Long-Term Treatment With Angiotensin Converting Enzyme Inhibitor Restores Reduced Calcitonin Gene-Related Peptide-Containing Vasodilator Nerve Function in Mesenteric Artery of Spontaneously Hypertensive Rats

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Received October 1, 1998 Accepted November 25, 1998

ABSTRACT—Effects of long-term treatment with angiotensin converting enzyme (ACE) inhibitor on decreased function of calcitonin gene-related peptide (CGRP)-containing vasodilator nerves (CGRP nerves) in mesenteric resistance artery were investigated in spontaneously hypertensive rats (SHR). Eight-week-old SHR were treated for 7 weeks with 0.1% captopril, 0.01% temocapril, 0.05% pindolol or 0.005% hydralazine in drinking water. Long-term treatment with each drug significantly lowered mean blood pressure of SHR. In isolated and perfused mesenteric vascular beds with active tone, periartrial nerve stimulation (PNS) (0.5 to 8 Hz) produced frequency-dependent vasodilations, which were abolished by CGRP(8–37) (CGRP-receptor antagonist) and significantly smaller in SHR than in normotensive Wistar Kyoto rats. Treatment of SHR with captopril and temocapril but not with pindolol and hydralazine resulted in significantly greater PNS-induced vasodilation than in non-treated SHR, but ACE-inhibitor treatment did not affect vasodilation induced by exogenous CGRP. In captopril-treated SHR preparations, PNS evoked significantly larger CGRP-like immunoreactive release than in non-treated SHR. In non-treated 15-week-old SHR preparations, direct perfusion of captopril or temocapril (0.1 μM and 1 μM) did not modify frequency-dependent vasodilation in response to PNS. These results suggest that long-term ACE inhibitor treatment prevents or restores CGRP nerve function reduction in SHR.

Keywords: Angiotensin converting enzyme inhibitor, Neurogenic vasodilation, Calcitonin gene-related peptide, Spontaneously hypertensive rat, Mesenteric resistance blood vessel

It is widely accepted that sympathetic adrenergic vasoconstrictor nerves play a major role in maintaining the tone of resistance blood vessels. However, recent studies have revealed nonadrenergic noncholinergic (NANC) vasodilator innervation in blood vessels and the involvement of vasodilator nerves in the regulation of vascular tone (1, 2). We have demonstrated that the mesenteric resistance blood vessels of the rat are innervated by NANC vasodilator nerves in which calcitonin gene-related peptide (CGRP), a potent vasodilator neuropeptide, acts as the vasodilator neurotransmitter (1, 3–5). CGRP-containing vasodilator nerves (CGRP nerves) suppress vasoconstrictor responses to adrenergic nerve stimulation through released CGRP, and conversely, adrenergic nerves inhibit the release of CGRP to decrease the function of CGRP nerves (3–5). Thus, we proposed that CGRP nerves as well as sympathetic vasoconstrictor nerves regulate the tone of mesenteric resistance blood vessels.

Increased total peripheral vascular resistance maintains the elevated blood pressure in chronic hypertension (6, 7); therefore, impairment of the control systems regulating peripheral resistance might be a cause of chronic hypertension (7, 8). In studies with spontaneously hypertensive rats (SHR), the enhanced activity of sympathetic vasoconstrictor nerves has been shown to be an important factor in the increased tone of peripheral resistance vessels (8, 9). We have demonstrated that the function of CGRP nerves in SHR decreases with age, and we previously proposed that the malfunction of CGRP nerves...
involved in peripheral vascular resistance control plays an important role in the development and maintenance of hypertension in SHR (10, 11). However, mechanisms underlying the reduced function of CGRP nerves in SHR remain unresolved. In a preliminary study, we have shown that long-term treatment (7 weeks) with captopril, an angiotensin (Ang)-converting enzyme (ACE) inhibitor, restores the reduced vasodilator response mediated by CGRP nerves in SHR, whereas a calcium antagonist (nicardipine) and beta-adrenoceptor antagonist (propranolol) have no such effect (12). Furthermore, a recent study provided evidence that Ang II in the mesenteric artery of SHR prejunctionally inhibits neurotransmission of CGRP nerves through Ang II receptors (13), suggesting that the renin-angiotensin system might be involved in the reduced function of CGRP nerves in SHR. The present study was, therefore, undertaken to investigate further the effects of long-term treatment with ACE inhibitors (captopril and temocapril) on the function of CGRP nerves in SHR and compare it with treatment with a vasodilator drug (hydralazine) and a β-adrenoceptor antagonist (pindolol).

