Difference among Angiotensin-Converting Enzyme Inhibitors in Potentiating Effects on Bradykinin-Induced Microvascular Leakage in Guinea Pig Airways

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ABSTRACT—We investigated the effect of imidapril, a novel angiotensin-converting enzyme (ACE) inhibitor, on augmentation of airway microvascular leakage induced by bradykinin (BK) and substance P (SP) in guinea pigs and compared it with those of enalapril and captopril. The three ACE inhibitors significantly potentiated BK- and SP-induced airway microvascular leakage in a dose-dependent manner. In spite of the compatible or higher ACE inhibitory activity of imidapril, its potentiating activity in BK-induced leakage was lower than those of enalapril and captopril both by single administration (0.3–30 mg/kg, p.o.) and repeated administration for eight days (0.1–10 mg/kg/day, p.o.). The potentiating activities of the three ACE inhibitors were suppressed by pretreatment with a BK₂-receptor antagonist, but not by neurokinin 1 and neurokinin 2 antagonists, suggesting that neurokinins may not be involved in BK-induced leakage under the conditions used. On the other hand, the potentiating effect of imidapril in SP-induced leakage was weaker than those of enalapril and captopril only after single high doses. The present study shows that the ACE inhibitors have different activity in potentiation of the airway microvascular leakage induced by BK, which may be ascribable to the difference in their inhibition of BK hydrolysis. This evidence may partly explain the smaller incidence of dry cough induced by imidapril compared with other ACE inhibitors when clinically used as antihypertensive drugs.

Keywords: Angiotensin-converting enzyme inhibitor, Bradykinin, Vascular permeability, Plasma exudation, Airway (guinea pig)
be possible mediators of cough induction.

MATERIALS AND METHODS

Experimental animals

Male Hartley guinea pigs (SLC, Hamamatsu), 5 weeks of age, weighing 350–450 g were used. They were kept in an animal room with controlled temperature (23 ± 1°C) and humidity (55 ± 5%).

Airway microvascular leakage

According to the method of Rogers et al. (23, 24), extravasation of Evans blue dye to the airway tissue was measured. This reaction has been reported to correlate well with extravasation of radiolabeled albumin in the skin (25) and airways (26). Imidapril (0.3–100 mg/kg), enalapril and captopril (0.1–100 mg/kg) were orally administered 2 hr before BK or SP injection, and BK2 (1.2 mg/kg)-, neurokinin 1 (NK1) (0.5 mg/kg)- or NK2 (2 mg/kg)-antagonists were intravenously given immediately before BK injection. In some experiments, ACE inhibitors were given orally once a day for 8 days, and the last treatment was done 2 hr before BK or SP injection. Then the animals were anesthetized with sodium pentobarbital (30 mg/kg, i.p.), and the left jugular vein was cannulated to administer agents. Evans blue (30 mg/kg) and BK (3 nmol/kg) or SP (1 nmol/kg) were intravenously injected through the cannula over a period of 1 min. After 5 min, the animals were sacrificed by bleeding from the abdominal aorta. The thorax was opened and the lung was perfused with 50 ml of saline through the right atrium. The airway organs were removed, and the connective tissue, vasculature and parenchyma were gently scraped off. The trachea, main bronchi and intrapulmonary airways were blotted and weighed. The dye extracted by placing the tissues for 22 hr in 2 ml of formamide at room temperature was quantified photometrically at 620 nm (VPR-35; Otsuka Electronics, Osaka) and was expressed as pg/g wet tissue. ACE inhibitors were dissolved in 0.5% carboxymethylcellulose solution and BK- and NK-antagonists with physiological saline containing Tween 80.

Statistical analyses

Data are expressed as means with the standard error. Statistical analyses of the data were performed by analysis of variance (ANOVA) followed by Dunnett's method or the Tukey-Kramer method. When the P value was less than 0.05, the difference was considered to be significant.

RESULTS

Effect of BK and SP treatment on the airway microvascular leakage in guinea pigs and augmentation by enalapril

Intravenous injection of BK and SP caused a dose-dependent leakage of Evans blue in the trachea and main bronchi at doses above 3 nmol/kg and 30 pmol/kg, respectively (data not shown).

