Vasodepressor Actions of Angiotensin-(1–7) Unmasked During Combined Treatment With Lisinopril and Losartan

Shridhar N. Iyer, Mark C. Chappell, David B. Averill, Debra I. Diz, Carlos M. Ferrario

Abstract—Blockade of angiotensin II (Ang II) function during 8 days of oral therapy with lisinopril (20 mg/kg) and losartan (10 mg/kg) normalized the arterial pressure (112±3/70±3 mm Hg) and raised the plasma concentrations of the vasodilator peptide angiotensin-(1–7) [Ang-(1–7)] of 21 male spontaneously hypertensive rats (SHR). Treated animals were then given a 15-minute infusion of either mouse immunoglobulin G, or a specific monoclonal Ang-(1–7) antibody while their blood pressure and heart rate were recorded continuously in the awake state. The concentrations of Ang II and Ang-(1–7) in arterial blood were determined by radioimmunoassay. Infusion of the Ang-(1–7) antibody caused significant elevations in mean arterial pressure that were sustained for the duration of the infusion and were accompanied by transient bradycardia. Although the hemodynamic effects produced by infusion of the Ang-(1–7) antibody had no effect on plasma levels of Ang II, they caused a twofold rise in the plasma concentrations of Ang-(1–7). A pressor response of similar magnitude and characteristics was obtained in a separate group of SHR, treated with the combination of lisinopril and losartan for 8 days during an infusion of [Sar1-Thr8]Ang II. The pressor response induced by the administration of this competitive, non–subtype-selective Ang II receptor blocker was not modified by pretreatment of the rats with an angiotensin type-2 (AT2) receptor blocker (PD123319). Plasma concentrations of Ang II and Ang-(1–7) were not changed by the administration of [Sar1-Thr8]Ang II either in the absence or in the presence of PD123319 pretreatment. These results are the first to indicate an important contribution of Ang-(1–7) in mediating the vasodilator effects caused by combined inhibition of angiotensin-converting enzyme and AT1 receptors. The comparable results obtained by administration of [Sar1-Thr8]Ang II suggest that the vasodepressor effects of Ang-(1–7) during the combined treatment is modulated by a non-AT1/AT2 angiotensin subtype receptor. (Hypertension. 1998;31:699–705.)

Key Words: angiotensin-(1–7) ■ angiotensin peptides ■ receptors, angiotensin ■ blood pressure ■ losartan ■ renin-angiotensin system

Previous studies from this laboratory showed that the heptapeptide Ang-(1–7) is a biologically active component of the renin-angiotensin system that acts to oppose the pressor and proliferative actions of Ang II by stimulation of vasodilator prostaglandins, increased production of nitric oxide, or both. The vasodepressor actions of Ang-(1–7) are particularly distinct in conditions of high plasma renin activity, a finding that suggests that this heptapeptide may oppose the hypertensive actions of Ang II. Characterization of the enzymatic pathways responsible for the synthesis and metabolism of Ang-(1–7) provides additional evidence for this proposal. Ang-(1–7) is generated from Ang I by tissue-specific endopeptidases and from Ang II by a postproline carboxypeptidase. Ang-(1–7) is catabolized into smaller fragments [Ang-(2–7) and Ang-(3–7)] by aminopeptidases and into Ang-(1–5) by ACE. Characterization of the metabolic pathways leading to the formation and catabolism of the heptapeptide led to the demonstration that ACE inhibition is associated with significant increases in the circulating levels of Ang-(1–7). Because the hemodynamic and hormonal effects produced by Ang-(1–7) resemble those produced during chronic blockade of ACE, we evaluated whether high circulating levels of Ang-(1–7) may contribute to the normalization of arterial pressure. To test this hypothesis, we measured the effect of endogenous neutralization of circulating Ang-(1–7) on the blood pressure of SHR treated with a combination of an ACE inhibitor and an Ang II subtype 1 receptor antagonist for 9 days before experimentation.

