Abstract. Objective: To demonstrate tissue selective bradykinin (BK) potentiating action of angiotensin converting enzyme inhibitors, we studied effects of imidaprilat and ramiprilat, active metabolites of imidapril and ramipril, respectively, on bronchoconstriction and hypotension both induced by BK in vasopressin-infused anesthetized guinea pigs.

Methods: We measured pulmonary inflation pressure and blood pressure in vasopressin-infused anesthetized guinea pigs at the same time. BK-induced changes in pulmonary inflation pressure and blood pressure before and after the administration of ACE inhibitor were compared.

Results: Imidaprilat and ramiprilat enhanced BK-induced hypotension comparably, and this effect was inhibited by Nω-nitro-L-arginin-methylester (L-NAME, a nitric oxide synthase inhibitor). Although imidaprilat did not affect BK-induced bronchoconstriction, ramiprilat enhanced the bronchoconstriction significantly. SR48968, a selective NK2 receptor antagonist, significantly inhibited the enhancing effect of ramiprilat on BK-induced bronchoconstriction.

Conclusion: These results suggest that enhancement of BK-induced hypotension by imidaprilat and ramiprilat is mediated by nitric oxide (NO), but the mediator of the enhancing action of ramiprilat on BK-induced bronchoconstriction is mainly neurokinin A.

Key words: Imidaprilat – Ramiprilat – Bradykinin – Bronchoconstriction – Hypotension

Introduction

Angiotensin converting enzyme (ACE) inhibitors are among the first drugs of choice for the treatment of hypertension [1]. ACE inhibitors are now also widely used to treat patients with heart failure [2]. On the surface of endothelial cells, ACE converts the inactive decapeptide angiotensin I to the vasopressor octapeptide angiotensin II. ACE is also known as one of dipeptidyl carboxypeptidases, kininase II, which can degrade bradykinin (BK), a vasodilatory nonapeptide [3]. BK shows endothelium-dependent relaxation of blood vessels [4]. It has been reported that ACE inhibitors-induced hypotension was partly inhibited by a BK B2 receptor antagonist [5]. Thus, it is possible that BK accumulated by treatment with ACE inhibitors is associated with hypotension, which is a main therapeutic effect of ACE inhibitors. However, BK has various actions, such as contraction of tracheal smooth muscle [6], acceleration of tachykinin release by stimulating bronchial C-fibres [7] and acceleration of prostaglandins (PGs) synthesis through activation of phospholipase A2 (PLA2) [8, 9] beside an hypotensive effect. Thus, it is important to study the various effects of BK with or without ACE inhibitors to understand the characteristics of ACE inhibitors in vivo.

In this study, we investigated the effects and mechanisms of ACE inhibitors on the BK-induced hypotension and bronchoconstriction in anesthetized guinea pigs simultaneously. As ACE inhibitors, we used imidaprilat, an active metabolite of imidapril, which showed a very low incidence of cough in clinical trials [10], and ramiprilat, an active metabolite of ramipril, which has been reported to exhibit strong potentiation of BK [11].

Materials and methods

Materials

Imidaprilat, ramiprilat, FR173657 (bradykinin B2 receptor antagonist), CP96345 (NK1 receptor antagonist), SR48968 (NK2 receptor antagonist) and BM13505 (thromboxane A2 receptor antagonist) were synthesized at Tanabe Seiyaku Co., Ltd., (Osaka, Japan). Other chemicals were purchased from commercial sources; BK (Peptide Institute Inc., Osaka, Japan), angiotensin I (Peptide Institute Inc.), urethane (Sigma, St. Louis, MO, USA), gallamine triethiodide (Sigma), Nω-nitro-L-arginin-methylester (L-NAME, Sigma), indomethacin (cyclooxygenase inhibitor, Sigma) and [Arg8]-vasopressin (Sigma). Imidaprilat and ramiprilat were dissolved in 0.5 N NaHCO3 (0.02 ml/mg) and then diluted...
with physiological saline solution. FR173657 and CP96345 were dissolved in 0.1 N HCl (0.02 ml/mg) and then diluted with physiological saline solution. SR48968 was dissolved in 10% hydroxypropyl-β-cyclodextrine. BM13505, BK, angiotensin I, and L-NAME were dissolved in physiological saline solution. All drugs were administered intravenously at a volume of 1 ml/kg except [Arg⁸]-vasopressin and urethane. Urethane was dissolved in deionized water, and administered intraperitoneally at a volume of 5 ml/kg. [Arg⁸]-vasopressin was dissolved in physiological saline solution at a volume of 100 μl/kg/min.

**Animals**

Male Hartley guinea pigs, weighing 300–500 g were used. The guinea pigs were purchased from Japan SLC (Hamamatsu, Shizuoka, Japan) at the age of 4 weeks and were then kept in our animal room (25 ± 1 °C, 12–12 hour light-dark cycle) for at least a week before use. Food and water were freely accessible during this period. Experimental procedures in this study adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals guideline.

**Fig. 1.** The time-schedule of experiments