg p.o.) the addition of indomethacin (5 mg/kg p.o.) and an infusion of AII (200 ng/kg/min) in subsequently pithed rats totally reversed the normally observed inhibition to sympathetic responses in SHR treated with captopril alone (fig. 5). Positive chronotropic responses to sympathetic stimulation as well as depressor responses to AI, AII, and NE in these rats were no different from those treated only with captopril (fig. 5; table 3).

Effect of Bilateral Nephrectomy on Sympathetic Function in Captopril-Treated SHR

In SHR treated with captopril (100 mg/kg p.o.) and subsequently bilaterally nephrectomized, responses to sympathetic stimulation in these pithed animals were significantly reduced in comparison with untreated bilaterally nephrectomized SHR (fig. 6). Bilateral nephrectomy alone or in combination with captopril had no effect on pressor responses to AII and NE whereas captopril alone, but not bilateral nephrectomy, markedly reduced the AII pressor response (table 4).

Infusion of AII alone (200 ng/kg/min) in nephrectomized SHR previously receiving captopril totally reversed the inhibition of pressor responses to sympathetic stimulation observed in SHR treated with captopril alone (fig. 6). The AII infusion was without effect on the pressor responses to AI and NE usually caused by captopril, but significantly inhibited that to AII (table 4).

**Discussion**

The present study demonstrates that acute administration of captopril can cause inhibition of responses to sympathetic nerve stimulation without in-

**Table 3. Effects of Various Treatments on Pressor Responses to Norepinephrine, Angiotensin I and Angiotensin II in Pithed SHR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Norepinephrine (1 µg/kg)</th>
<th>Angiotensin I (1 µg/kg)</th>
<th>Angiotensin II (1 µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12</td>
<td>45.0 ± 4.2</td>
<td>60.1 ± 5.2</td>
<td>46.6 ± 2.2</td>
</tr>
<tr>
<td>Captopril, (100 mg/kg p.o.)</td>
<td>6</td>
<td>32.3 ± 2.5</td>
<td>49.0 ± 4.1</td>
<td>5.3 ± 1.4</td>
</tr>
<tr>
<td>Captopril + AII infusion</td>
<td>6</td>
<td>26.5 ± 3.8</td>
<td>30.3 ± 3.4</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>AII infusion + indomethacin</td>
<td>6</td>
<td>40.3 ± 2.9</td>
<td>40.5 ± 2.9</td>
<td>27.8 ± 1.5</td>
</tr>
<tr>
<td>Captopril, AII infusion + indomethacin</td>
<td>10</td>
<td>25.4 ± 5.4</td>
<td>32.2 ± 5.6</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>Captopril + indomethacin</td>
<td>6</td>
<td>34.3 ± 4.9</td>
<td>57.8 ± 8.6</td>
<td>7.0 ± 0.6</td>
</tr>
<tr>
<td>AII infusion</td>
<td>6</td>
<td>45.2 ± 4.9</td>
<td>38.2 ± 2.4</td>
<td>23.5 ± 1.5</td>
</tr>
</tbody>
</table>

**FIGURE 4.** Effects of captopril alone (100 mg/kg p.o.), in combination with indomethacin treatment (5 mg/kg p.o.) and during angiotensin II infusion (200 ng/kg/min) on changes in blood pressure and heart rate to sympathetic stimulation in pithed SHR. See figure 1 for details.
Inhibition of the NE-induced pressor response, an effect consistent with a prejunctional inhibition of NE release. The prejunctional effect occurs preferentially at lower doses of captopril and can be totally dissociated from, but also appears to be less prominent than, the postjunctional effect. Furthermore, the prejunctional inhibition of NE release is specific for the vascular system since cardiac responses to sympathetic stimulation were unaltered even at the high doses of captopril given for prolonged periods of time. However, after chronic dosing with high doses of captopril, there was a significant and rather marked inhibition of the postjunctional pressor response to NE as well as to All.

Since captopril is a potent and specific inhibitor of ACE, inhibition of All formation is likely to play a role in the pre- as well as the postjunctional sympathetic inhibition seen in this study. All enhances vasoconstriction and positive chronotropic responses to activation of sympathetic nerves. This enhancement occurs in vitro and in vivo in hind-limb, cutaneous, renal, mesenteric, aortic, and splanchnic vessels as well as in cardiac tissue.\textsuperscript{10-14} Although All may cause an enhancement of the response to exogenous

