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European Journal of Pharmacology 337 (1997) 259–265

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Angiotensin-converting enzyme inhibitors can potentiate ozone-induced airway hyperresponsiveness

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Received 26 June 1997; revised 25 August 1997; accepted 29 August 1997

Abstract

We investigated the effects of single and chronic oral administration of angiotensin-converting enzyme inhibitors on ozone-induced airway hyperresponsiveness in guinea pigs. Ozone exposure (3 ppm for 2 h) significantly increased airway responsiveness in vehicle-treated animals and in animals with either single or chronic administration (8 days) of drugs. Single administration of imidapril, enalapril and captopril significantly potentiated ozone-induced airway hyperresponsiveness at a dose of 100, 50 and 50 mg/kg, respectively, although these doses did not influence airway responsiveness in normal guinea pigs, i.e., the magnitude of potentiation was captopril > enalapril > imidapril. In the study of chronic administration of the drugs, imidapril (10–100 mg/kg per day) had no influence on airway responsiveness in both normal and ozone-treated animals. In contrast, captopril and enalapril (10–100 mg/kg per day) dose-dependently potentiated ozone-induced airway hyperresponsiveness, with no influence on airway responsiveness in normal animals. That is, the magnitude was enalapril > captopril. These results indicate that angiotensin-converting enzyme inhibitors potentiate airway responsiveness in ozone-treated guinea pigs but not in normal guinea pigs and that imidapril is less potent than enalapril and captopril in potentiating ozone-induced airway hyperresponsiveness in guinea pigs. © 1997 Elsevier Science B.V.

Keywords: Imidapril; Enalapril; Captopril; Ozone; Angiotensin-converting enzyme; Airway hyperresponsiveness

1. Introduction

Angiotensin-converting enzyme inhibitors, which block the renin–angiotensin–aldosterone system and activate the kallikrein–kinin system, are used to treat hypertension and congestive heart failure (Lindgren and Andersson, 1989). Their use results in a lowering of blood pressure without adverse effects on the central nervous system, cardiac function and metabolism of lipids, glucose and uric acid (Tobian et al., 1994; Ito et al., 1995). However, dry cough has been recognized as a side effect of angiotensin-converting enzyme inhibitors (Coulter and Edwards, 1987; Lindgren et al., 1989). It has not yet been clarified how angiotensin-converting enzyme inhibitors produce cough, although several mechanisms such as airway hyperresponsiveness (Bucknall et al., 1988; Kaufman et al., 1989), increased cough reflex (Fuller and Choudry, 1987), or increase in bradykinin (Takahama et al., 1996) and/or a local increase in perineuronal substance P (Ogihara et al., 1991) have been proposed.

Airway hyperresponsiveness is an important pathophysiological feature of asthma. The mechanism of airway hyperresponsiveness has not been clarified because it is extremely complicated. The ozone-induced airway hyperresponsiveness model in guinea pigs has been used as a tool to clarify the mechanism of development of airway hyperresponsiveness. It has been reported that the development of airway hyperresponsiveness and airway inflammation induced by ozone are associated with an increase in perineuronal tachykinin (Murlas et al., 1993; Tepper et al., 1993; Koto et al., 1995). It is possible that the development of airway hyperresponsiveness induced by ozone is associated with the mechanism of cough induction by angiotensin-converting enzyme inhibitors.

Imidapril is a novel angiotensin-converting enzyme inhibitor which has a potent and long-lasting hypotensive action (Kubo et al., 1991) with a very low incidence of cough in clinical trials (Sasaguri et al., 1994; Saruta et al.,

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1995). It has been also reported that the drug has a very weak effect on 1,1-dimethyl-4-phenyl piperazinium iodide-, citric acid- and capsaicin-induced cough reflex in experiments using guinea pigs (Sumikawa et al., 1992; Takahama et al., 1996).

In this study, we investigated the effect of single and 8-day chronic administration of imidapril on ozone-induced airway hyperresponsiveness in guinea pigs compared with the effects of enalapril and captopril.

