RXP 407, a Selective Inhibitor of the N-Domain of Angiotensin I-Converting Enzyme, Blocks in Vivo the Degradation of Hemoregulatory Peptide Acetyl-Ser-Asp-Lys-Pro with No Effect on Angiotensin I Hydrolysis

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ABSTRACT
The phosphinic peptide RXP 407 has recently been identified as the first potent selective inhibitor of the N-active site (domain) of angiotensin-converting enzyme (ACE) in vitro. The aim of this study was to probe the in vivo efficacy of this new ACE inhibitor and to assess its effect on the metabolism of AcSDKP and angiotensin I. In mice infused with increasing doses of RXP 407 (0.1–30 mg/kg/30 min), plasma concentrations of AcSDKP, a physiological substrate of the N-domain, increased significantly and dose dependently toward a plateau 4 to 6 times the basal levels. RXP 407 significantly and dose dependently inhibited ex vivo plasma ACE N-domain activity, whereas it had no inhibitory activity toward the ACE C-domain. RXP 407 (10 mg/kg) did not inhibit the pressor response to an i.v. angiotensin I bolus injection in mice. In contrast, lisinopril infusion (5 and 10 mg/kg/30 min) affected the metabolism of both AcSDKP and angiotensin I. Thus, RXP 407 is the first ACE inhibitor that might be used to control selectively AcSDKP metabolism with no effect on blood pressure regulation.

Angiotensin I-converting enzyme, ACE (peptidyl dipeptidase A, EC 3.4.15.1), is a key player in cardiovascular homeostasis. ACE inhibitors are widely used for the treatment of patients with high blood pressure, heart failure, and diabetic nephropathy (Waeber et al., 1995). Elucidation of the primary structure of human endothelial somatic ACE, by complementary DNA cloning, revealed the unexpected presence of two homologous domains in this enzyme (hereafter called N- and C-domain). Each domain contains an active site, characterized by the presence of a zinc-metallopeptidase consensus sequence (Soubrier et al., 1988), and whose functionality was demonstrated by site-directed mutagenesis (Wei et al., 1992).

The presence of two active sites in ACE has stimulated many attempts to establish whether their catalytic efficiency to cleave physiological substrates may differ, leading each domain to control distinct physiological functions. In this respect, besides its important role in angiotensin (Ang) I and bradykinin metabolism, two peptides involved in cardiovascular homeostasis, ACE has also been shown to hydrolyze in vitro a negative regulator of the hematopoietic stem cells differentiation and proliferation (Robinson et al., 1992; Rieger et al., 1993), N-acetyl-Ser-Asp-Lys-Pro (AcSDKP) (Lenfant et al., 1989). In vivo, captopril administration was shown to increase the plasma levels of AcSDKP, suggesting a new physiological role for ACE in the regulation of hematopoiesis (Azizi et al., 1996). Interestingly, although Ang I and bradykinin are cleaved with approximately the same catalytic efficiency by both the N- and C-domain of ACE (Jaspard et al., 1993), AcSDKP is hydrolyzed 50 times faster in vitro by the N- than by the C-terminal active site (Rousseau et al., 1995). This suggests that selective inhibition of the N-domain of ACE should be sufficient to block the degradation of AcSDKP in vivo. We recently identified the first N-domain-spe-

ABBREVIATIONS: ACE, angiotensin I-converting enzyme; Ang, angiotensin; AcSDKP, N-acetyl-Ser-Asp-Lys-Pro; AcSDAcKP, N-acetyl-Ser-Asp-acetyl-Lys-Pro; HHL, hippuryl-histidyl-leucine; AUC, area under the curve.
cific and potent inhibitor of ACE, by screening phosphinic peptide libraries (Dive et al., 1999). This inhibitor, called RXP 407 (Scheme 1), was shown to be metabolically stable in vivo (Dive et al., 1999), enabling determination of its in vivo potency.

The aim of the present study was to demonstrate that RXP 407, by only inhibiting the N-domain of ACE, is able to significantly increase plasma AcSDKP levels with no effect on Ang I metabolism in vivo. Effects of lisinopril, a mixed N- and C-domain ACE inhibitor (Michaud et al., 1997), on the metabolism of these two peptides were also determined for comparison.

**Experimental Procedures**

**Animal Studies**

**Animals.** Male OF1 mice weighing about 30 g were used for all in vivo experiments (Charles River, Saint-Aubin-Les-Elbeufs, France). All studies on animals were conducted in accordance with the Décret sur l’Expérimentation Animale (French law on rules for animal experimentation, Decree 87-848, October 19, 1987).