Methods

Studies were performed in 27 12-week-old male SHR (273±6 g, Charles River Laboratories Inc), housed individually in a room maintained at 22°C with a 12-hour light/dark cycle. Animals were fed rat chow (Purina Mills Inc) that provided a daily intake of 17 mmol of sodium and 28 mmol of potassium per 100 g of solid weight. Experiments were performed in accordance with the guidelines of the Animal Care and Use Committee of the Bowman Gray School of Medicine.

Twenty-one rats were medicated with a combination of lisinopril and losartan potassium, whereas 6 other rats were medicated with losartan only. All drugs were given per os for 9 days by dissolving the stock solution into the drinking tap water. The concentration of the...
**Selected Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>Ang I, II</td>
<td>angiotensin I, II</td>
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<tr>
<td>Ang-(1–5)</td>
<td>angiotensin-(1–5)</td>
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<td>Ang-(1–7)</td>
<td>angiotensin-(1–7)</td>
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<td>Ang-(2–7)</td>
<td>angiotensin-(2–7)</td>
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<tr>
<td>Ang-(3–7)</td>
<td>angiotensin-(3–7)</td>
</tr>
<tr>
<td>Ang-(1–7)-Ab</td>
<td>monoclonal angiotensin-(1–7) antibody</td>
</tr>
<tr>
<td>AT1</td>
<td>angiotensin type-1 receptor</td>
</tr>
<tr>
<td>AT2</td>
<td>angiotensin type-2 receptor</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>[Sar1-Thr8]Ang II</td>
<td>Sarthran</td>
</tr>
<tr>
<td>SHR</td>
<td>spontaneously hypertensive rat(s)</td>
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</tbody>
</table>

**Animal Protocols**

On day 8 of the treatment period, a plastic catheter (PE-50, Clay Adams, Becton Dickinson) was implanted under aseptic conditions into a carotid artery of rats given inhalation anesthesia (1% halothane, Ayerst Laboratories Inc, in 95% O2/5% room air). A second PE-50 catheter was implanted into a jugular vein. The free end of each catheter was tunneled cephalad and exteriorized at the nape of the neck. Direct measurements of arterial pressure and heart rate were obtained in awake, freely moving rats 24 hours later. On the day of the experiment, arterial pressure was recorded continuously with a strain-gauge transducer (Unflow Pressure Transducer, Baxter Healthcare Corp) connected to the arterial line. The electronic signal was directed to an analog-to-digital converter for beat-by-beat analysis of arterial pressure and heart rate as described in detail elsewhere.

**Angiotensin Assays**

Plasma concentrations of Ang II and Ang-(1–7) were determined as described previously. Arterial blood was collected in a cocktail of protease inhibitors (25 mmol/L EDTA, 0.44 mmol/L a-phenanthroline, and 0.12 mmol/L pepstatin A). Plasma was extracted using Sep-Pak columns activated with 5-mL sequential washes of a mixture of ethyl alcohol/water/4% acetic acid (83:13:4), methanol, ultrapure water, and 4% acetic acid. After the sample was applied to the column, it was washed with ultrapure water and acetone and eluted with 2.1 mL and 1.15 mL washes of a mixture of ethanol/water/4% acetic acid. The sample was reconstituted in assay buffer. Ang II was measured using the Nichols Institute radioimmunoassay, whereas Ang-(1–7) was detected using an antibody characterized by us in detail previously.

**Statistical Analysis**

Data are expressed as mean±SEM and analyzed by repeated measures ANOVA followed by Scheffe’s test. A value of P<.05 was considered statistically significant.

**Results**

**Characterization of the Ang-(1–7)-Ab**

Fig 1 shows that the antibody produced by the G3-A10 clone was selective for Ang-(1–7). Among the various peptides tested for displacement of [125I]Ang-(1–7), the native peptide showed the lowest IC50 value (0.12 pmol). In comparison to Ang-(1–7), the N-terminal fragments Ang-(2–7) and Ang-(3–7) exhibited a cross-reactivity of 1.25% (IC50 of 7.5 pmol) and 0.63% (IC50 of 20.0 pmol), respectively. Ang II and Ang I displayed significantly lower cross-reactive values, averaging 0.06% (IC50 of 200 pmol) and 0.005% (IC50 of 2.7 nmol), respectively.
the N-terminal and C-terminal sites of Ang-(1–7) were recognized by the monoclonal antibody.