2. Materials and methods

2.1. Animals

Male Hartley guinea pigs, weighing 250 to 580 g, were obtained from Japan SLC (Hamamatsu, Shizuoka, Japan). These animals were acclimatized in an environmentally controlled room (temperature; 23 ± 2°C, humidity; 55 ± 5%, illumination time; 7.00 to 19.00) with food and water available ad libitum for 1 week before the experiment. Animals to receive single administration were fasted for 16 to 20 h before administration, but animals for chronic administration were not. Experimental procedures followed in this study adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals guideline.

2.2. Chemicals

Imidapril and enalapril were synthesized at the Lead Optimization Research Laboratory of Tanabe Seiyaku. Captopril was obtained from Sigma (St. Louis, MO, USA).

Other chemicals were obtained as follows: pentobarbital sodium (Abbott, North Chicago, IL, USA), gallamine triethiodide (Sigma), methacholine chloride (Nakalai Tesque, Kyoto, Japan) and carboxymethylcellulose (Kokusan Chemical, Tokyo, Japan).

2.3. Ozone exposure

Animals were placed in a chamber (size; $29 \times 19 \times 25$ cm) and inhaled 3 (± 0.5) ppm ozone produced by an ozone generator (OZX-02, Silver Seikou, Tokyo, Japan) for 2 h. The concentration of ozone in the chamber was closely monitored by an ozone detector (SOZ-3000 and -3100, Seki Electronics, Tokyo, Japan) during ozone exposure. Animals in the air-exposed group were placed in cages until the measurement of airway responsiveness to methacholine.

2.4. Measurement of airway responsiveness to methacholine

Air- or ozone-exposed animals were anesthetized by intraperitoneal injection of 60 mg/kg pentobarbital sodium and artificially ventilated with a Harvard 683 respirator (volume, 10 ml/kg; rate, 60 strokes/min) through a tracheal cannula immediately after air or ozone exposure. Spontaneous respiration was prevented by intravenous injection of 5 mg/kg gallamine triethiodide. Pulmonary inflation pressure as an index of airway responsiveness was measured by a pressure transducer (LPU-0.1, Nihon Kohden, Tokyo, Japan) connected to the tracheal cannula. Airway responsiveness to methacholine was evaluated by measurement of pulmonary inflation pressure using a pressure transducer. Pulmonary inflation pressure is considered to give a combined measure of airway smooth muscle contraction, mucous secretion and/or edema. To evaluate airway responsiveness, challenge with methacholine as a spasmogen was performed by inhalation and the concentration–response curves 120 min after air or ozone exposure were obtained. The tracheal cannula was connected to a container (inside diameter, 29 mm; height, 50 mm) containing 5 ml methacholine saline solution (0.1 to 1000 μg/ml) and under the above conditions of respiration, an aerosol was generated from the solution in the container by means of an ultrasonic nebulizer (TUR-3000, Nihon Kohden) for 2 min.

2.5. Drug administration

Drugs were orally administered once a day for one day or 8 days using a sterile polyethylene tube. Ozone exposure was performed 30 min after the last administration of angiotensin-converting enzyme inhibitors. The drugs were dissolved or suspended in 0.5% carboxymethylcellulose to 5 ml/kg to give doses of 10, 30, 50 and 100 mg/kg, p.o.

2.6. Analysis

All results were expressed as the mean ± S.E.M. The magnitude of airway responsiveness after air or ozone exposure was determined as the log-transformed methacholine provocative concentration (ng/ml) causing a 5 or 10 cmH_2O increase in pulmonary inflation pressure ($\log PC_5$ and $\log PC_{10}$). A comparison of mean values was made by the Student's *t*-test or one-way analysis of variance (ANOVA) followed by Tukey–Kramer's method. Differences were considered to be statistically significant when $P < 0.05$.