**Determination of Inhibiting Properties of RXP 407 in Vivo.**

**Effects of RXP 407 on AcSDKP metabolism and on ex vivo plasma ACE activity.** Inactin-anesthetized (3 mg for 30 g of body weight) mice were cannulated via the jugular vein for 30 min i.v.: infusion of 0.1, 0.5, 1, 10, and 30 mg/kg RXP 407 and 5 and 10 mg/kg lisinopril. A control group was infused with saline. Blood samples were collected in heparinized tubes with ice-cold syringes by abdominal vein puncture 15, 30, 45, and 60 min after the infusion start, for AcSDKP, ex vivo plasma N- and C-domain ACE activity. Eight mice were used at each individual time point. Blood was centrifuged at 4°C to obtain plasma and all samples were stored at −30°C before analysis.

**Blood pressure response to Ang I and Ang II bolus injections.** Blood pressure responses to single i.v. bolus injections of Ang I (and Ang II as control) were determined in absence or presence of RXP 407 (10 mg/kg). The doses of Ang I (0.5 μg/kg) and Ang II (0.15 μg/kg) selected were those that increased systolic blood pressure by more than 20 mm Hg in the animals. Ang I or Ang II was injected via the jugular vein 30 min after the start of the infusion of either saline, 10 mg/kg lisinopril, or 10 mg/kg RXP 407 (10 mice/group). Ang I or Ang II injections were separated by a 10-min interval to allow blood pressure to return to baseline values. Intra-arterial systolic blood pressure responses to Ang I and Ang II injections were monitored from femoral artery with a Gould transducer system (Ballainvilliers, France) and the maximum increase in systolic blood pressure was used for analysis.

**Peptides and Reagents**

RXP 407 was obtained by solid-phase peptide synthesis, as previously described (Dive et al., 1999). AcSDKP, Ang I, Ang II, and lisinopril were from Sigma (St. Louis, MO). Acetyl-Ser-Asp-acetyl-Lys-Pro (AcSDAcKP) was from Neosystem (Strasbourg, France) and the synthetic tripeptide hippuryl-histidyl-leucine (HHL) from Bachem (Bubendorf, Switzerland). RXP 407, lisinopril, Ang I, and Ang II were dissolved in sterile saline solution immediately before each experiment.

**Laboratory Methods**

**AcSDKP Measurements.** For AcSDKP determination, lisinopril 10−6 M was added to heparinized tubes to prevent AcSDKP degradation by endogenous ACE. AcSDKP was determined in plasma by a competitive enzyme immunoassay described elsewhere (Pradelles et al., 1990). Polyclonal antibodies were obtained after immunization of AcSDKP conjugated to bovine serum albumin. The tracer was AcSDKP bound to Electrophorus electricus acetylcholinesterase (EC 3.1.1.7). Before assay, plasma samples were treated with methanol. After centrifugation, the supernatants were collected, evaporated to dryness, and reconstituted in enzyme immunoassay buffer. Sample concentrations were calculated from a standard curve linearized with a cubic spline fitting. All measurements of standards and samples were performed in duplicate. Assay repeatability and reproducibility were inferior to 20%, and the limit of quantification was 0.2 nM in plasma.

**Ex Vivo Plasma ACE Activity.** HHL and AcSDAcKP were used as C- and N-domain-specific substrates, respectively, as previously described (Azizi et al., 2000). Briefly, the hydrolysis of HHL and AcSDAcKP by plasma ACE was calculated from the production of hippuric acid and N-ε-acetyl-Lys-Pro, respectively. Reactions were performed at 37°C with 10 or 20 μl of plasma during 60 and 120 min for the determination of ex vivo plasma C- and N-domain ACE activities, respectively. Lisinopril, as well as RXP 407, are characterized by dissociation rate constants corresponding to a very slow dissociation of the inhibitor from the enzyme-inhibitor complex. Accordingly, effects of the plasma dilution and substrate addition on the position of the EI equilibrium can be neglected on the scale of experiments. Substrate concentrations were 2.5 × 10−5 M. Both substrates and reaction products were resolved and quantified by reversed phase high performance liquid chromatography (Waters, Milford, MA). Results were expressed in nanomoles per milliliter per minute generated hippuric acid and N-ε-acetyl-Lys-Pro.