MATERIALS AND METHODS

Long-term treatment with antihypertensive drugs

Male SHR at 8 weeks of age (purchased from Charles River Japan, Shizuoka) received 0.1% captopril (100 mg/kg/day), 0.05% pindolol (50 mg/kg/day), 0.01% temocapril (10 mg/kg/day) or 0.005% hydralazine (5 mg/kg/day) in their drinking water and normal rat chow. Each SHR received the respective treatment for a period of 7 weeks. Non-treated control SHR and normotensive Wistar Kyoto rats (WKY) received normal drinking water and rat chow.

Mean blood pressure (MBP) measurement

The animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg). The left carotid artery was cannulated and MBP was measured with a pressure transducer (model MPU-0.5A; Nihon Kohden; Tokyo) and recorded on a polygraph (model RM-6000, Nihon Kohden).

Perfusion of mesenteric vascular bed

Under pentobarbital anesthesia, the mesenteric vascular bed was isolated and prepared for perfusion as described previously (1, 3). The isolated mesenteric vascular bed was separated from the intestine by cutting it close to the intestinal wall. Only four main arterial branches from the superior mesenteric trunk running to the terminal ileum were perfused. All other branches of the superior mesenteric artery were tied off. The preparation was perfused with a modified (see below) Krebs-Ringer bicarbonate solution (Krebs’ solution) at a constant flow rate of 5 ml/min with a peristaltic pump (model SJ-1215; ATTO Co., Tokyo). The preparation was also superfused with the same solution at a rate of 0.5 μl/min to prevent drying. Modified Krebs’ solution of the following composition was used: 120.0 mM NaCl, 5.0 mM KCl, 2.4 mM CaCl₂, 1.2 mM MgSO₄, 25.0 mM NaHCO₃, 0.027 mM 2NaEDTA and 11.0 mM dextrose (pH 7.4). The Krebs’ solution was bubbled with a mixture of 95% O₂ - 5% CO₂ before passage through a warming coil maintained at 37°C. Changes in the perfusion pressure were measured with a pressure transducer (model MPU-0.5A, Nihon Kohden).

Periarterial nerve stimulation (PNS) and bolus injection of CGRP

After allowing the basal perfusion pressure to stabilize, the preparation was subjected to PNS at 8 and 12 Hz, which produced an increase in perfusion pressure due to vasoconstriction. PNS was applied for 30 sec through bipolar platinum ring electrodes placed around the superior mesenteric artery. Rectangular pulses of 1 msec in duration and supramaximum voltage (50 V) were applied using an electronic stimulator (model SEN 3301, Nihon Kohden). The preparations were then contracted with methoxamine at a submaximal concentration of 7 μM in the presence of 5 μM guanethidine, which was added to block adrenergic neurotransmission. The increased perfusion pressure was allowed to stabilize and preparations were then subjected to PNS at 0.5, 1, 2, 4 and 8 Hz, producing a perfusion pressure decrease due to vasodilation. After the decrease in perfusion pressure induced by 8 Hz PNS returned to prestimulation levels, 10 and 100 pmol CGRP were directly injected into the perfusate proximal to the arterial cannula using an injection pump (model 975; Harvard Apparatus, South Natick, MA, USA). The volume of the injection was 100 μl over 10 sec.