3. Results

3.1. Effect of single administration of angiotensin-converting enzyme inhibitors on airway responsiveness in air- or ozone-exposed guinea pigs

Aerosolized methacholine dose-dependently increased pulmonary inflation pressure at concentrations of 10

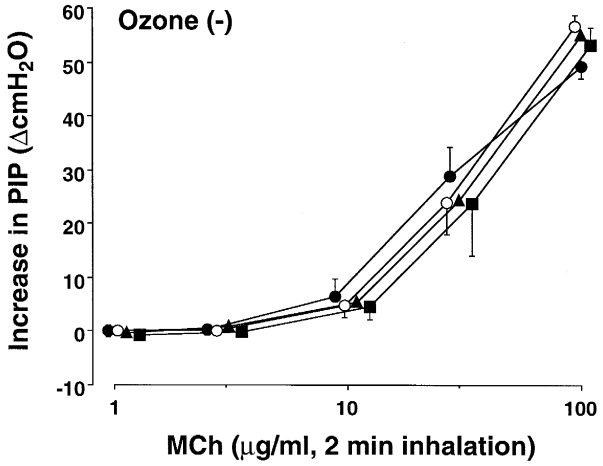

Fig. 1. Effect of single administration of imidapril, enalapril and captopril on airway responsiveness to methacholine (MCh) aerosol in air-exposed guinea pigs. Vehicle (○), imidapril (100 mg/kg, ●), enalapril (50 mg/kg, ▲) or captopril (50 mg/kg, ■) was orally administered to animals 270 min before methacholine aerosol challenge. Each symbol with bar represents the mean ± S.E.M. of 6–12 experiments. PIP; pulmonary inflation pressure.

μg/ml and higher in the vehicle-air control (Fig. 1). Single administration of imidapril (100 mg/kg, p.o.), enalapril (50 mg/kg, p.o.) or captopril (50 mg/kg, p.o.) did not influence airway responsiveness to methacholine in air-exposed animals (Fig. 1 and Table 1).

In the vehicle-ozone control, methacholine dose-dependently increased pulmonary inflation pressure at concentrations of 1 μg/ml and higher (Fig. 2). Log PC_5 and log PC_{10} of vehicle-treated control were significantly ($P < 0.001$ by Student's *t*-test) decreased by ozone exposure (Tables 1 and 2). Imidapril, enalapril or captopril dose-dependently potentiated the airway responsiveness to methacholine after ozone exposure (Fig. 2). Log PC_5 and log PC_{10} of each angiotensin-converting enzyme inhibitor were decreased dose-dependently (Table 2). Decreases in log PC_5 of 100 mg/kg imidapril, 50 mg/kg enalapril and 50 mg/kg captopril were statistically significant compared to vehicle-ozone control at $P < 0.05$. Furthermore, log PC_{10} of 50 mg/kg captopril was also significantly decreased compared to vehicle-ozone control at $P < 0.05$ (Table 1).

Table 1
Effects of imidapril, enalapril and captopril on airway responsiveness to methacholine in air-treated guinea pigs

Drugs (mg/kg per day)	Single administration		8-day administration	
	log PC_5	log PC_{10}	log PC_5	log PC_{10}
Vehicle	4.10 ± 0.10	4.23 ± 0.09	4.34 ± 0.06	4.42 ± 0.05
Imidapril 100	3.91 ± 0.12	4.08 ± 0.12	4.10 ± 0.08	4.22 ± 0.06
Enalapril 50	4.13 ± 0.15	4.24 ± 0.13	n.d.	n.d.
Enalapril 100	n.d.	n.d.	4.15 ± 0.14	4.33 ± 0.09
Captopril 50	4.18 ± 0.14	4.29 ± 0.12	n.d.	n.d.
Captopril 100	n.d.	n.d.	4.12 ± 0.11	4.27 ± 0.11

Values are mean ± S.E.M., $n = 6–12$. n.d., not determined.