**Dose-Response Curves and Statistical Analysis**

**Dose-Response Curves of RXP 407 for Inhibition of the N- and C-Domain ACE Activities.** Inhibition profiles were modeled according to an $E_{	ext{max}}$ model with maximal effects for the inhibition of ACE N- and C-domain activities arbitrarily fixed at 10 and 5 mg/kg lisinopril, respectively. Values are expressed as percentages of maximal $AUC_{15–60}$ calculated by using the trapezoidal method.

**Statistical Analysis.** Calculations were done by using SIGMA-STAT software (Jandel Corporation, San Rafael, CA). Blood pressure responses to Ang I and Ang II bolus injections and, at each sampling time, plasma AcSDKP, AcSDAcKP, and Hip-His-Leu hydrolysis were analyzed by one-way ANOVA for the dose effect. The assumptions of ANOVA (homogeneity of variance and normality) were checked for each variable, and natural logarithmic, square root transformations, or ANOVA on the ranks were applied where appropriate. If the $F$ test was significant, the mean values of each group were compared by the Newman-Keuls method. A $p$ value less than 0.05 was considered as significant. Data are expressed as mean ± S.D. in the tables and figures, or as otherwise specified.

**Results**

**Effect of RXP 407 on ex Vivo Plasma ACE N- and C-Domain Activities (Tables 1 and 2 and Fig. 1).** In the absence of ACE inhibitors, mean values of AcKP (ex vivo marker of N-domain ACE activity, Table 1) and hippuric acid (ex vivo marker of C-domain ACE activity, Table 2) ranged from 5.9 to 6.1 and from 71.8 to 82.6 nmol/ml/min, respectively. Lisinopril inhibited significantly and dose dependently both the N- and the C-domains of ACE. Maximal...
inhibition of the N- and C-domains of ACE was achieved with lisinopril either infused at 10 or 5 mg/kg: minimal values for AcKP and hippuric acid concentrations were 0.1 and 2.1 nmol/ml/min, respectively.

RXP 407 induced a dose-dependent inhibition of the N-domain ACE activity that was significant from the dose 0.5 mg/kg onwards compared with the control group. N-Domain inhibition reached a plateau at the doses of 10 and 30 mg/kg (Table 1 and Fig. 1). The N-ACE domain inhibition achieved with 10 mg/kg RXP 407 did not statistically differ from that obtained with 10 mg/kg lisinopril, indicating a similar inhibition of N-domain ACE activity (Table 1). In contrast, RXP 407 had no inhibitory effect on the C-domain ACE activity up to the 10-mg/kg dose (Table 2). At 30 mg/kg RXP 407, a weak C-domain inhibition was observed, but was not significant (Table 2 and Fig. 1).

**In Vivo Activity of RXP 407 on Plasma AcSDKP Levels (Table 3).** In the control group, plasma AcSDKP concentrations remained stable with values ranging from 0.5 to 1.8 nM. Compared with the control group, lisinopril significantly raised plasma AcSDKP concentrations to a plateau with no major differences between the 5- and 10-mg/kg doses. Peak AcSDKP concentrations (7.5–26.2 nM) were achieved 60 min after the start of the infusion (Table 3).

When administered between the doses of 0.1 and 10 mg/kg, RXP 407 induced a dose-dependent increase of plasma AcSDKP levels, which was significantly different from that of the control group from the lowest dose of 0.1 mg/kg onwards. The plasma AcSDKP plateau was achieved with 10 and 30 mg/kg RXP 407 with mean concentrations that were significantly lower than those obtained with lisinopril.

Thirty minutes after the end of the infusion of both RXP 407 (10 and 30 mg/kg) and lisinopril (5 and 10 mg/kg), plasma AcSDKP concentrations remained significantly higher than in the control group.

**Blood Pressure Responses to Ang I and Ang II Bolus Injections (Fig. 2).** To determine whether RXP 407 affects the cleavage of Ang I in vivo, blood pressure responses to single i.v. bolus injections of Ang I (and of Ang II, as control) were determined in the absence or presence of RXP 407 (10 mg/kg). At this dose, the C-domain activity is unaltered, whereas the N-domain inhibition is totally achieved (Tables 1 and 2), raising plasma AcSDKP to the maximal values obtained with RXP 407 (Table 3).

As expected, the maximal pressor response to Ang I was highly and significantly reduced in the lisinopril-treated mice (5.6 ± 4.4 mm Hg) compared with the control mice (21.7 ± 11.9 mm Hg, p < 0.001, Fig. 2). In contrast, 10 mg/kg RXP 407 did not modify the pressor response to Ang I (18.7 ± 8.5 mm Hg) compared with the control. Ang II induced similar increases in systolic blood pressure in all three groups.
with mean values ranging from 25 to 39 mm Hg (data not shown).