In separate experiments, the final concentrations of captopril or temocapril diacid (active form of temocapril), diluted with Krebs’ solution containing methoxamine and guanethidine, was perfused in preparations isolated from non-treated 15-week-old SHR, and PNS was applied to the preparations for 30 sec at 0.5 to 8 Hz.

At the end of each experiment, 100 μM papaverine was perfused through the preparations to produce complete relaxation. Vasodilation was expressed as a percentage of the maximum relaxation induced by papaverine.

Release of CGRP-like immunoreactivity (CGRP-LI)

Mesenteric vascular beds isolated from 15-week-old SHR treated with 0.1% captopril and age-matched non-treated SHR were perfused with Krebs’ solution containing 7 μM methoxamine and 5 μM guanethidine at a con-
stant flow rate of 5 ml/min and superfused with Krebs' solution (0.5 ml/min). The perfusate was collected for 5 min before and after PNS at 4 and 8 Hz for 30 sec. Each sample was applied to a Sep-Pak C18 cartridge (Waters Associates, Milford, MA, USA), and the absorbed peptides were eluted with 3 ml of 60% acetonitrile in 0.1% trifluoroacetic acid. The eluates were evaporated under a vacuum and stored at −80°C until they were radioimmunoassayed for CGRP as described previously (10). The lower detection limit was 1 fmol/tube for CGRP-LI.

**Statistical analyses**

Experimental results are presented as the mean ± S.E.M. One-way analysis of variance (ANOVA) followed by Dunnett’s test was used to determine the significance between values of different doses or groups. The unpaired Student’s t-test was used to determine the significance of difference between two means. A value of P<0.05 was considered statistically significant.

**Drugs**

The following drugs were used: captopril, temocapril and temocapril diacid (active form of temocapril) (Sankyo Pharmaceutica, Tokyo); guanethidine sulfate (Tokyo Kasei, Tokyo); human CGRP (8-37) and rat α-CGRP (Peptide Institute, Osaka); hydralazine HCl, pindolol and tetrodotoxin (TTX) (Sigma Chemical Co., St. Louis, MO, USA); and methoxamine HCl (Nihon Shinyaku, Kyoto). Captopril, hydralazine and pindolol were dissolved in drinking water at the final concentrations of 0.1%, 0.005% and 0.05%, respectively. Temocapril was dissolved at the final concentration of 0.01% in drinking water containing 0.1% NaHCO₃ and 0.1% KHCO₃. All other drugs were dissolved in distilled water and diluted with Krebs' solution containing 7 μM methoxamine and 5 μM guanethidine, when perfused or injected directly.

**RESULTS**

**MBP of perfused mesenteric vascular bed and vasoconstrictor responses to PNS and to perfusion of methoxamine following long-term treatment with antihypertensive drug**

As shown in Table 1, MBP in SHR was lowered by long-term treatment with captopril, temocapril, pindolol or hydralazine, as compared with non-treated and vehicle-treated SHR. Significant differences were found between non-treated SHR and captopril-, hydralazine- or pindolol-treated SHR. Significant differences were also found between vehicle-treated SHR and temocapril-treated SHR.

There were no significant differences in mean perfusion pressure between non- or vehicle-treated SHR and antihypertensive drug-treated SHR or between non-treated SHR and WKY (Table 1).