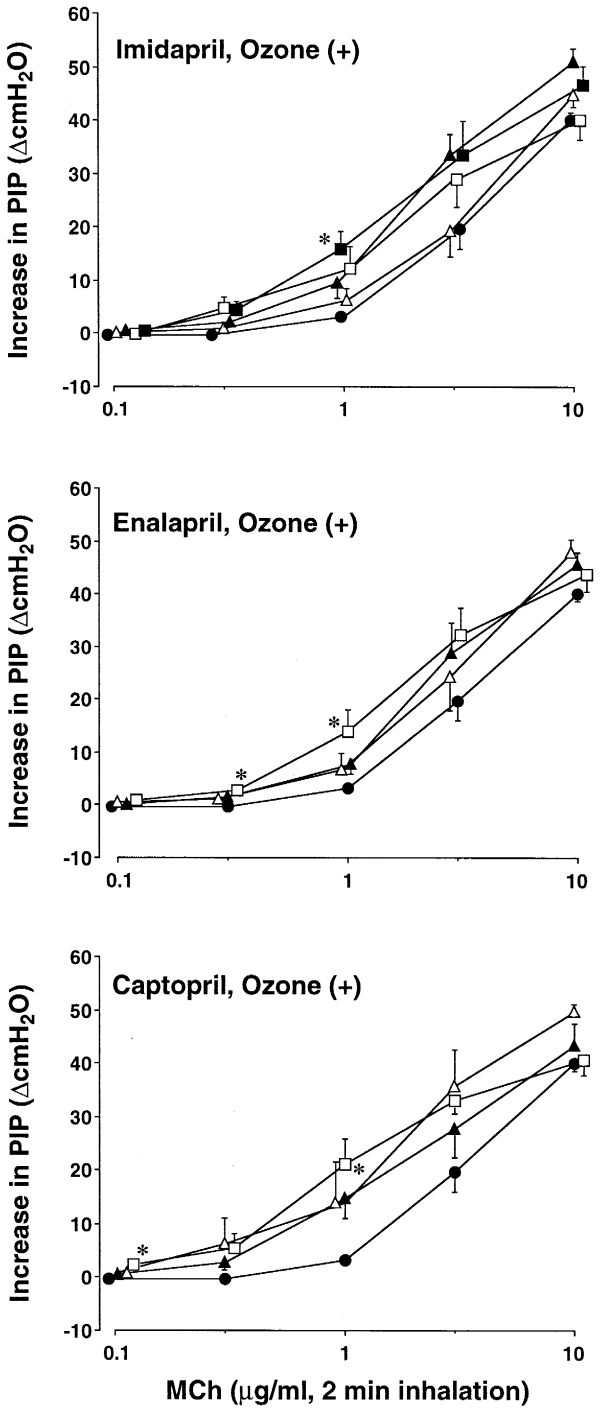

Fig. 2. Effect of single administration of imidapril, enalapril and captopril on ozone-induced airway hyperresponsiveness in guinea pigs. Imidapril, enalapril and captopril at doses of 10 (△), 30 (▲), 50 (□) and 100 (■) mg/kg and vehicle (●) were orally administered to animals 30 min before ozone exposure. Animals inhaled 3 ppm ozone for 2 h. Methacholine aerosol challenge was performed 2 h after ozone exposure. Each symbol with bar represents the mean ± S.E.M. of 6–8 experiments. * $P < 0.05$; statistically significant compared with vehicle-treated group by one-way ANOVA (Tukey–Kramer's method). PIP; pulmonary inflation pressure.

Table 2
Effects of imidapril, enalapril and captopril on airway responsiveness to methacholine in ozone-treated guinea pigs

Drugs (mg/kg per day)	Single administration		8-day administration	
	$\log PC_5$	$\log PC_{10}$	$\log PC_5$	$\log PC_{10}$
Vehicle	3.07±0.05 [c]	3.26±0.07 [c]	3.30±0.09 [c]	3.51±0.08 [c]
Imidapril 10	3.01±0.15	3.21±0.12	3.20±0.06	3.40±0.07
Imidapril 30	2.79±0.11	2.96±0.09	3.32±0.11	3.61±0.09
Imidapril 50	2.68±0.16	2.85±0.15	n.d.	n.d.
Imidapril 100	2.54±0.09 [a]	2.91±0.16	3.20±0.16	3.45±0.13
Enalapril 10	3.04±0.12	3.19±0.12	2.98±0.14	3.17±0.13
Enalapril 30	2.86±0.10	3.08±0.10	2.94±0.16	3.09±0.16
Enalapril 50	2.64±0.11 [a]	2.93±0.11	n.d.	n.d.
Enalapril 100	n.d.	n.d.	2.69±0.08 [b]	3.01±0.09 [b]
Captopril 10	2.76±0.17	2.95±0.19	3.08±0.21	3.33±0.16
Captopril 30	2.72±0.18	2.91±0.14	3.24±0.11	3.54±0.12
Captopril 50	2.44±0.13 [a]	2.68±0.14 [a]	n.d.	n.d.
Captopril 100	n.d.	n.d.	2.83±0.13 [a]	3.10±0.12