Discussion

Our results show that RXP 407 specifically inhibited the N-domain of ACE in vivo without affecting the C-domain activity, contrary to lisinopril, which, as expected, blocked both the N- and the C-domain activity of ACE. Injection of RXP 407 in mice dose dependently induced a complete ex vivo inhibition of ACE N-domain activity and significantly increased plasma AcSDKP levels. In contrast, RXP 407 neither affected ex vivo plasma C-domain activity nor inhibited the systolic blood pressure response to Ang I bolus injection.

Plasma AcSDKP concentrations achieved with RXP 407, even at the highest dose (30 mg/kg), were significantly lower than those achieved with lisinopril, even though both drugs were similarly potent in inhibiting ex vivo plasma ACE N-domain activity. Difference in tissue distribution between the two drugs may explain this observation. Indeed, AcSDKP metabolism is not only dependent on plasma but also on endothelial and tissue ACE (Azizi et al., 1999; Junot et al.,

TABLE 3
AcSDKP concentrations in plasma from mice treated with RXP 407 and lisinopril

<table>
<thead>
<tr>
<th>Treatment</th>
<th>15 min&lt;sup&gt;a&lt;/sup&gt;</th>
<th>30 min&lt;sup&gt;b&lt;/sup&gt;</th>
<th>45 min&lt;sup&gt;b&lt;/sup&gt;</th>
<th>60 min&lt;sup&gt;b&lt;/sup&gt;</th>
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<td></td>
<td>pmol/ml</td>
<td></td>
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<tr>
<td>Control</td>
<td>0.9 (0.5–1.2)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.9 (0.6–1.3)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.9 (0.5–1.3)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.1 (0.6–1.8)&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>RXP 407</td>
<td></td>
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<tr>
<td>0.1 mg/kg</td>
<td>1.2 (0.7–2.0)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.1 (0.7–1.9)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.5 (0.8–2.8)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>1.6 (0.9–6.9)&lt;sup&gt;cd&lt;/sup&gt;</td>
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<tr>
<td>0.5 mg/kg</td>
<td>1.4 (0.7–4.3)</td>
<td>2.3 (1.6–3.6)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>1.6 (1.2–2.7)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>2.2 (1.5–5.7)&lt;sup&gt;cd&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>1.6 (1.1–2.4)</td>
<td>2.4 (1.4–7.7)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>2.4 (1.2–8.6)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>2.4 (1.2–10.2)&lt;sup&gt;cd&lt;/sup&gt;</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>1.7 (1.1–2.8)</td>
<td>3.3 (2.4–3.9)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>4.3 (2.5–15.9)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>6.2 (2.5–30.8)&lt;sup&gt;cd&lt;/sup&gt;</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>1.9 (1.3–2.4)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.7 (2.1–3.4)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>4.0 (1.9–11.7)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>3.8 (2.4–5.7)&lt;sup&gt;cd&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lisinopril</td>
<td></td>
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<tr>
<td>5 mg/kg</td>
<td>2.8 (2.1–3.6)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4.3 (1.0–7.3)&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>8.4 (4.3–12.5)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>7.9 (1.1–31.7)&lt;sup&gt;cd&lt;/sup&gt;</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>2.4 (1.7–3.3)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5.4 (2.7–9.9)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>7.1 (2.8–14.5)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>13.2 (7.5–26.2)&lt;sup&gt;cd&lt;/sup&gt;</td>
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<sup>a</sup>Expressed as geometric mean (range) (<i>n</i> = 8).

<sup>b</sup>After the infusion start.

<sup>c</sup><i>p</i> < 0.05 versus 10 mg/kg lisinopril by Student-Newman-Keuls test.

<sup>d</sup><i>p</i> < 0.05 versus control group by Student-Newman-Keuls test.

Fig. 1. Dose-response curves of RXP 407 for the ex vivo inhibition of plasma N- (■) and C-domain (▲) ACE activity. Inhibition profiles were modeled according to an <i>E</i><sub>max</sub> model. Maximal effects for the inhibition of ACE N- and C-domain activities were arbitrarily fixed at 10 and 5 mg/kg lisinopril, respectively. Mean values (<i>n</i> = 8) are expressed as percentages of maximal AUC<sub>15–60</sub>.

