Converting Enzyme Determines Plasma Clearance of Angiotensin-(1–7)

Kazuo Yamada, Shridhar N. Iyer, Mark C. Chappell, Detlev Ganten, Carlos M. Ferrario

Abstract—We determined the mechanism accounting for the removal and metabolism of angiotensin-(1–7) [Ang-(1–7)] in 21 anesthetized spontaneously hypertensive (SHR), 18 age-matched normotenive Sprague-Dawley (SD), and 36 mRen-2 transgenic (TG') rats. Animals of all 3 strains were provided with tap water or tap water containing losartan, lisinopril, or a combination of losartopril and lisartan for 2 weeks. On the day of the experiment, Ang-(1–7) was infused for a period of 15 minutes at a rate of 278 nmol kg⁻¹ min⁻¹. After this time, samples of arterial blood were collected rapidly at regular intervals for the assay of plasma Ang-(1–7) levels by radioimmunoassay. Infusion of Ang-(1–7) had a minimal effect on vehicle-treated SD rats but elicited a biphasic pressor/depressor response in vehicle-treated SHR and TG' rats. In lisinopril-treated rats, Ang-(1–7) infusion increased blood pressure, whereas losartan treatment abolished the pressor component of the response without altering the secondary fall in arterial pressure. Combined treatment with lisinopril and losartan abolished the cardiovascular response to Ang-(1–7) in all 3 strains. In vehicle-treated SD, SHR and TG' the half-life (t₁/₂) of Ang-(1–7) averaged 10±1, 10±1, and 9±1 seconds, respectively. Lisinopril alone or in combination with losartan produced a statistically significant rise in the half-life of Ang-(1–7) in all 3 strains of rats. Plasma clearance of Ang-(1–7) was significantly greater in the untreated SD rats compared with either the SHR or TG' rat. Lisinopril treatment was associated with reduced clearance of Ang-(1–7) in all 3 strains. Concurrent experiments in pulmonary membranes from SD and SHR showed a statistically significant inhibition of [125I-Ang-(1–7) metabolism in the presence of lisinopril. These studies showed for the first time that the very short half-life of Ang-(1–7) in the circulation is primarily accounted for peptide metabolism by ACE. These findings suggest a novel role of ACE in the regulation of the production and metabolism of the two primary active hormones of the renin angiotensin system. (Hypertension. 1998;32:496-502.)

Key Words: angiotensin-(1–7) ■ blood pressure ■ angiotensin-converting enzyme ■ lisinopril ■ losartan ■ rats, inbred SHR ■ rats, transgenic

Substantial evidence now exists that angiotensin-(1–7) [Ang-(1–7)] is an important product of the renin-angiotensin system. In contrast to Ang II, the cumulative effects of Ang-(1–7) suggest an antihypertensive role for this peptide.1 Ang-(1–7) exhibits natriuretic and diuretic actions in the rat kidney2–4 and induces relaxation in rat thoracic aorta,5 coronary vessels of dog and pig6,7 and the mesenteric bed of the cat.8 Low concentrations of Ang-(1–7) enhance the vasodepressor actions of bradykinin9 and facilitate the baroreceptor reflex.10–12 As recently reviewed,1 the responses to Ang-(1–7) appear to be increased in hypertensive models. Ang-(1–7) infusion reduced blood pressure and increased prostaglandin release in spontaneously hypertensive rats (SHR); these actions were not observed in the Wistar-Kyoto (WKY) strain.13 Similarly, ventricular administration of an antibody to trap Ang-(1–7) increased blood pressure in mRen-2 (TG') renin transgenics but not in normotensive rats.14 Additionally, the potentiation of the kinin response by Ang-(1–7) is augmented in renal hypertensive animals and SHR.15 Although the biosynthetic pathway for the production of Ang-(1–7) is now understood, the process by which the peptide is degraded or cleared from the plasma remains under investigation. Understanding the mechanism(s) of clearance of Ang-(1–7) is an important criterion for the determination of the role of this peptide in the regulation of blood pressure and cardiovascular function. Moreover, alterations in the metabolic clearance of Ang-(1–7) (MCRAng-(1–7)) may contribute to the increased responsiveness in hypertensive animals. Several different mechanisms have been postulated to mediate the plasma clearance of bioactive peptides from the plasma. These include enzymatic degradation by circulating or membrane-bound peptidases, hemodynamic factors, or internalization by the process of receptor-mediated endocytosis.16 The concept of a clearance receptor has been suggested to mediate the plasma clearance of atrial natriuretic factor,17 glycoprotein,18 and lipoprotein.19 Regarding the involvement of peptidase degradation, we20,21 and others22 have recently shown that Ang-(1–7) is a substrate in vitro for angiotensin-converting enzyme (ACE). Furthermore, treatment with various ACE inhibitors augment peptide levels substantially (5- to 25-fold) in the circulation.23–27 These data