**Neutralization of Endogenous Ang-(1–7)**

Tail-cuff systolic blood pressure of SHR before initiation of treatment averaged 180 ± 2 mm Hg. Group systolic and diastolic pressures averaged 112 ± 3 mm Hg and 70 ± 3 mm Hg (n = 21), respectively, at day 9 after initiation of the combined therapy (lisinopril and losartan). In all experiments, injection of Ang II (0.1 μmol/kg) did not elicit an increase in blood pressure, a finding that confirmed that the doses of losartan consumed by the rats as a part of the cotreatment protocol were sufficient to block the binding of Ang II to AT1 receptors.

Table 1 summarizes group baseline values of arterial pressure, heart rate, and plasma concentrations of Ang II and Ang-(1–7) in awake SHR treated with the combination of lisinopril and losartan. The combined treatment normalized the blood pressure of SHR, and this normalization was associated with high plasma concentrations of Ang-(1–7) but not Ang II. Fig 2 shows the changes in mean arterial pressure and heart rate produced by the infusion of either the Ang-(1–7)-Ab or IgG1 in lisinopril-losartan–treated SHR. Administration of the monoclonal Ang-(1–7)-Ab resulted in a rapid and significant increase in mean arterial pressure that peaked within 1 minute after starting the infusion and amounted to an average rise of 19 ± 3% above basal values. The elevation in mean arterial pressure produced by endogenous neutralization of Ang-(1–7) was primarily caused by a rise in diastolic blood pressure averaging 14 ± 2 mm Hg, whereas systolic blood pressure rose by 9 ± 2 mm Hg. The pressor response produced by endogenous neutralization of Ang-(1–7) lasted throughout the 15-minute infusion and was associated with a transient decrease in heart rate (Fig 2). An infusion of comparable amounts of a purified IgG1 had no effect on the arterial pressure and heart rate of chronically treated SHR (Fig 2).

A separate group of SHR similarly treated with the combination of lisinopril and losartan was given [Sar-Thr]

**TABLE 1. Baseline Values in Awake SHR After 8-Day Treatment With Lisinopril and Losartan**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Values</th>
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<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112 ± 3</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 ± 3</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>86 ± 2</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>375 ± 9</td>
</tr>
<tr>
<td>Plasma Ang II concentration, pmol/L</td>
<td>31 ± 1</td>
</tr>
<tr>
<td>Plasma Ang-(1–7) concentration, pmol/L</td>
<td>223 ± 22</td>
</tr>
<tr>
<td>Plasma Ang-(1–7)/Ang II ratio</td>
<td>7.30 ± 2.00</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
</tr>
</tbody>
</table>

Figure 1. Specificity of the Ang-(1–7) monoclonal G3-A10 antibody. Competing ligands for [125I]Ang-(1–7) binding include Ang-(1–7), Ang-(2–7), Ang-(3–7), Ang II, Ang I, bradykinin (BK), and vasopressin (VP). The binding data were analyzed and fit to a one-site competition curve using the GraphPad Prism-plotting and statistical program.

Figure 2. Time course of the changes in mean arterial pressure (MAP) and heart rate (HR) during the infusion of 400 μg/min of either a specific Ang-(1–7) monoclonal antibody (○, ———) or the control IgG1 (•, ——–) at a rate of 50 μL/min in awake SHR receiving oral therapy with lisinopril and losartan for 8 days before experimentation. Baseline values for MAP and HR for the group of 6 rats given the Ang-(1–7) antibody are 91 ± 4 mm Hg and 345 ± 22 bpm, respectively. Group baseline values for 5 SHR given the IgG1 control are 94 ± 5 mm Hg and 378 ± 8 bpm, respectively.
(16±2% above baseline values) and duration with the changes obtained in the group of chronically treated SHR given the Ang-(1–7)-Ab (Fig 2). As in the group of rats given the Ang-(1–7)-Ab, SHR given [Sar1-Thr8]Ang II but not PD123319 showed a statistically significant greater rise in diastolic (+14±2 mm Hg) than in systolic arterial pressure (+7±1 mm Hg).