In the preliminary experiments, pretreatment of guinea pigs with enalapril (100 mg/kg, p.o.) 2 hr before BK and SP injection showed significant augmentation of the microvascular leakage in the airway at agonist doses of 3 and 1 nmol/kg, i.v., respectively (data not shown). Thus, the respective doses of the agonists were used in the following experiments. Neither imidapril, enalapril nor captopril, at 100 mg/kg, p.o., induced Evans blue leakage in the trachea and main bronchi (data not shown).

Effects of ACE inhibitors on BK-induced microvascular leakage in the guinea pig airway

All three ACE inhibitors dose-dependently augmented the BK (3 nmol/kg, i.v.)-induced leakage (Fig. 1). Significant augmentation by captopril, enalapril and imidapril was observed at 1, 3 and 30 mg/kg or more, respectively, in the trachea and at 3, 3 and 30 mg/kg or more, respectively, in the main bronchi. As compared with the control group (vehicle treated: 8.1 ± 1.2 pg Evans blue/g tissue), the potentiating activity of the leakage by imidapril, enalapril and captopril at 10 mg/kg was about 2.1 (17.2 ± 3.4 pg Evans blue/g tissue), 4.5 (36.8 ± 3.3) and 4.4 (35.4 ± 5.6) times higher than the control, respectively, in the trachea. In the main bronchi (control 9.0 ± 1.0), it was about 1.9 (16.8 ± 4.0 pg Evans blue/g tissue), 6.1 (55.1 ± 2.9) and 6.2 (55.4 ± 5.6) times higher, respectively, at the same dose. By multiple treatments for 8 days with the ACE inhibitors, a dose-dependent augmentation of BK-induced microvascular leakage was also observed both in the trachea and main bronchi (Fig. 2). The augmentation by imidapril was less than those by
enalapril and captopril. The augmentation of BK-induced microvascular leakage by multiple treatments was observed at lower doses than that for the single treatment.

Effects of a BK2 antagonist on augmentation of BK-induced microvascular leakage by ACE inhibitors

Pretreatment with a BK2 antagonist, d-Arg-[Hyp3-Thi5-γ-n-Phe7]-BK (1.2 mg/kg, i.v.), just before BK injection significantly reversed the augmentation of micro-
vascular leakage in the trachea, main bronchi and intrapulmonary airway induced by the ACE inhibitors that were given 2 hr prior to BK injection (Table 1). Airway microvascular leakage potentiations by imidapril (10 mg/kg) and enalapril (3 mg/kg) were almost completely inhibited by BK2 antagonist at all airway levels. At 10 mg/kg, the potentiating effect of captopril was also inhibited by more than 70% in all the airway tissues. At high doses of each inhibitor (30 mg/kg), it was also inhibited by more than 50-90%. However, no remarkable difference in the effect of BK2 antagonist on Evans blue leakage was observed among the ACE inhibitors tested in all the airway tissues.

Table 1. Effect of BK2 antagonist (D-Arg-[Hyp3, Thi5,8, D-Phe]-BK) on microvascular leakage induced by bradykinin in airway tissues of the guinea pigs