In perfused mesenteric vascular beds with resting tone, PNS at 8 and 12 Hz induced a frequency-dependent increase in perfusion pressure due to vasoconstriction. This response to PNS was abolished by 100 nM TTX and 5 μM guanethidine (data not shown), indicating that sympathetic adrenergic nerves mediate the response. As shown in Table 2, the PNS-induced pressor response at 12 Hz but not 8 Hz in non-treated SHR was significantly greater than that in WKY. PNS at 12 Hz after long-term treatment with 0.1% captopril induced significantly smaller pressor responses than in non-treated SHR. PNS of 0.05%-pindolol-treated SHR preparations caused a greater pressor response than in non-treated SHR. However, there was no significant difference between

<table>
<thead>
<tr>
<th>Treatments</th>
<th>n</th>
<th>Mean blood pressure (mmHg)</th>
<th>Mean perfusion pressure (mmHg)</th>
<th>Pressor response to methoxamine (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treated SHR</td>
<td>14</td>
<td>164.6±4.7</td>
<td>33.5±0.9</td>
<td>90.7±8.2</td>
</tr>
<tr>
<td>0.1% Captopril</td>
<td>10</td>
<td>113.7±6.3**</td>
<td>31.5±1.6</td>
<td>69.8±8.1</td>
</tr>
<tr>
<td>0.05% Pindolol</td>
<td>6</td>
<td>139.8±6.6*</td>
<td>37.0±1.0</td>
<td>109.2±8.8</td>
</tr>
<tr>
<td>0.005% Hydralazine</td>
<td>6</td>
<td>119.7±12.1**</td>
<td>33.2±2.4</td>
<td>69.0±5.1</td>
</tr>
<tr>
<td>Vehicle-treated SHR</td>
<td>7</td>
<td>153.9±7.1</td>
<td>34.3±1.6</td>
<td>81.2±9.9</td>
</tr>
<tr>
<td>0.01% Temocapril</td>
<td>8</td>
<td>123.8±8.3†</td>
<td>33.5±1.8</td>
<td>72.9±5.9</td>
</tr>
<tr>
<td>WKY</td>
<td>5</td>
<td>94.0±8.3**</td>
<td>37.1±4.4</td>
<td>35.5±7.1**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, compared with non-treated control SHR (Dunnett’s test). †P<0.05, compared with vehicle (0.1% NaHCO₃ + 0.1% KHCO₃)-treated SHR (Student’s t-test). WKY, normotensive Wistar Kyoto rats.
Table 2. Effects of long-term treatment with antihypertensive drugs on vasoconstrictor responses to periarterial nerve stimulation (PNS) and vasodilator responses to a bolus injection of calcitonin gene-related peptide (CGRP) in perfused mesenteric vascular beds of spontaneously hypertensive rats (SHR)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>n</th>
<th>Vasoconstrictor responses to PNS (mmHg)</th>
<th>Vasodilator responses to CGRP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8 Hz</td>
<td>12 Hz</td>
</tr>
<tr>
<td>Non-treated SHR</td>
<td>14</td>
<td>20.2±3.1</td>
<td>54.4±8.0</td>
</tr>
<tr>
<td>0.1% Captopril</td>
<td>10</td>
<td>8.1±1.2*</td>
<td>24.1±4.1*</td>
</tr>
<tr>
<td>0.05% Findolol</td>
<td>6</td>
<td>27.0±4.7</td>
<td>81.4±13.2</td>
</tr>
<tr>
<td>0.005% Hydralazine</td>
<td>6</td>
<td>29.8±3.4</td>
<td>60.2±5.8</td>
</tr>
<tr>
<td>Vehicle-treated SHR</td>
<td>7</td>
<td>25.2±4.3</td>
<td>59.8±11.2</td>
</tr>
<tr>
<td>0.01% Temocapril</td>
<td>8</td>
<td>19.4±2.0</td>
<td>45.2±4.3</td>
</tr>
<tr>
<td>WKY</td>
<td>5</td>
<td>10.9±2.9*</td>
<td>22.0±3.9*</td>
</tr>
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</table>

*P<0.05, **P<0.01, compared with non-treated control SHR (Dunnett's test). WKY, normotensive Wistar Kyoto rats.

A. Control SHR

![Graph showing vasoconstrictor and vasodilator responses to methoxamine and guanethidine in control SHR.]

B. Captopril-treated SHR

![Graph showing vasoconstrictor and vasodilator responses to methoxamine and guanethidine in captopril-treated SHR.]