**TABLE 4. Effects of Various Treatments on Pressor Responses to Norepinephrine, Angiotensin I and Angiotensin II in Pithed SHR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in mean blood pressure to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Norepinephrine (1 µg/kg)</td>
</tr>
<tr>
<td>None</td>
<td>12</td>
</tr>
<tr>
<td>Captopril (100 mg/kg p.o.)</td>
<td>6</td>
</tr>
<tr>
<td>Bilateral nephrectomy</td>
<td>5</td>
</tr>
<tr>
<td>Bilateral nephrectomy + captopril</td>
<td>6</td>
</tr>
<tr>
<td>Bilateral nephrectomy + captopril + All infusion</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angiotensin II (1 µg/kg)</th>
<th>Angiotensin I (1 µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.0 ± 4.2</td>
<td>60.1 ± 5.2</td>
</tr>
<tr>
<td>32.3 ± 2.5</td>
<td>49.0 ± 4.1</td>
</tr>
<tr>
<td>46.0 ± 6.4</td>
<td>61.8 ± 6.6</td>
</tr>
<tr>
<td>37.4 ± 8.9</td>
<td>53.0 ± 10.3</td>
</tr>
<tr>
<td>32.6 ± 4.5</td>
<td>28.6 ± 5.6</td>
</tr>
</tbody>
</table>

\( p < 0.02 \) for all comparisons.
NE, it causes a preferential facilitation of NE release, the consequence of which is the observed enhanced response to sympathetic stimulation. Renin substrate also potentiated vasoconstrictor responses to sympathetic nerve stimulation in isolated rat mesenteric arteries, while causing only a slight increase in the response to injected NE. Furthermore, this enhancement was abolished both by an ACE inhibitor as well as an All antagonist. It was concluded that utilization of renin substrate within the vessel wall by renin or renin-like enzymes resulted in the final formation of All which, in turn, was responsible for the potentiated vasoconstrictor responses, presumably by facilitating NE release. The present results are in accord with these suggestions. Captopril, by inhibiting the formation of All, prevents its facilitatory actions on sympathetic function which results in a preferential prejunctional inhibition of sympathetic responses. Cardiac responses to sympathetic function are unaltered since no renin or All exists in cardiac tissue.

It would be anticipated that if reductions in All formation, either in plasma or the vasculature, were responsible for sympathetic inhibition after captopril, then infusion of All might restore the inhibited responses back to normal. To our surprise, infusion of All alone in a sufficient amount to raise BP did not restore responses to sympathetic nerve stimulation in intact SHR pretreated with captopril. However, indomethacin administered prior to captopril in intact SHR did allow the All infusion to restore the inhibited sympathetic responses normally observed after captopril, whereas indomethacin alone had no effect on these responses. Furthermore, the All infusion fully restored the inhibited sympathetic responses in bilaterally nephrectomized SHR pretreated with captopril. The restored responses were of a prejunctional nature since the pressor responses to exogenous NE were not enhanced with any treatment used.

The restoration of the sympathetic responses by All infusions only in indomethacin pretreated intact SHR receiving captopril suggests that the All infusions alone were releasing prostaglandins (PGs) which were themselves inhibitory to sympathetic nerve stimulation and counteracting the facilitatory effect of All. Furthermore, the PG release caused by All was probably renal in origin since All alone, without indomethacin, was capable of restoring sympathetic responses in bilaterally nephrectomized SHR. The PGs were not involved in the inhibitory effects of captopril alone on sympathetic function since indomethacin alone did not alter the inhibition caused by captopril. All is well known to cause PG release, especially in kidneys, an effect mediated by specific All receptors. Both All pressor responses as well as responses to renal sympathetic nerve stimulation are enhanced by blockade of PG synthesis by indomethacin. Finally, the inhibitory effects of several PGs themselves and enhancement by indomethacin on sympathetic nerve function are well established. Thus, all of our data are quite consistent with the hypothesis linking All infusions with renal PG release and the observed interactions on sympathetic function in captopril-treated SHR.

The specific inhibitory action of captopril on vascular in preference to cardiac sympathetic responses deserves special note since its implications might be far-reaching. Renin or a renin-like enzyme is present in blood vessel walls including arteries and veins. Many experiments have demonstrated the functional importance of the vascular RAS. Evidence that vascular renin may be important in the etiology and/or maintenance of hypertension comes from studies in which the actual concentrations of vascular renin have been measured and All receptor antagonists used. In acute two-kidney RHR in which PRA and vascular renin levels are consistently high, All antagonists and captopril are both effective in reducing BP, an obvious reflection of high circulating All levels. However, in chronic two-kidney RHR in which PRA and All levels are normal, All antagonists are ineffective in decreasing BP. Interestingly, vascular renin levels are elevated in chronic two-kidney RHR and captopril, in contrast to All antagonists, is also effective in reducing BP in this model. This suggests that the vascular RAS is hyperactive and helping to maintain hypertension but inhibited by captopril, which is capable of reaching the appropriate site of action, something that All peptide receptor antagonists and antibodies appear to be incapable of.