| Treatment | n  | Evans blue dye content (μg/g wet tissue) |
|-----------|----|----------------------------------------|
| Control   | 5  | 7.7 ± 2.3, 8.0 ± 0.8, 3.0 ± 0.4         |
| 0.5% CMC  |    |                                        |
| Imidapril | 6  | 14.0 ± 3.1, 12.1 ± 2.0, 5.9 ± 1.2       |
| 10 mg/kg + saline | 6  | 5.9 ± 0.6, 9.2 ± 0.9, 3.1 ± 0.5       |
| 10 mg/kg + BK2 antagonist (1.2 mg/kg) | 6  | 46.9 ± 3.7**, 45.8 ± 2.7**, 27.0 ± 1.7** |
| 30 mg/kg + saline | 5  | 13.3 ± 3.6**, 20.6 ± 3.7**, 10.3 ± 3.0** |
| 30 mg/kg + BK2 antagonist (1.2 mg/kg) | 5  |                                      |
| Enalapril | 4  | 22.8 ± 7.4, 32.4 ± 11.8**, 12.0 ± 3.6   |
| 3 mg/kg + saline | 4  | 4.2 ± 0.4, 7.5 ± 0.7, 3.9 ± 1.0        |
| 3 mg/kg + BK2 antagonist (1.2 mg/kg) | 4  | 42.4 ± 7.4**, 37.5 ± 6.1**, 25.2 ± 4.0** |
| 10 mg/kg + saline | 3  | 11.7 ± 1.1**, 17.8 ± 1.2, 11.0 ± 1.7** |
| 10 mg/kg + BK2 antagonist (1.2 mg/kg) | 4  | 45.4 ± 2.3**, 55.9 ± 9.3**, 24.9 ± 1.3** |
| 30 mg/kg + saline | 4  | 21.3 ± 4.0**, 26.6 ± 3.7**, 14.4 ± 3.5** |
| 30 mg/kg + BK2 antagonist (1.2 mg/kg) | 5  |                                      |
| Captopril | 5  | 47.1 ± 3.4**, 34.3 ± 2.0**, 20.2 ± 2.7** |
| 10 mg/kg + saline | 5  | 12.3 ± 3.6**, 15.3 ± 2.9**, 7.3 ± 1.6** |
| 10 mg/kg + BK2 antagonist (1.2 mg/kg) | 5  | 50.9 ± 3.8**, 50.1 ± 4.3**, 29.4 ± 2.6** |
| 30 mg/kg + saline | 5  | 9.3 ± 1.4**, 13.1 ± 2.1**, 7.4 ± 1.4** |
| 30 mg/kg + BK2 antagonist (1.2 mg/kg) | 5  |                                      |

ACE inhibitors were orally administered 2 hr before BK injection. The BK2 antagonist D-Arg-[Hyp3, Thi5,8, D-Phe]-BK was given i.v. to the animal immediately before administration of BK (3 nmol/kg, i.v.). Each value is a mean ± S.E.M. Statistical significance: *P < 0.05, **P < 0.01, compared with the control value (Dunnett's method); 1P < 0.05, 1**P < 0.01, compared with the ACE inhibitor group at the same dose (Tukey-Kramer method). I.P.A.: intrapulmonary airway.

Effects of NK1- and NK2-antagonist on augmentation of BK-induced microvascular leakage by ACE inhibitors

Neither the NK1 antagonist CP-96,345 (0.5 mg/kg, i.v.) nor the NK2 antagonist SR 48968 (2 mg/kg, i.v.) given just before BK injection affected the augmentation of Evans blue leakage in the airway tissues induced by the ACE inhibitors (Table 2). Co-administration of NK1 (0.5 mg/kg, i.v.)- and NK2 (2 mg/kg, i.v.)-antagonists did not show any effects either (data not shown).

Effects of ACE inhibitors on SP-induced microvascular leakage in the guinea pig airway

Enalapril dose-dependently augmented SP (1 nmol/kg, i.v.)-induced microvascular leakage in the trachea and main bronchi only at high doses of 30-100 and 100 mg/kg, p.o., respectively (Fig. 3). Captopril 10-100 mg/kg, p.o., enhanced the leakage only in the trachea. In contrast, imidapril (10-100 mg/kg, p.o.) did not augment leakage in either the trachea or the main bronchi. When the ACE inhibitors (10-100 mg/kg/day, p.o.) were given for 8 days, however, no significant augmentation of leakage was observed (Fig. 4).

DISCUSSION

Recently, ACE inhibitors have been reported to induce dry cough as a side effect in spite of their usefulness as antihypertensive drugs. ACE inhibitor-induced dry cough is independent of its antihypertensive and vasodilating effects (27) and does not correlate with serum ACE activ-
ity in patients (6). However, from the fact that angiotensin II-receptor antagonists that are being developed as antihypertensive agents do not induce cough in their clinical trials (28), ACE inhibition itself is thought to be one of the main mechanisms of dry cough induction. Clinically, the incidence of dry cough varies among individual inhibitors, being smaller for imidapril compared with enalapril and captopril (4, 20, 21).