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generate a new perspective on the factors that regulate the opposing actions of Ang II and Ang-(1–7) on blood pressure and cell growth. To establish the mechanisms contributing to the removal of Ang-(1–7) from the circulation and ascertain whether clearance is altered in hypertensive animals, we determined the MCR\textsubscript{Ang-(1–7)} in Sprague-Dawley (SD), SHR, and TG\textsuperscript{+} rats given long-term treatment with an ACE inhibitor or in combination with concurrent therapy with a selective AT\textsubscript{1} receptor blocker.

Methods
Experiments were conducted in 21 10-week-old male SHR (body weight, 261 ± 5 g), 18 aged-matched SD (body weight, 375 ± 7 g), and a third group of 18 [\textit{mRen-2}]27 transgenic hypertensive TG\textsuperscript{+} rats (body weight, 345 ± 9 g). Rats with spontaneous hypertension were withdrawn from the arterial catheter before infusion of Ang-(1–7) for measurement of baseline plasma concentrations of Ang-(1–7). Blood samples were collected from the arterial catheter without 10

\begin{align*}
\text{MCR}\textsubscript{Ang-(1–7)} &= \frac{\text{Infusion rate}}{\text{Plasma concentration of Ang-(1–7)}}
\end{align*}

\text{Ang-(1–7)} used in these experiments prevented changes in the endogenous production of Ang-(1–7) from interfering in the calculation of the MCR\textsubscript{Ang-(1–7)}. The half-life (t\textsubscript{1/2}) of Ang-(1–7) in the circulation was calculated with the equation

\begin{align*}
t\textsubscript{1/2} &= \frac{0.693}{K_e} K_e
\end{align*}

\text{Ang-(1–7) Radioimmunoassay}
Plasma concentrations of Ang-(1–7) were determined in arterial blood as described in detail by our laboratory elsewhere. Briefly, blood was collected in a cocktail of protease inhibitors [25-mmol/L ethylenediaminetetraacetic acid, 0.44-mmol/L o-phenanthroline, 1 mmol/L 4-chloromercuribenzoic acid, and 0.12 mmol/L pepstatin A\textsubscript{1}, as described by us in detail elsewhere. \text{The minimum detectable level of the assay was 4 fmol/tube; the intra-assay coefficient of variation averaged 9%}.

\text{Ang-(1–7) Metabolism}
The metabolism of \text{125I-Ang-(1–7)} was determined in pulmonary membranes prepared by homogenization of SHR lung tissue (1:10 wt/vol, previously frozen at −80°C in 20 mmol/L HEPES, 300 mmol/L mannitol, pH 7.4, and centrifuged at 30 000 g for 20 minutes at 4°C. The resultant pellet was homogenized again in the HEPES buffer with a Potter-Elvehjem Teflon pestle and recentrifuged. The assay contained 10 μg protein of pulmonary membrane and 5 mmol/L \text{125I-Ang-(1–7)} (2200 Curies/mmol) in a 0.1 mL with or without 10 μmol/L lisinopril. The reaction was terminated with 80% acetonitrile/0.4% phosphoric acid and stored at −80°C until high-performance liquid chromatography (HPLC) analysis (see below). Synthesis and HPLC purification of \text{125I-Ang-(1–7)} has been described previously. \text{The t}_{1/2} for Ang-(1–7) was calculated with a plotting and statistical package (GraphPad).}