Values are mean±S.E.M., $n = 6–17$. n.d., not determined.
[a] $P < 0.05$ and [b] $P < 0.01$; statistically significant compared with vehicle control by one-way ANOVA (Tukey–Kramer's method).
[c] $P < 0.001$; statistically significant compared with air-exposed vehicle control (Table 1) by Student's *t*-test.

3.2. Effect of chronic administration of angiotensin-converting enzyme inhibitors on airway responsiveness in air- or ozone-exposed guinea pigs

Aerosolized methacholine dose-dependently increased pulmonary inflation pressure at concentrations of 10 μg/ml and higher in vehicle-air control group. Chronic administration of imidapril, enalapril or captopril did not influence airway responsiveness to methacholine aerosol in air-exposed animals (Fig. 3 and Table 1).

In vehicle-ozone control, methacholine dose-dependently increased pulmonary inflation pressure at concentra-

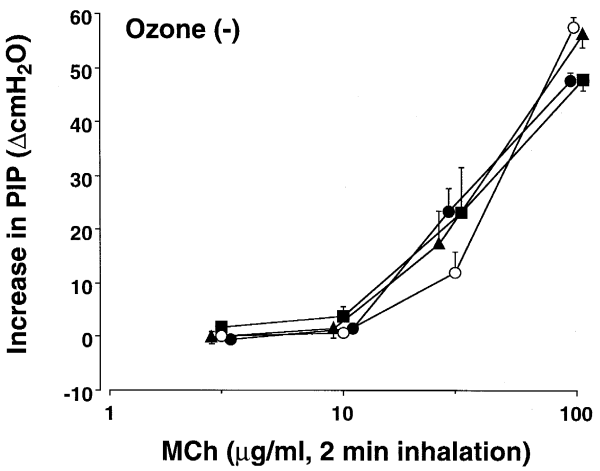

Fig. 3. Effect of 8-day chronic administration of imidapril, enalapril and captopril on airway responsiveness to methacholine (MCh) in air-exposed guinea pigs. Vehicle (○), imidapril (100 mg/kg per day, ●), enalapril (100 mg/kg per day, ▲) or captopril (100 mg/kg per day, ■) was orally administered to animals. Each symbol with bar represents the mean±S.E.M. of 6–12 experiments. PIP; pulmonary inflation pressure.