In the present study, the influences of ACE inhibitors on biological activities of BK and SP were investigated in guinea pig airway. These peptides are possible mediators of cough induction and are also the substrates of ACE (kininase II) (7, 8). Augmentation of BK-induced microvascular leakage by imidapril was smaller than that by enalapril and captopril both by single (Fig. 1) and multiple treatment (Fig. 2). The main pharmacological effects of BK in the airway are bronchoconstriction and enhancement of vascular permeability, and it is reported that the BK₂ receptor is involved in these responses (29).

Table 2. Effects of the NK₁ antagonist CP-96,345 and the NK₂ antagonist SR 48968 on microvascular leakage induced by bradykinin in airway tissues of the guinea pig

| Treatment                      | Evans blue dye content (µg/g wet tissue) |
|--------------------------------|----------------------------------------|
|                                |       | trachea | main bronchi | I.P.A. |
| Control                        | 0.5% CMC | 8       | 8.8 ± 1.8 | 5.9 ± 1.3 | 3.6 ± 0.7 |
| Imidapril                      |        |         |           |         |
| 10 mg/kg + saline              | 6      | 17.1 ± 4.5 | 15.9 ± 4.1 | 9.8 ± 2.7 |
| 10 mg/kg + CP-96,345 (0.5 mg/kg) | 6     | 19.1 ± 3.7 | 13.7 ± 2.6 | 7.3 ± 1.3 |
| 10 mg/kg + SR 48968 (2 mg/kg)  | 6      | 11.0 ± 3.7 | 14.9 ± 4.1 | 7.7 ± 2.1 |
| 30 mg/kg + saline              | 6      | 37.9 ± 6.0** | 47.7 ± 4.5** | 31.5 ± 5.1** |
| 30 mg/kg + CP-96,345 (0.5 mg/kg) | 6     | 47.0 ± 4.4** | 51.7 ± 7.0** | 33.7 ± 4.8** |
| 30 mg/kg + SR 48968 (2 mg/kg)  | 6      | 35.7 ± 2.5** | 40.0 ± 6.4** | 26.1 ± 3.5** |
| Enalapril                      |        |         |           |         |
| 3 mg/kg + saline               | 6      | 21.7 ± 5.9 | 30.4 ± 6.7** | 15.1 ± 3.7 |
| 3 mg/kg + CP-96,345 (0.5 mg/kg) | 6     | 26.3 ± 5.2 | 29.1 ± 5.3** | 21.3 ± 3.7** |
| 3 mg/kg + SR 48968 (2 mg/kg)  | 6      | 25.1 ± 3.5 | 43.4 ± 8.4** | 20.0 ± 4.2** |
| 10 mg/kg + saline              | 6      | 34.8 ± 6.6** | 40.6 ± 3.9** | 26.4 ± 3.1** |
| 10 mg/kg + CP-96,345 (0.5 mg/kg) | 7     | 41.8 ± 3.1** | 37.8 ± 3.4** | 31.6 ± 2.8** |
| 10 mg/kg + SR 48968 (2 mg/kg)  | 6      | 44.0 ± 4.6** | 47.8 ± 4.1** | 34.0 ± 4.8** |
| Captopril                      |        |         |           |         |
| 3 mg/kg + saline               | 6      | 43.9 ± 3.7** | 42.3 ± 2.8** | 28.5 ± 3.3** |
| 3 mg/kg + CP-96,345 (0.5 mg/kg) | 6     | 44.3 ± 5.2** | 32.3 ± 6.7** | 25.2 ± 2.5** |
| 3 mg/kg + SR 48968 (2 mg/kg)  | 6      | 34.2 ± 5.7** | 44.3 ± 3.0** | 29.9 ± 2.7** |
| 10 mg/kg + saline              | 7      | 43.5 ± 6.7** | 42.6 ± 4.9** | 34.4 ± 4.1** |
| 10 mg/kg + CP-96,345 (0.5 mg/kg) | 7     | 46.4 ± 5.7** | 49.2 ± 6.2** | 35.0 ± 4.7** |
| 10 mg/kg + SR 48968 (2 mg/kg)  | 5      | 54.5 ± 4.0** | 56.2 ± 4.3** | 33.1 ± 2.3** |

ACE inhibitors were orally administered 2 hr before BK injection. NK₁ antagonist (CP-96,345) and NK₂ antagonist (SR 48968) was given i.v. to the animal immediately before administration of BK (3 nmol/kg, i.v.). Each value is a mean ± S.E.M. Statistical significance: **P < 0.01, compared with the control value (Dunnett's method). I.P.A.: intrapulmonary airway.