C. Hydralazine-treated SHR

![Graph showing vasoconstrictor and vasodilator responses to methoxamine and guanethidine in hydralazine-treated SHR.]

Fig. 1. Typical records showing effects of long-term treatment with captopril and hydralazine on vasodilator responses to periarterial nerve stimulation (PNS) in perfused mesenteric vascular beds of spontaneously hypertensive rats (SHR) with active tone produced by 7 μM methoxamine and 5 μM guanethidine. A: non-treated control SHR. B: 0.1% captopril-treated SHR. C: 0.005% hydralazine-treated SHR. PNS was applied at the closed triangles. Drugs were administered in drinking water for 7 weeks from 8 weeks of age. PPV: 100-μM papaverine perfusion.
pindolol-treated and non-treated SHR. Treatment with 0.005% hydralazine in SHR did not cause any significant changes in PNS-induced pressor responses.

Effects of long-term treatment with antihypertensive drugs on vasodilator responses to PNS or bolus injection of CGRP

The active tone of perfused mesenteric vascular beds isolated from non-treated and drug-treated SHR was

Fig. 2. Effects of long-term treatment with hydralazine (upper left), pindolol (upper right), captopril (lower left) and temocapril (lower right) on vasodilator responses to periarterial nerve stimulation (PNS) in mesenteric vascular beds of spontaneously hypertensive rats (SHR). The active tone was produced by 7 µM methoxamine and 5 µM guanethidine. The 0.005% hydralazine, 0.05% pindolol, 0.1% captopril and 0.01% temocapril were administered in drinking water for 7 weeks from 8 weeks of age. *P<0.05, **P<0.01, as compared with non-treated control SHR or vehicle (0.1% NaHCO₃ + 0.1% KHCO₃)-treated SHR (Dunnett’s test). WKY, non-treated normotensive Wistar Kyoto rats. Relaxation is expressed as a percentage of the maximum relaxation induced by perfusion of 100 µM papaverine at the end of the experiment.
produced by continuous perfusion of 7 μM methoxamine in the presence of 5 μM guanethidine. There was no significant difference in vasoconstrictor responses to methoxamine between non- or vehicle-treated SHR and antihypertensive drug-treated SHR (Table 1). In WKY, the methoxamine-induced vasoconstriction was significantly smaller than in that non-treated SHR (Table 1).

In preparations from non-treated SHR, PNS at 0.5 to 8 Hz caused a frequency-dependent decrease in perfusion pressure due to vasodilatation (Fig. 1A), which was abolished by the perfusion of 100 nM TTX (neurotoxin) or 500 nM CGRP(8–37) (CGRP-receptor antagonist) (data not shown).

Vasodilations in response to PNS in non-treated SHR preparations were significantly smaller than those in WKY preparations (Fig. 2).

As shown Figs. 1B and 2, vasodilator responses to PNS in the preparation isolated from captopril- or temocapril-treated SHR were similar in magnitude compared to the PNS-induced responses from age-matched WKY and significantly greater than those in non-treated SHR. However, long-term treatment with pindolol or hydralazine did not affect vasodilator responses to PNS, as shown in Figs. 1C and 2.

Bolus injections of CGRP at concentrations of 10 and 100 pmol produced a long-lasting depressor response, which mimicked PNS-induced vasodilatation and was blocked by CGRP(8–37) (data not shown). The vasodilator response to 100 pmol CGRP injection in hydralazine-treated SHR was significantly smaller than that in control SHR (Table 2). However, there were no significant differences in CGRP-induced vasodilatation between non-treated SHR and drug-treated SHR or between vehicle- and temocapril-treated SHR (Table 2).