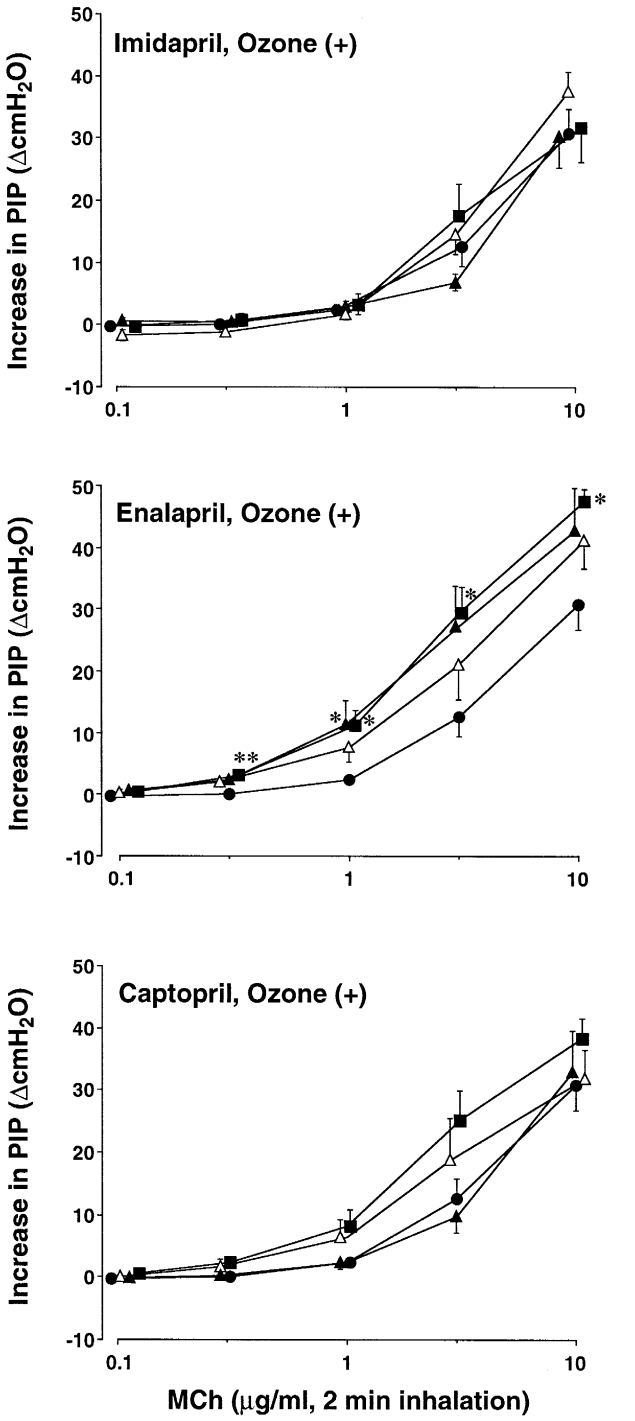

Fig. 4. Effects of chronic administration of imidapril, enalapril and captopril on ozone-induced airway hyperresponsiveness in guinea pigs. Imidapril, enalapril and captopril at doses of 10 (△), 30 (▲) and 100 (■) mg/kg per day and vehicle (●) were orally administered to animals for 8 days. Animals inhaled 3 ppm ozone (for 2 h) 30 min after the last administration of drugs. Each symbol with bar represents the mean± S.E.M. of 9–17 experiments. * $P < 0.05$ and * * $P < 0.01$; statistically significant compared with vehicle-treated group by one-way ANOVA (Tukey–Kramer's method). PIP; pulmonary inflation pressure.

Table 3
Effects of imidapril, enalapril and captopril on baseline pulmonary inflation pressure in air- or ozone-treated guinea pigs

Drugs (mg/kg per day)	Baseline pulmonary inflation pressure (cm H_2O)			
	single administration		8-day administration	
	air	ozone	air	ozone
Vehicle	12.1 ± 0.7	20.9 ± 0.8 [a]	12.5 ± 0.5	23.4 ± 0.5 [a]
Imidapril 100	12.0 ± 0.9	21.8 ± 0.5 [a]	12.2 ± 1.4	25.1 ± 0.5 [a]
Enalapril 50	13.1 ± 1.5	21.0 ± 0.9 [a]	n.d.	n.d.
Enalapril 100	n.d.	n.d.	15.9 ± 1.4	24.4 ± 0.7 [a]
Captopril 50	11.9 ± 1.5	20.1 ± 0.4 [a]	n.d.	n.d.
Captopril 100	n.d.	n.d.	12.9 ± 1.0	23.0 ± 0.8 [a]

Values are mean ± S.E.M., $n = 6–17$. n.d.: not determined.
[a] $P < 0.001$; statistically significant compared with air-exposed group by Student's *t*-test.

tions of 1 μg/ml and higher (Fig. 4). $\log PC_5$ and $\log PC_{10}$ of vehicle-treated control were significantly ($P < 0.001$ by Student's *t*-test) decreased by ozone exposure (Tables 1 and 2). $\log PC_5$ and $\log PC_{10}$ of enalapril and captopril were decreased dose-dependently but those of imidapril were not (Table 2). The decreases in $\log PC_5$ of 100 mg/kg per day enalapril and captopril were statistically significant compared to control exposed to ozone at $P < 0.01$ and $P < 0.05$, respectively. Furthermore, the decrease in $\log PC_{10}$ of 100 mg/kg per day enalapril was also statistically significant compared to vehicle-ozone control at $P < 0.01$ (Table 2).