\text{HPLC Analysis}
Separation of Ang-(1–7) and Ang-(1–5) was achieved by HPLC with 0.1% phosphoric acid/water (mobile phase A) and 80% acetonitrile/0.1% phosphoric acid (mobile phase B). The analysis was performed on an Applied Biosystems 400 HPLC (ABI) equipped with a narrow-bore Nova-Pak C\textsubscript{18} column (Waters, 2.1×150 mm) and an Aquapore C\textsubscript{8} guard column (Applied Biosystems, 3.2×15 mm). The gradient consisted of 15% mobile phase B for 2 minutes, 15% to 30% B linear for 15 minutes, and 30% mobile phase B for 10 minutes at a flow rate of 0.3 mL/min at ambient temperature. HPLC fractions were collected at a 1-minute interval and counted in a gamma counter (Packard Instrument Co).

\text{Statistical Analysis}
All data are expressed as mean ± SEM. Differences between drug treatments were analyzed by 1- or 2-way analysis of variance (ANOVA) followed by Scheffe's post hoc test or by unpaired Student's \text{t} test for the in vitro metabolism. Values of \text{P} ≤ 0.05 were considered statistically significant.

\text{Drugs}
Ang-(1–7) was purchased from Bachem Inc. Losartan and lisinopril were a gift from Merck & Co, Inc.

\text{Results}
Effects of Treatments on Hemodynamic Actions of Ang-(1–7)
Figure 1 shows the time course of the changes in mean arterial pressure produced by a 15-minute infusion of Ang-(1–7) in SD, SHR, and TG\textsuperscript{+} rats in the 4 treatment groups. Among animals given vehicle (tap water), the biphasic effects of Ang-(1–7) are most marked in the hypertensive SHR and TG\textsuperscript{+} rats. A small depressor response is present in SD rats, whereas in TG\textsuperscript{+} hypertensive animals the pressor component lasted longer than that determined in SHR. In the presence of

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Lisinopril, Ang-(1–7) produced a pressor effect with no evidence of a depressor component for the 15 minutes of Ang-(1–7) infusion (middle panel of Figure 1). In contrast, treatment with losartan abolishes the pressor component of the response while having no effect on the vasodilator phase of the pressor response. Ang-(1–7) had no effect on SD, SHR, and TG rats medicated with the combination of lisinopril and losartan (rightmost panel of Figure 1).

**Effect of Ang-(1–7) Infusion on Plasma Ang-(1–7) Concentrations**

Baseline plasma concentrations of Ang-(1–7) before administration of Ang-(1–7) were significantly higher in SHR and TG– rats compared with vehicle-treated SD animals (Table). Treatment with lisinopril, losartan, or both agents in combination was associated with significant increases in plasma levels of Ang-(1–7) when compared with corresponding vehicle-treated rats. Baseline plasma Ang-(1–7) levels were higher, however, in TG– given lisinopril than in similarly treated SD rats (Table).

Figure 2 illustrates the steady-state plasma concentrations of Ang-(1–7) achieved at the end of the 15-minute infusion period for each strain and treatment regimen. Among strains, the highest values of Ang-(1–7) were observed in TG+. Within each strain, however, the highest concentrations of Ang-(1–7) are present in rats treated with lisinopril either alone or in combination with losartan. Compared with vehicle-treated rats, the final plasma concentrations of Ang-(1–7) in lisinopril-treated rats increased by 68% in SD (P<0.02), 76% in SHR (P<0.0001), and 55% (P<0.005) in TG+. Plasma concentrations of Ang-(1–7) are not significantly increased in relation to their corresponding vehicle control values for animals treated with losartan.

**Half-life of Ang-(1–7) in SD, SHR, and TG+ Rats**

Half-life (t1/2) values of Ang-(1–7) in the circulation are shown in Figure 3. The t1/2 values for Ang-(1–7) averaged 10±1, 10±1, and 9±1 seconds in vehicle-treated SD, SHR, and TG+ rats. Long-term treatment with losartan had no effect on the half-life of Ang-(1–7). In lisinopril-treated rats, irrespective of the strain, the t1/2 of Ang-(1–7) increased 4- to 6-fold (P<0.0001) compared with their corresponding untreated control group. Combined lisinopril and losartan treatment produced high t1/2 values of Ang-(1–7), but these values are not different from those measured in the corresponding strain given only lisinopril therapy.