**Effect of long-term treatment with captopril on CGRP-LI release induced by PNS**

As shown in Table 3, PNS (4 and 8 Hz) of perfused mesenteric vascular beds isolated from non-treated SHR evoked a frequency-dependent release of CGRP-LI into the perfusate. We have found that this release is abolished both by TTX and by calcium removal from the medium and the release is smaller in SHR than in WKY (10). In preparations treated with captopril, CGRP-LI release induced by PNS at 4 and 8 Hz was significant greater than that in non-treated SHR (Table 3).

**Effect of direct perfusion of ACE inhibitors on the PNS-induced vasodilatation**

In preparations from non-treated SHR at 15 weeks of age, perfusion of captopril or temocapril at concentrations of 0.1 and 1 μM did not modify frequency-dependent vasodilatation in response to PNS, as shown in Fig. 3.

**DISCUSSION**

The present study, in agreement with previous studies, has shown that in both SHR and WKY, PNS of perfused mesenteric vascular beds with active tone produced by methoxamine in the presence of guanethidine results in a frequency-dependent decrease in perfusion pressure due to vasodilatation (10). This vasodilatation is sensitive to the neurotoxin TTX and the CGRP-receptor antagonist CGRP(8–37), and PNS evokes a TTX-sensitive release of CGRP-LI (5, 11), indicating that this PNS-induced response is mediated by endogenous CGRP released from CGRP nerves. Furthermore, vasodilatation in response to PNS is significantly less in SHR than in WKY in accordance with previous findings (10). We have reported that both CGRP nerve-mediated vasodilatation and PNS-induced CGRP-LI release in SHR are smaller than in WKY and both phenomena decrease with age (10, 11). Moreover, the previous study has shown that the mesenteric arteries of 15 and 30-week-old SHR have a lower density of CGRP-LI-containing fibers compared with age-matched WKY and 8-week-old SHR (10). Taken together, this evidence strongly suggests that the function of CGRP vasodilator nerves in the mesenteric resistance blood vessel of SHR decreases with age.

In the present study, the long-term treatment of SHR for 7 weeks with the ACE inhibitors (captopril and temocapril) but not with the vasodilator (hydralazine) and the β-adrenoceptor antagonist (pindolol) resulted in a greater PNS-induced vasodilator response than in non-treated SHR. In ACE inhibitor-treated SHR, the neurogenic vasodilatation level was similar to the level in WKY.

Table 3. Effect of long-term treatment with 0.1% captopril on the release of CGRP-like immunoreactivity (CGRP-LI) induced by periarterial nerve stimulation in (PNS) perfused mesenteric vascular beds of the spontaneously hypertensive rats (SHR) at 15 weeks of age

<table>
<thead>
<tr>
<th></th>
<th>Non-treated SHR (fmol/ml)</th>
<th>Captopril-treated SHR (fmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=7</td>
<td>n=5</td>
</tr>
<tr>
<td>Pre-PNS</td>
<td>0.419±0.076</td>
<td>0.387±0.033</td>
</tr>
<tr>
<td>PNS (4 Hz)</td>
<td>0.778±0.100</td>
<td>1.153±0.248</td>
</tr>
<tr>
<td>Net-release</td>
<td>0.359±0.065</td>
<td>0.781±0.233*</td>
</tr>
<tr>
<td>Pre-PNS</td>
<td>0.624±0.150</td>
<td>0.415±0.034</td>
</tr>
<tr>
<td>PNS (8 Hz)</td>
<td>1.314±0.253</td>
<td>1.648±0.133</td>
</tr>
<tr>
<td>Net-release</td>
<td>0.703±0.143</td>
<td>1.233±0.125**</td>
</tr>
</tbody>
</table>

*S* spontaneous release of CGRP-LI before PNS. **CGRP-LI release during PNS. ‡CGRP-LI release minus spontaneous release. *P<0.05. **P<0.01, compared with non-treated SHR (Student's t-test).
Modification of PNS-induced vasodilation by long-term ACE inhibitor use is not a result of lowered blood pressure as neither hydralazine nor pindolol affects PNS-induced vasodilation in spite of lowering MBP in SHR. Thus, it seems likely that long-term ACE inhibitor treatment restores and prevents the reduction in CGRP nerve function in SHR.