Administration of PD123319 had no effect on the baseline mean arterial pressure (78±2 mm Hg before and 78±2 mm Hg 1 hour after, P>.05) and heart rate (394±11 bpm before and 385±12 bpm 1 hour after, P>.05) of lisinopril-losartan–treated SHR. Subsequent infusion of [Sar1-Thr8]Ang II in treated SHR administered PD123319 produced an increase in mean arterial pressure of a magnitude that did not differ from that recorded in treated SHR given the vehicle (Fig 3). In SHR given PD123319 before administration of [Sar1-Thr8]Ang II, the elevations in systolic and diastolic arterial pressures averaged +9±2 mm Hg and +18±3 mm Hg, respectively (P<.05). Neither the peak increase in mean arterial pressure (19±2% above baseline values) nor the characteristics of the pressor response elicited by the infusion of [Sar1-Thr8]Ang II in PD123319-treated SHR were different than those obtained in SHR given the vehicle (Fig 3). The changes in heart rate that accompanied the pressor response elicited by the infusion of [Sar1-Thr8]Ang II were not statistically significant in PD123319-treated SHR (Fig 3). To test for the possibility that the pressor response to [Sar1-Thr8]Ang II was caused by the known agonist activity of this peptide antagonist, [Sar1-Thr8]Ang II (80μmol/kg per minute) was injected into a vein of SHR treated with only losartan for 8 days (n=6). Mean arterial pressure was not changed significantly (+2±1 mm Hg, P>.05) by a 15-minute intravenous infusion of [Sar1-Thr8]Ang II at the highest dose tested (80μmol/kg per minute).

Plasma levels of Ang-(1–7) and Ang II before and after infusions of either the Ang-(1–7)-Ab or IgG1 are shown in Table 2. The infusion of the Ang-(1–7)-Ab produced a twofold increase in plasma levels of Ang-(1–7), whereas plasma levels of Ang II did not change. In contrast, the infusion of IgG1 did not alter plasma levels of either Ang-(1–7) or Ang II.

Table 3. The infusion of the Ang-(1–7)-Ab produced a statistically significant greater rise in mean arterial pressure (MAP) and heart rate (HR) in the subgroup of 5 SHR chronically treated with the combination of lisinopril and losartan and given vehicle with 80±2 mm Hg and 384±20 bpm, respectively. Baseline values for MAP and HR for the subgroup of a separate 5 SHR given PD123319 before the injection of [Sar1-Thr8]Ang II are 76±4 mm Hg and 386±15 bpm, respectively. Differences in baseline values between SHR receiving either vehicle or PD123319 were not statistically significant (P>.05).

**Table 2.** Effect of Ang-(1–7)-Ab on Plasma Levels of Ang-(1–7) and Ang II

<table>
<thead>
<tr>
<th></th>
<th>IgG1 Infusion</th>
<th>Ang-(1–7)-Ab</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Plasma Ang-(1–7), pmol/L</td>
<td>188±18</td>
<td>420±18</td>
</tr>
<tr>
<td>Plasma Ang II, pmol/L</td>
<td>40±5</td>
<td>38±5</td>
</tr>
</tbody>
</table>

Data are mean±SEM. *P<.05 compared with before.
mimics the effects of the Ang-(1–7)-Ab suggests that the antihypertensive actions of Ang-(1–7) are mediated by a non-AT1/AT2 receptor subtype. Collectively, the results of the present studies add support to the concept that Ang-(1–7) counterbalances the pressor actions of Ang II.13