The plasma clearance of Ang-(1–7) averaged 6.5±0.9 L·min−1·kg−1 in vehicle-treated SD rats. The MCRAng-(1–7) was reduced by 39% (4.0±0.2 L·min−1·kg−1, P<0.001) in vehicle-treated SHR and by 60% (2.6±0.1 L·min−1·kg−1, P<0.001) in vehicle-treated TG+ rats. Long-term treatment with losartan had no effect on the MCRAng-(1–7) whereas the clearance of Ang-(1–7) was significantly reduced in SD

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**Baseline Values of Ang-(1–7) in Various Treatment Groups**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Plasma Ang-(1–7) Concentration, pmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD Rats</td>
</tr>
<tr>
<td><strong>Vehicle</strong></td>
<td>137±18</td>
</tr>
<tr>
<td><strong>Losartan</strong></td>
<td>684±252</td>
</tr>
<tr>
<td><strong>P&lt;</strong>**</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Lisinopril</strong></td>
<td>692±262</td>
</tr>
<tr>
<td><strong>P&lt;</strong>**</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>709±155</td>
</tr>
<tr>
<td><strong>P&lt;</strong>**</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values are mean±1 SE of the mean. P values denote statistical difference compared with vehicle-treated rats for each strain.

*P=0.05 for differences between strains.
(3.7±0.2 L · min⁻¹ · kg⁻¹, P<0.001), SHR (2.2±0.1 L · min⁻¹ · kg⁻¹, P<0.01), and TG⁺ rats (1.7±0.1 L · min⁻¹ · kg⁻¹, P<0.001) after treatment with lisinopril. Combination therapy had no further effect on the reduced MCR_{Ang-(1–7)} found in lisinopril-treated rats.

Figure 4 shows the effects of the various treatment protocols on the MCR_{Ang-(1–7)} of SD, SHR, and TG⁺ as a function of the final concentration of Ang-(1–7) at the completion of the infusion of Ang-(1–7). For the 3 groups as a whole, MCR_{Ang-(1–7)} is inversely correlated with the steady-state levels of Ang-(1–7) achieved by the infusion of the peptide [r = −0.91 (F=43.02, P<0.0001)]. Interestingly, the correlations within each strain were similar for the various treatments and did not deviate significantly (P>0.05) from the overall relation as a whole (Figure 4). From inspection of Figure 4 it can be appreciated that the MCR_{Ang-(1–7)} in lisinopril-treated SD rats is significantly higher than the values achieved in either lisinopril-treated SHR or lisinopril-treated TG⁺ rats. Moreover, vehicle-treated TG⁺ rats show a substantial reduction in MCR_{Ang-(1–7)} because their clearance values fall within the MCR_{Ang-(1–7)} determined between SD and SHR rats given the combination of lisinopril and losartan. These findings suggest that plasma concentrations of Ang-(1–7) are markedly influenced by metabolic activity of ACE. In keeping with this interpretation, baseline levels of Ang-(1–7) correlated with both the steady-state concentration of Ang-(1–7) at the end of the infusion period (r=0.60, P<0.04) and the MCR_{Ang-(1–7)} (r=0.55, P<0.06).

Ang-(1–7) Metabolism

The observation that lisinopril as a single agent had a profound effect on the t₁/₂ values of Ang-(1–7) in the circulation led to the analysis of the metabolism of the peptide in pulmonary membranes of untreated SHR, a tissue with high peptidase activity. As shown in Figure 5, ¹²⁵I-Ang-(1–7) was degraded by peptidase activities within 15 minutes. The t₁/₂ of the peptide in the in vitro preparation averaged 3.0±0.4 minutes (n=3); consistent with previous studies, the primary metabolite resulting from the hydrolysis of Ang-(1–7) was identified as Ang-(1–5). Addition of 10 μmol/L lisinopril significantly attenuated the metabolism of Ang-(1–7) (+Lis) and abolished the generation of Ang-(1–5). In the presence of the ACE inhibitor, the t₁/₂ of ¹²⁵I-Ang-(1–7) increased approximately 15 fold (43±3 minutes, P<0.01 versus control). A similar pattern of ¹²⁵I-Ang-(1–7) metabolism was found in pulmonary membranes of SD rats (data not shown).