Previous studies have shown that long-term treatment with ACE inhibitors (captopril and cilazapril) but not hydralazine restores the decreased function of vascular endothelium in SHR because ACE inhibitor treatment enhances acetylcholine-induced endothelium-dependent relaxation in the aorta (14). In addition, captopril treatment prevents hypertrophy of the medial wall in the small mesenteric artery and an increase in the number of smooth cell layers in the large mesenteric artery (15). These findings raise the possibility that ACE inhibitor treatment increases the smooth muscle relaxability of SHR. However, vasorelaxation induced by a bolus injection of CGRP was found to be similar in ACE inhibitor-treated and non-treated SHR. The mesenteric vasorelaxation induced by CGRP is independent of the endothelium (16). Therefore, the present results suggest that the facilitatory effect of long-term captopril and temocapril treatment on CGRP nerve-mediated vasorelaxation in response to PNS is due to altering the function of CGRP nerves. This is supported by the present finding that neurogenic release of CGRP-LI in response to PNS is enhanced by long-term captopril treatment.

Captopril has been shown to cause a prejunctional inhibition of noradrenaline release in response to adrenergic nerve stimulation by preventing formation of Ang II, which facilitates adrenergic neurotransmission (17). The present finding that long-term treatment with ACE inhibitors resulted in a reduced vasoconstriction in response to PNS, which is mediated by activation of sympathetic adrenergic nerves, may be attributed to the sympathoinhibitory effect of ACE inhibitors on the vascular system. Long-term sympathectomy by use of guanethidine in developing rats has been shown to cause a marked increase in CGRP-containing nerve fiber density (18, 19). We have previously reported that sympathetic adrenergic nerves, through released neurotransmitter noradrenaline and neuropeptide Y, prejunctionally suppresses CGRP nerve function (5, 10). Furthermore, we have shown that both circulatory Ang II and Ang II locally converted from Ang I or renin substrate (N-acetyl tetradecapeptide) in the mesenteric artery of SHR prejunctionally inhibits neurotransmission of CGRP nerves through Ang II receptors (13). Therefore, it seems likely that the increased vasodilation mediated by CGRP nerves following long-term ACE inhibitor treatment is
due to ACE inhibitors suppressing sympathetic nerve function and conversion into Ang II.

Recently, evidence for the existence of a local renin-angiotensin system in blood vessel walls has been found (20–23). Such a system could synthesize and release Ang II, exerting local autocrine-paracrine influences on vascular and periarial nerve function (24, 25). Although renin, which is synthesized in blood vessel walls and partly taken up from plasma (26, 27), increases in the SHR vasculature (28), there is little evidence for increased production of Ang II in SHR blood vessels (29). This is supported by our observation that direct perfusion of ACE inhibitor into the mesenteric artery of non-treated SHR has no effect on vasodilation mediated by CGRP nerves. On the other hand, there is evidence that Ang II receptor sensitivity is enhanced in the mesenteric artery of SHR (9, 25, 30). In a preliminary study, we have shown that long-term treatment with an Ang II receptor I antagonist (TCV-116) restored the decreased CGRP nerve functions in SHR as ACE inhibitors did (31). Thus, either Ang II converted in blood vessel walls or enhanced sensitivity to Ang II receptors seems to be responsible for reduction of CGRP nerve function in the SHR mesenteric vasculature.

In conclusion, ACE inhibitors have the ability to restore or prevent the reduction of CGRP nerve function in SHR. It is also suggests that Ang II locally converted in the mesenteric vasculature is essential for inhibition of CGRP-containing vasodilator nerve function.

Acknowledgments

This study was supported by Grants-in-Aid (03671100, 08672611, 09672326, 10557244) for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

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