Although [Sar-Thr]Ang II effectively antagonized the actions of Ang-(1–7), its nonselective affinity for the AT1 and AT2 receptor subtypes impeded characterization of a specific role of Ang-(1–7) in the regulation of blood pressure. To circumvent this problem, we first evaluated the physiological actions of Ang-(1–7) with a purified anti-Ang-(1–7) polyclonal antibody. In these experiments, we showed that neutralization of endogenous brain Ang-(1–7) elicited a dose-dependent increase in the arterial pressure of transgenic hypertensive rats both in the absence and in the presence of lifetime treatment with lisinopril.12 These data encouraged us to obtain a monoclonal antibody to Ang-(1–7) in order to enhance its specificity and provide a reliable and constant source of material in amounts greater than those resulting from the harvesting of polyclonal antibodies. The monoclonal antibody used in these experiments has a high affinity for Ang-(1–7), possesses little or no cross-reactivity with other angiotensin fragments (including Ang II), and does not bind to either bradykinin or vasopressin.

Infusion of the Ang-(1–7)-Ab in treated SHR elicited a prominent pressor response associated with transient bradycardia and increased levels of plasma Ang-(1–7). These effects were not duplicated by administration of IgG1. Although we did not perform a dose-response curve for the effect of increasing doses of the Ang-(1–7) antibody, we did ascertain that the amounts of the Ang-(1–7)-Ab used in the current experiments were sufficient to block the depressor response produced by 100 nmol of the peptide in the pithed rat.13 From the data obtained in these experiments, we estimate that neutralization of Ang-(1–7) is associated with a reversal of at least one-third of the antihypertensive action produced by the combined medication. This interpretation is in keeping with the finding that a continuous infusion of Ang-(1–7) in SHR transiently reduced their elevated blood pressure by increasing the gain of the baroreceptor reflex and restoring vascular reactivity.11,22 Thus, the current experiments provide additional evidence for an important role of Ang-(1–7) in the chronic regulation of arterial pressure in hypertensive states.

Further evidence for the specificity of the response elicited by the monoclonal Ang-(1–7)-Ab is derived from the observation of a twofold rise in the plasma levels of Ang-(1–7). We interpret these findings as an indication that endogenous neutralization of Ang-(1–7) may retard peptide metabolism, because the bound peptide-antibody complex is prevented from binding to the catalytic site of aminopeptidases and ACE.5,6 Detection of high plasma levels of Ang-(1–7) after administration of the Ang-(1–7)-Ab may result from dissociation of the ligand-antibody complex during sample extraction, thus allowing a measure of both bound and unbound Ang-(1–7). Pacz-Asciak et al23,24 reached a similar conclusion in studies of the endogenous trapping of 5,6-dihydroprostaglandin I2. In keeping with this interpretation, plasma levels of Ang II were not affected by endogenous neutralization of Ang-(1–7), whereas administration of [Sar-Thr]Ang II caused no changes in the plasma Ang-(1–7) levels. This interpretation does not exclude, however, the possibility that sequestration of endogenous Ang-(1–7) by the circulating antibodies may prevent clearance of the peptide by the kidneys.20

[Sar-Thr]Ang II reverses the hemodynamic,13 hormonal,21 and antitrophic25 actions of Ang-(1–7). Infusion of this peptide antagonist in lisinopril- and losartan-treated SHR produced a hemodynamic response comparable in magnitude, characteristics, and time course to that obtained with the Ang-(1–7)-Ab. The similar characteristics of the pressor response produced by [Sar-Thr]Ang II in rats given PD123319 before infusion of [Sar-Thr]Ang II suggests that Ang-(1–7) may act at a non-AT1/AT2 receptor site. It has been suggested that AT1 receptors may account for the vasodilator and antiproliferative effects of high doses of Ang II during blockade of AT1 receptors.20,27 In our studies, administration of PD123319 at doses reported to produce complete blockade of AT1 receptors30 had no effect on the blood pressure of lisinopril- and losartan-treated SHR. Thus, AT2 receptors may not contribute to the normalization of blood pressure in SHR treated with the ACE inhibitor and the AT1 receptor blocker. We tested for the possibility that the pressor response produced by [Sar-Thr]Ang II was accounted for by the agonistic activity of this peptide antagonist.29,30 Infusion of [Sar-Thr]Ang II had no effect on the arterial pressure or the heart rate of SHR treated with losartan for an equivalent time period. These data indicate that [Sar-Thr]Ang II did not displace losartan from its AT1 binding site. Moreover, in all of our studies injection of high doses of Ang II did not elicit a pressor response, a finding that suggested complete blockade of AT1 receptors. Therefore, our data provide additional evidence for the existence of a functional subtype receptor mediating the endogenous action of Ang-(1–7) and possessing pharmacological characteristics distinct from AT1 and AT2 receptor subtypes. Other studies31,32 suggest the existence of a unique Ang-(1–7)-binding site that is not recognized by either losartan or PD123319. Tallant et al31 described a high-affinity Ang-(1–7) binding site in bovine aortic endothelial cells that was displaced by [Sar-Ile]Ang II but not losartan or PD123319. Nickenig et al32 described a binding site for Ang-(1–7) in human skin fibroblasts that enhances DNA synthesis by a mechanism that is not prevented by pretreatment with either EXP-3174 or PD123319.