Discussion

These studies demonstrate an important role of ACE in the in vivo clearance of Ang-(1–7). They provide a new dimension to the understanding of the mechanisms by which ACE contributes to the regulation of blood pressure because the prevailing concentrations of Ang-(1–7) in plasma in both normotensive and hypertensive rats appear to be predominantly determined by the mechanisms that control the inactivation of the peptide by degradation. These observations in vivo are consistent with kinetic studies that ACE exhibits a high specificity constant ($K_{c/a}/K_{m}$) for Ang-(1–7) comparable to that reported for bradykinin. Moreover, this interpretation agrees with the concurrent demonstration that ACE was the predominant enzyme involved in the metabolism of Ang-(1–7) by pulmonary membranes from SHR and SD rats. Our studies also demonstrate that the AT₁ receptor does not contribute to the clearance of Ang-(1–7) from the circulation. To our knowledge, these data demonstrate for the first time a novel role of ACE in determining the plasma clearance of Ang-(1–7) in vivo. In addition, the finding that the half-life of Ang-(1–7) in the circulation of normotensive and hypertensive rats is one-fourth that reported for Ang II explains the need to use high doses of the peptide in experiments that initially characterized the biological actions of the heptapeptide.

Several precautions were taken to obtain accurate estimates of the plasma clearance of Ang-(1–7) because determination of this variable assumes that a steady-state equilibrium is achieved at the time of estimating the rate of peptide disappearance from the plasma compartment. First, our data showed that Ang-(1–7) was removed from the circulation with a t₁/₂ ranging between 9 and 10 seconds in untreated rats from all 3 strains. Thus infusion of Ang-(1–7) for a 15-minute
period greatly exceeded the t1/2 of the peptide in vivo. Ang-(1–7) was given at a high dose to ensure that endogenous production would not have artificially altered the concentration of Ang-(1–7) achieved at the end of the infusion period. This precaution resulted in steady-state levels of Ang-(1–7) exceeding by >1000-fold the baseline levels of the peptide before infusion. Third, our data showed that hemodynamic effects produced by a high dose of Ang-(1–7) had no significant influence on the determination of the plasma clearance because differences in arterial pressure were not correlated with changes in the plasma clearance of the heptapeptide.

Baseline plasma concentrations of Ang-(1–7) were significantly higher in vehicle-treated hypertensive SHR and TG+ rats compared with normotensive vehicle-treated SD rats. Yet, the t1/2 values for Ang-(1–7) were approximately the same in all 3 strains given vehicle. The baseline values of Ang-(1–7) were not significantly correlated (r = 0.45, P > 0.10) with the half-life of the peptide, which suggest that plasma levels of Ang-(1–7) reflect both synthesis and degradation in conditions in which disposal mechanisms are not inhibited. The finding that losartan treatment increases baseline concentrations of Ang-(1–7) is consistent with this interpretation as AT1 receptor blockade inhibits the negative feedback of Ang II on renin release. In contrast, inhibition of ACE unmasked the role of the enzyme in the metabolism of the heptapeptide. Lisinopril therapy caused significant increases in baseline and steady-state levels of Ang-(1–7) as well as the half-life of the peptide in the circulation. As expected, these changes were accompanied by a marked reduction in the MCRAng-(1–7) in all 3 strains. The comparative effects of lisinopril on t1/2 and clearance among the strains argues against a direct relation between the blood pressure disorder and the mechanism for removal of circulating Ang-(1–7). However, the decline in blood pressure after treatment was correlated with a change in MCRAng-(1–7) for each strain (SD: r = 0.73, P = 0.0008; SHR: r = 0.63, P < 0.003; TG+: r = 0.75, P < 0.0005). Because we observed a greater decline in blood pressure with lisinopril than losartan and no further decline with the combined regimen, the reduction in MCRAng-(1–7) (or increased t1/2) may, in part, contribute to the greater effect of the ACE inhibitor. We have previously shown that Ang-(1–7) blockade partially reverses the decrease in blood pressure in both lisinopril/losartan and lisinopril-treated SHR (unpublished observations). Moreover, kinins do not contribute to the blood pressure–lowering actions of long-term ACE inhibitor or lisinopril/losartan treatment in SHR. Further studies comparing the reduction in blood pressure to changes in MCRAng-(1–7) with lower doses of lisinopril are necessary to fully address this relation.