3.3. Effects of single and chronic administration of angiotensin-converting enzyme inhibitors on baseline pulmonary inflation pressure in air- or ozone-exposed guinea pigs

The effects of single and chronic administration of the drugs on baseline pulmonary inflation pressure were investigated and the results are shown in Table 3. Baseline pulmonary inflation pressure in the air-exposed group was not influenced by single or chronic administration of angiotensin-converting enzyme inhibitors at all. Baseline pulmonary inflation pressure was increased by ozone exposure; however, the increase of baseline pulmonary inflation pressure was not influenced by single or chronic administration of angiotensin-converting enzyme inhibitors.

4. Discussion

It has been reported that inflammatory responses could be potentiated by angiotensin-converting enzyme inhibitors (Lindgren et al., 1987). Angiotensin-converting enzyme inhibitors have also been suggested to be a good alternative in the treatment of hypertension in asthmatic patients (Ziment, 1983; Krane and Walling, 1987). Meanwhile there are only a few reports of patients developing asthma while receiving angiotensin-converting enzyme inhibitors (Popa, 1987). It needs to be investigated whether there is a point in common between the mechanisms of cough and asthma underlying airway hyperresponsiveness. In this study, we investigated the effects of angiotensin-converting enzyme inhibitors on ozone-induced airway hyperresponsiveness in guinea pigs. Airway responsiveness to methacholine in air-exposed guinea pigs was not influenced by either single or chronic administration of high doses of angiotensin-converting enzyme inhibitors. However, angiotensin-converting enzyme inhibitors given by the two types of administration potentiated ozone-induced airway hyperresponsiveness without any change in baseline, although there was a difference in the degree of potentiation among the drugs. On single administration, imidapril significantly potentiated airway hyperresponsiveness at a dose of 100 mg/kg and potentiation by enalapril and captopril was significant at a dose of 50 mg/kg. Thus, the order of potentiation of ozone-induced airway hyperresponsiveness was captopril > enalapril > imidapril. On chronic administration, enalapril significantly potentiated airway hyperresponsiveness at a dose of 30 mg/kg per day in dose–response curves of methacholine and at a dose of 100 mg/kg per day with respect to both $\log PC_5$ and $\log PC_{10}$ values. Captopril also dose-dependently potentiated airway hyperresponsiveness and the decrease in $\log PC_5$ value was significant. In contrast to enalapril and captopril, chronic administration of imidapril did not potentiate airway hyperresponsiveness. Taking these results into consideration, imidapril was less potent than enalapril and captopril in potentiating ozone-induced airway hyperresponsiveness. The difference is not a result of the difference between the angiotensin-converting enzyme inhibiting activity of imidapril and enalapril, because the potencies of their inhibitory effect on angiotensin-I-induced hypertension in guinea pigs were identical (unpublished data). However, Okamura et al. (1993) reported that the potency of imidaprilat (an active metabolite of imidapril) to potentiate bradykinin responses of isolated dog mesenteric blood vessels and coronary arteries is lower than that of enalaprilat (an active metabolite of enalapril). These reports suggest the possibility that the amount of bradykinin after administration of enalapril and captopril is greater than that after administration of imidapril, while the reason the difference occurs has not been identified. It has been reported that angiotensin-converting enzyme has two active domains (N and C domains) with different specificity and enzymatic properties (Wei et al., 1991; Wei et al., 1992; Jaspard et al., 1993). The relative affinity of the drugs for the two active domains may have a great influence on the amount of bradykinin in the airway.