This augmentation of BK-induced microvascular leakage by ACE inhibitors was blocked by the selective BK₂ antagonist d-Arg-[Hyp³-Thi⁴,₈-D-Phe⁷]-BK (Table 1), and without ACE inhibitors, microvascular leakage was not observed by the amount of BK used (data not shown). These lines of evidence suggest that ACE inhibitors suppress the breakdown of BK by ACE in the airway and the extent of breakdown is different among the ACE inhibitors. It has been demonstrated that enalapril significantly increased the blood BK levels, whereas imidapril did not have any influence on it in guinea pigs (personal communication, T. Miyata et al.). Regarding the augmentation of BK-induced hypotension which may influence the vascular permeability, imidapril was almost as potent as enalapril and less active than captopril in the rat (19). In SP-induced microvascular leakage, similar augmentation was observed. However, the extent was weak in imidapril compared with other ACE inhibitors only after single high doses (Fig. 3). The effects of multiple treatment with
the three ACE inhibitors were almost the same (Fig. 4). Vascular leakage induced by BK was more sensitive to ACE inhibitors than that induced by SP. One of the explanations of the results is substrate specificity of BK degrading enzymes, namely ACE and neutral endopeptidase (NEP). According to Turner et al. (30), SP has more than 1000 times higher affinity to NEP in comparison with ACE, while BK has about 10 times higher affinity to NEP. From the results observed by us and others described above, it is considered that the degradation of BK is more extensively inhibited by ACE inhibitors than in the case of SP.

Wei et al. (31, 32) have reported that ACE has two
active centers (N and C domains) in its molecule and that the affinities of ACE inhibitors to each domain are different among the inhibitors. It is interesting to know whether the difference in the affinities correlates with the difference in the degree of augmentation of BK-induced vascular leakage and with the incidence of dry cough induction after treatment with ACE inhibitors. Because imidapril has lower activities in these two responses than enalapril and captopril in spite of its compatible or higher inhibitory activity of ACE (17–20). Okamura et al. (33) studied the activity of ACE inhibitors from the viewpoint of substrate specificity using the isolated dog mesenteric artery and vein. They demonstrated that imidaprilat showed relatively lower inhibitory activity on BK degradation than enalaprilat at the concentrations that exhibit equal inhibiting activity, where imidaprilat and enalaprilat were active metabolites of imidapril and enalapril, respectively. These facts may partly explain our present results in the BK-induced vascular leakage experiment.

We also investigated the effects of NK receptor antagonists in the augmentation of the ACE inhibitors. It is reported that BK is a potent stimulant of the sensory nerve (C-fiber) of the airways (34) and releases tachykinins (35, 36) and that augmentation of BK-induced vascular permeability is inhibited by NK1-receptor antagonists (37, 38). The present results showed, however, that neither the NK1 antagonist nor the NK2 antagonist had any effect on augmenting activities of the ACE inhibitors (Table 2). Therefore, it is supposed that tachykinins are not involved in the potentiating effect by the ACE inhibitors in our protocol. Though the reason for this discrepancy is unclear, the differences in the route of administration (36, 37), the dosage of BK or estimating systems (bronchoconstriction, vascular leakage) may be involved.

In conclusion, when the ACE inhibitors were given, augmentation of the BK-induced vascular leakage was smaller for imidapril compared with enalapril and captopril. This difference could be ascribed to the difference in the effects of ACE inhibitors on BK degradation by ACE (kininase II) or other peptidylic enzymes. Therefore, we suppose that imidapril is a more selective inhibitor of angiotensin I conversion compared with BK degradation than enalapril and captopril, and that BK is thought to be one of the main mediators involved in dry cough formation induced in patients by the treatment with ACE inhibitors. The above evidence may partly explain the smaller incidence of dry cough induced by imidapril compared with other ACE inhibitors.

Acknowledgments

We thank Dr. T. Oh-ishi and Dr. T. Iwasaki for their encouragement and advice. Thanks are also due to Dr. K. Kikuta for his helpful support.

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