The potential role of angiotensin fragments, other than Ang II, in the long-term regulation of arterial pressure has just begun to be appreciated.20,33,34 Studies by us6,8 and others35,36 suggest that chronic inhibition of ACE does not suppress the formation of Ang II. The combination of an ACE inhibitor with an AT1 receptor blocker may circumvent the limitations inherent in the mode of action of these

**TABLE 3. Plasma Concentrations of Ang-(1-7) and Ang II Before and After Administration of [Sar-Thr]Ang II**

<table>
<thead>
<tr>
<th></th>
<th>Plasma Ang-(1-7)</th>
<th>Plasma Ang II</th>
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<tbody>
<tr>
<td></td>
<td>PMOL/L</td>
<td>LEVELS, PMOL/L</td>
</tr>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Vehicle</td>
<td>237±35</td>
<td>252±36</td>
</tr>
<tr>
<td>PD123319</td>
<td>210±22</td>
<td>224±25</td>
</tr>
</tbody>
</table>

Data are mean±SEM.
classes of antihypertensive agents. In humans, the combination of losartan with either captopril or enalapril has an additive effect on lowering blood pressure. The additive effect suggests that Ang II production persists during chronic ACE inhibition. We now suggest that the additional antihypertensive effect achieved by the combined therapy may be related, at least in part, to increased production of Ang-(1–7) and reduced Ang-(1–7) metabolism. This interpretation is consistent with the finding of a 357% rise in plasma levels of Ang-(1–7) when compared with the values found in losinopril-treated SHR. In addition, the increases in plasma Ang-(1–7) levels during the combined treatment were accompanied with blood pressure levels that were significantly below those determined in SHR treated with losinopril or transgenic hypertensive rats given losartan alone for a comparable time period. Thus, these data suggest that Ang-(1–7) contributes to mediating the antihypertensive effects obtained with the combined therapy.

The observation that [Sar1-Thr8]Ang II reversed the antihypertensive effects of the combined treatment is a new finding. As indicated above, we confirmed that the combined treatment was associated with inhibition of the pressor response to systemic injections of Ang II and that concomitant blockade of AT1 receptors had no additional effect on baseline blood pressure or plasma concentrations of Ang II. The new findings support the existence of a [Sar1-Thr8]Ang II–sensitive site contributing directly to the mechanism by which blockade of the renin-angiotensin system translates into the reversal of arterial hypertension in SHR.

In summary, our study provides physiological evidence for a role of endogenous Ang-(1–7) in contributing to the antihypertensive action of combined blockade of ACE and AT1 receptors in SHR. The mechanism of action may involve a receptor site recognized by [Sar1-Thr8]Ang II but not by AT1– or AT2–selective antagonists. The question of whether the acute effects of endogenous neutralization of Ang-(1–7) play a long-term role in the maintenance of the controlled blood pressure needs further investigation. Nevertheless, the present studies extend the observation that chronic infusions of Ang-(1–7) mimic the effects of ACE inhibition in SHR, whereas neutralization of endogenous brain Ang-(1–7) reverses the antihypertensive actions of lifetime treatment with losinopril in transgenic hypertensive rats.

Acknowledgments

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