Interestingly, the hemodynamic effects obtained by the infusion of Ang-(1–7) suggest that at high doses, Ang-(1–7) acts at AT1 receptor sites to produce pressor responses because the AT1 antagonist losartan blocks this response. In contrast to SD rats, the pressor response of Ang-(1–7) in both hypertensive strains may be attributed, in part, to the lower clearance rates of the peptide. As discussed previously,1 the depressor response observed in the hypertensive animals appears to require an activated renin-angiotensin system. The depressor component was not attenuated by losartan, which supports action at a non-AT1, non-AT2 receptor site.7,22,24 The combined regimen of lisinopril and losartan may reduce blood pressure to the point where Ang-(1–7) exhibits no further depressor action. In support of the former concept, recent studies demonstrate that removal of circulating Ang-(1–7) by antibody infusion or neprilysin inhibition increased blood pressure in SHR with long-term treatment with lisinopril and losartan.29,40

The findings that both hypertensive strains had a reduced MCRAng-(1–7), compared with the SD are noteworthy because it suggests that endogenous inhibition of metabolism may contribute to the vasopressor actions of Ang-(1–7). As shown in Figure 4, the MCRAng-(1–7) in untreated SHR was lower than that determined in SD rats given lisinopril alone or in combination with losartan. The more severe hypertension found in vehicle-treated TG+ rats was associated with an even lower MCRAng-(1–7). These data suggest that hypertension may be associated with activation of endogenous inhibitors of ACE expression or activity. Although various studies have reported the presence of endogenous inhibitors of ACE, further work will be required to ascertain the nature and role of this mechanism in hypertension. Interestingly, a recent study suggests that whereas the N-domain of human somatic ACE is involved in the degradation of Ang-(1–7), the peptide may act as an endogenous inhibitor of the C-domain.22 The possibility thus exists that the reduced MCRAng-(1–7) in vehicletreated SHR and TG+ rats may reflect an action of Ang-(1–7) or other endogenous inhibitors on the activity of ACE. This interpretation does not negate the possible contribution of other receptor subtypes in the removal of Ang-(1–7) from the circulation. On the other hand, this is consistent with the finding that baseline levels of Ang-(1–7) were higher in hypertensive compared with normotensive vehicle-treated strains.

The determination of the half-life of Ang-(1–7) has provided a first insight into the fate of Ang-(1–7) in the circulation. The demonstration that the t1/2 of Ang-(1–7) is approximately 4- to 6-fold less than Ang II (t1/2 of 45 seconds)13 puts to rest the argument that the actions of Ang-(1–7) are outside the range of physiological responses. Several endogenous vasodilators including bradykinin and nitric oxide also share a short half-life (10 and 6 seconds, respectively).27–40 The short half-life of vasodilator peptides, in contrast to that of vasoconstrictor peptides, may be one mechanism that the system adapts to maintain vascular tone in a constricted rather than a vasodilator state. In conclusion, these findings bear importance in the understanding of the mechanism regulating the opposing actions of Ang II and Ang-(1–7) in the regulation of arterial pressure. A progressive unfolding of the intrinsic properties and mechanisms of Ang-(1–7) continues to bear fruit in expanding the scope of the understanding of the complex role that the renin-angiotensin system plays in the regulation of tissue perfusion and blood pressure.

Acknowledgments

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References

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