As in two-kidney RHR, vascular renin levels are elevated in SHR whereas PRA is not elevated. As in chronic two-kidney RHR, captopril is effective in decreasing BP in SHR whereas All receptor antagonists and antibodies are not. These data further sup-
port the suggestion that accessibility to the vascular RAS is important and possible for captopril but not for AII antagonists. Thus, the heretofore unexplained efficacy of captopril in normoreninemic, two-kidney RHR and SHR may partially be a function of captopril’s accessibility to the vascular RAS, the result of which is reduced AII formation and a concomitant reduction of NE release, and also an inhibition of postjunctional NE pressor responses. In this study, neither the peptide ACE inhibitor teprotide nor the AII peptide antagonist Sar^3-Ala^4-AII had any consistent inhibitory effect on sympathetic function in SHR. Similarly, neither teprotide (not shown) nor Sar^3-Ala^4-AII decreased BP in SHR. This is taken as further indirect evidence that these large peptidic compounds are incapable of reaching appropriate intravascular sites. Furthermore, captopril maintained its inhibitory effects on sympathetic nerve stimulation in bilaterally nephrectomized SHR, strong evidence that the circulating renin-AII system was not the site at which captopril exerted its effects.

The implications of the vascular RAS in hypertension etiology and maintenance alluded to above deserve further comment. There is now little doubt that the sympathetic nervous system plays an important contributory role in the maintenance of two-kidney RHR, a role that grows more important as the duration of hypertension increases. Similarly, the sympathetic nervous system is important in the development as well as the maintenance of hypertension in SHR. Thus, drugs that interfere with sympathetic function are effective in reducing both chronic renal and spontaneous hypertension. The perplexing observation is the ability of captopril to decrease BP in chronic two-kidney RHR and SHR where PRA levels are normal. In addition, captopril prevents the development of both of these forms of hypertension.

If one assumes that the foregoing discussion is reasonable and that the concentration of circulating renin does not necessarily represent the effective concentration at the site of action, namely, the vascular wall, then a link between the RAS and sympathetic nervous system is established, the consequences of which are described diagrammatically in Fig. 7. In acute two-kidney renal hypertension, high PRAs are responsible for the initial BP rise and also for the anticipated effectiveness of both AII receptor antagonists and ACE inhibitors including captopril.

In addition to high PRAs in this model, however, there is also an elevated level of renin in the vasculature. The AII produced in this latter site would raise BP both by directly contracting smooth muscle and indirectly by facilitating NE release, an especially good probability given the location of renin, ACE, and NE terminals in the organization of smooth muscle. As PRA levels decline over time, vascular levels of renin remain elevated and help to maintain hypertension. Now, AII antagonists are ineffective since they cannot penetrate to the source of AII within the vessel wall whereas captopril has accessibility to the site and is consequently effective. A similar scenario could be conceived in SHR, the main difference being that the plasma RAS plays no important role in the maintenance of this form of hypertension. This is supported by the lack of efficacy of AII antagonists as opposed to the well-defined effects of captopril in SHR as well as the lack of effect of bilateral nephrectomy in reducing BP in SHR. It is also interesting to note that in SHR higher oral doses of captopril are required to decrease BP in comparison with RHR, that high intravenous doses of captopril are ineffective in reducing BP, and also that the reductions in BP increase with oral dosage duration. This is indirect evidence that accessibility to a portion of the RAS.
outside of the circulation must be reached and that high concentrations of captopril over long periods of time are the most effective means of doing this.

The proposed hypothesis that the vascular RAS may be functional and important in both renal hypertension and spontaneous hypertension, that it may help maintain hypertension under normal PRA conditions by constricting vessels and facilitating NE release, and that the different effectiveness of AIH antagonists and captopril under certain conditions may be explained in part by their relative abilities to inhibit this vascular system is an attractive one to us. It forms a long sought after link between the sympathetic and RAS at an unexpected though logical site. The importance and confirmation of such a hypothesis are by no means established by this report but, on the contrary, require much more testing before it might be considered as a reasonable one. Furthermore, the postsynaptic inhibitory effects of high doses of captopril on pressor responses to norepinephrine muddles any clear interpretation of the importance of any presynaptic effect of captopril or, indeed, on the entire relevance of AIH formation in its mechanism of action in normoreninemic models of hypertension. Certainly, the lack of antihypertensive action of captopril in DOCA-salt hypertension strengthens the argument against a nonspecific postsynaptic effect of captopril, but more mechanistic studies are necessary before final conclusions are drawn.

References

Pre- and postjunctional inhibition of vascular sympathetic function by captopril in SHR. Implication of vascular angiotensin II in hypertension and antihypertensive actions of captopril.

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Hypertension. 1981;3:154
doi: 10.1161/01.HYP.3.3_Pt_2.154

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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