Imidapril was less potent in experiments on cough than enalapril and captopril (Sumikawa et al., 1992; Takahama et al., 1996). From our results and in this context, the mechanism of potentiation of cough may be partly similar to that of ozone-induced airway hyperresponsiveness. As described above, both single and chronic administration of

the drugs did not potentiate airway responsiveness to methacholine in air-exposed guinea pigs. In the cough response of normal guinea pigs, however, enalapril and captopril potentiated the responses induced by capsaicin (Takahama et al., 1996). Capsaicin releases substance P from the C-fibres of the airway to stimulate coughing (Forsberg and Karlsson, 1986; Saria et al., 1988). We have previously demonstrated that damage to the airway epithelium is important in the development of ozone-induced airway hyperresponsiveness, but airway inflammatory cell infiltration is not (Matsubara et al., 1995; Matsubara et al., 1997). In this airway hyperresponsiveness model, we should consider the possibility that exposure of C-fibres to exogenous spasmogen occurred through disorder of epithelial cells by ozone exposure. Koto et al. (1995) reported that tachykinins may be responsible for ozone-induced airway hyperresponsiveness, possibly via neurogenic inflammation. These findings suggest that activities of tachykinins in the airway may be enhanced after airway epithelial damage by ozone. Hence angiotensin-converting enzyme inhibitors might not potentiate the airway responsiveness to methacholine in air-exposed guinea pigs because of the existence of normal airway epithelium.

We have speculated that damage to airway epithelium exposes C-fibre after ozone exposure and axon reflex is consequently accelerated. In asthma, there is a hypothesis for the pathogenesis of bronchial asthma that envisaged a role for bradykinin in exciting C-fibre afferent nerve endings, leading to bronchoconstriction by means of an axon reflex (Barnes, 1986). Thus, it is likely that a common mechanism between asthma and ozone-induced airway hyperresponsiveness exists. As described above, the angiotensin-converting enzyme inhibitors did not affect baseline pulmonary function, although the drugs potentiated the ozone-induced airway hyperresponsiveness. The drugs may potentiate the axon reflex via C-fibres attacked by exogenous spasmogen.

Angiotensin-converting enzyme activity is 1000 times less active than neutral endopeptidase activity in the degradation of tachykinins, and captopril has very low activity in the inhibition of neutral endopeptidase (Turner et al., 1985). Therefore, an angiotensin-converting enzyme inhibitor would increase the amount of bradykinin but not of tachykinins. Fox et al. (1996) reported that bradykinin-evoked sensitization of airway sensory nerves underlies the pathogenesis of angiotensin-converting enzyme inhibitor-induced cough. Murata et al. (1995) also reported that angiotensin-converting enzyme inhibitors augmented bradykinin-induced airway vascular leakage and that the magnitude was smaller for imidapril compared with enalapril and captopril. This is in agreement with the present result. Accordingly, we can consider that the increase in bradykinin by angiotensin-converting enzyme inhibition may potentiate ozone-induced airway hyperresponsiveness via activation of airway sensory nerves associated with endogenous tachykinins.

Chronic administration of imidapril and captopril was less potent in potentiating airway hyperresponsiveness than single administration of the drugs. On the other hand, enalapril potentiated airway hyperresponsiveness after chronic administration more than after single administration. It is unlikely that the difference in potentiation between the two types of administration results from the different bioavailability of each drug which was examined in a previous study (Takahama et al., 1996). No significant difference in the concentration of active metabolites of imidapril and enalapril in plasma, lung and trachea of guinea pigs was observed after 8-day chronic administration of the drugs (Kawashima et al., 1994). Taken together with the importance of neurogenic inflammation in the development of ozone-induced airway hyperresponsiveness, there is a possibility that chronic administration of imidapril and captopril, but not enalapril, produces desensitization of afferent nerve responsiveness to endogenous tachykinins and kinins such as substance P and bradykinin. Further study is needed to clarify the mechanism of the difference.

In conclusion, angiotensin-converting enzyme inhibitors potentiated ozone-induced airway hyperresponsiveness but not airway responsiveness in normal guinea pigs. However, imidapril given by single or chronic administration was less potent in potentiating ozone-induced airway hyperresponsiveness than enalapril or captopril.

Acknowledgements

We wish to thank Dr. K. Matsumoto and Dr. T. Iwasaki of Tanabe Seiyaku, for their support throughout the study.

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