Fig. 2. Blood pressure responses to Ang I bolus injections (0.5 μg/kg). Mice were pretreated with a 30-min i.v. infusion of saline, 10 mg/kg lisinopril, or 10 mg/kg RXP 407. Data are expressed as mean ± 1 S.D. (<i>n</i> = 10). aIndicates <i>p</i> < 0.05 versus control by the Student-Newman-Keuls method.

RXP 407 in mice dose dependently induced a complete ex vivo inhibition of ACE N-domain activity and significantly increased plasma AcSDKP levels. In contrast, RXP 407 neither affected ex vivo plasma C-domain activity nor inhibited the systolic blood pressure response to Ang I bolus injection.
1999). Thus, an incomplete inhibition of the N-ACE domain by RXP 407 at tissue level could explain the discrepancy between its inhibitory potency on plasma N-ACE activity and its effects on plasma AcSDKP concentrations, compared with lisinopril. Pharmacokinetic studies performed on rat (Dive et al., 1999) and mouse (data not shown) indicated that the distribution volume of RXP 407 is lower than the volume of total body water (725 ml/kg in mouse). In contrast, lisinopril has been shown to accumulate until 2 and 4 days in rat lung and plasma, respectively, when given at a single dose of 10 mg/kg (Cushman et al., 1989).

The fact that blood pressure response to exogenous Ang I was not affected by RXP 407, but was completely inhibited by lisinopril, demonstrates that RXP 407, at the selected doses, does not interfere in angiotensin I metabolism by ACE in vivo. Thus, the C-domain, which is free of RXP 407, is apparently able to convert Ang I to Ang II with an efficacy similar to that performed by the wild-type ACE. From these results, it seems imperative to reinvestigate further the respective in vivo contributions of the N- and C-domains of ACE to Ang I metabolism. C-Selective inhibitors (Deddish et al., 1998) would be of great interest to establish whether the free N-terminal active site can counterbalance the inhibition of the C-domain, or whether Ang I metabolism is only controlled by the C-domain. In this respect, the significance of the particular sensitivity of the C-domain to chloride concentration, which is still subject to debate (Corvol et al., 1995), supports the hypothesis of a distinct function for each ACE active site. Specific inactivation of the C-domain of ACE by developing transgenic mice or the use of specific C-domain inhibitors may help to elucidate the C-domain contribution to the in vivo metabolism of Ang I, as well as to other ACE physiological substrates.

Following the cloning of human endothelial somatic ACE, both in vitro and in vivo studies have been designed to uncover possible functions that could be either controlled by its N- or C-domain (Wei et al., 1992; Jaspard et al., 1993; Rousseau et al., 1995; Michaud et al., 1997; Deddish et al., 1998; Junot et al., 1999). Interestingly, a natural ACE fragment containing only the functional N-terminal domain has been recently discovered, and account for up to 90% of ACE present in the ileal fluid (Deddish et al., 1994). This ACE fragment is probably produced by proteolytic cleavage of intact somatic ACE. Even if the biological role of this ACE fragment still remains unknown, this observation supports the view that each ACE domain may have specific in vivo functions (Deddish et al., 1996). Besides AcSDKP, Ang-(1-7) has been also identified as a natural substrate of ACE N-domain (Deddish et al., 1998). Thus, the development of selective inhibitors of one or other of the active sites of ACE may help to uncover still unknown physiological functions of ACE and may contribute to the efforts aimed at discovering whether the ACE gene duplication is associated with particular functions of this enzyme in mammalian species. In this respect, it is worth noting that two related “angiotsin I-converting enzymes” expressed in Drosophila, which are proteins containing a single active site, are believed to control various different functions (Houard et al., 1998).

AcSDKP administration has been shown to increase survival in mice treated with sublethal doses of cytotoxic agents (Bogden et al., 1998; Masse et al., 1998) and to reduce neutropenia in cancer patients undergoing cytarabin chemotherapy (Carde et al., 1999). However, the extensive hydrolysis of the administered AcSDKP by ACE has precluded further therapeutic use of this peptide. The in vivo stability of RXP 407 (Dive et al., 1999) and its efficacy in rising plasmatic concentrations of AcSDKP justify further studies to establish whether injection of RXP 407 will elicit a protection of the hematopoietic tissue during aggressive cancer chemotherapy. The possibility to control the AcSDKP metabolism with RXP 407, without interfering with the blood pressure regulation, dictates the choice of RXP 407 to perform these experiments, compared with more conventional nonselective ACE inhibitors.

References


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