Role of Bradykinin in the Reduction of Left Ventricular Hypertrophy 
Induced by Angiotensin-Converting Enzyme Inhibitors 
in Spontaneously Hypertensive Rats 

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ABSTRACT—We examined the effects of icatibant, a specific bradykinin B2-receptor antagonist, on the regression of left ventricular mass (LVM) induced by angiotensin converting enzyme (ACE) inhibitors, ramipril and imidapril, in spontaneously hypertensive rats. Both ramipril and imidapril lowered blood pressure equally, which were not influenced by icatibant. Icatibant did not alter the regressive effect of imidapril, while it showed a tendency to increase LVM in the ramipril-treated rats. The changes of LVM induced by icatibant were significantly different between the ramipril- and the imidapril-treated rats, suggesting that the role of bradykinin in the antihypertrophic effect might differ among ACE inhibitors. 

Keywords: Angiotensin-converting enzyme inhibitor, Bradykinin, Left ventricular hypertrophy 

Cardiac left ventricular hypertrophy (LVH) is most commonly associated with hypertension and is an independent risk factor for cardiovascular events in patients with hypertension. Regression of cardiac hypertrophy induced by antihypertensive agents is considered to reduce cardiovascular complications in hypertensive patients. Among the many classes of antihypertensive agents, angiotensin-converting enzyme (ACE) inhibitors seem to have a more pronounced LVH regressive effect than the other classes of agents such as diuretics, β-blockers or Ca2+-antagonists (1). ACE inhibitors regress LVH by a reduction of hemodynamic burden and the suppression of angiotensin II (Ang II) production. Because ACE, a dipeptidyl carboxypeptidase (kininase II, EC 3.4.15.1), degrades vasodilatory bradykinin (BK), accumulation of endogenous BK caused by ACE inhibitors could be also involved in the antihypertrophic effect as well as the blood pressure (BP)-lowering effect of ACE inhibitors. 

Recently, an involvement of BK in the antihypertrophic effect of an ACE inhibitor has been demonstrated by using an animal model of LVH with aortic banding (2). However, it is unclear whether the contribution of BK to the effect on the reduction of LVH differs among ACE inhibitors. Sasaguri et al. have reported that the potency for inhibition of the hydrolysis of BK relative to the inhibition of Ang II formation was significantly less with imidaprilat (active form of imidapril) than with ramiprilat (active form of ramipril) in purified canine lung ACE (3). We thus hypothesized that the potentiation of the effects of BK might play a more important role in the cardiovascular actions of ramipril than those of imidapril. In the present study, we examined the effects of chronic treatment with icatibant (formerly HOE 140, [D-Arg5, His5, D-Tic4, Oic3]-BK), a selective bradykinin B2-receptor antagonist, on the hypotensive and the antihypertrophic actions of ACE inhibitors, ramipril and imidapril, on LVH in spontaneously hypertensive rats (SHR). 

Male SHRs were obtained from Japan SLC (Saitama). The rats were housed in the experimental animal center of Jichi Medical School at a controlled environment and given free access to standard rat chow (0.36% NaCl) and tap water. 

Eleven-week-old rats were assigned to five groups (n = 10 per group) and treated in parallel for 6 weeks. The first group received ramipril (3 mg/kg per day) once daily by gastric gavage and was injected with peanut oil (vehicle for icatibant) subcutaneously for 6 weeks. The second group received orally imidapril (10 mg/kg per day) and subcutaneous injection of peanut oil. From our preliminary experiments, this daily dose of imidapril is as potent as 3 mg/kg ramipril per day for BP reduction in SHR. In the third and fourth groups, icatibant (500 μg/kg per day
by daily subcutaneous injection) was coadministered with either oral ramipril or imidapril, respectively. Icatibant at a dose of 500 μg/kg per day was shown to block the depressor responses to exogenous BK in rats (4). The fifth group served as a control and received the vehicle alone. Ramipril and icatibant were obtained from Hoechst AG (Frankfurt/Main, Germany). Imidapril was obtained from Tanabe Pharmaceutical Co., (Osaka).

Systolic BP was measured weekly by a standard tail-cuff sphygmomanometer (KN-201-1; Natsume Seisakusho, Ltd., Tokyo) in prewarmed and awaked rats. Body weight was assessed weekly. At the end of drug treatment, rats were killed by cervical dislocation. The hearts were removed and blotted carefully after the blood had been flushed out with cold saline. Then the atria and the right ventricular free wall were dissected from the interventricular septum. The weight of the interventricular septum plus that of the left ventricle represented the left ventricular weight, and the left ventricular weight/body weight ratio was taken as an index of left ventricular mass (LVM).

Data each are expressed as the mean±S.E.M. Statistical differences were analyzed by the unpaired t-test or one-way ANOVA followed by the post-hoc test (Scheffe) for multiple comparisons. A P<0.05 was considered significant.

Six weeks after drug treatment, systolic BP rose from 189±1 to 224±3 mmHg in the control group (P<0.0001), while systolic BP significantly decreased from 185±1 to 178±2 mmHg in the ramipril-treated rats, from 187±1 to 179±3 mmHg in the imidapril-treated rats, from 185±1 to 177±2 mmHg in the group cotreated with ramipril and icatibant, and from 190±3 to 176±3 mmHg in the group cotreated with imidapril and icatibant (P<0.05 for each comparison). Both ramipril and imidapril blunted the development of hypertension and lowered the BP to a similar level (Fig. 1). Icatibant did not influence the BP-lowering effect of the ACE inhibitors.

At the end of the treatment, body weights were not significantly different among the groups. LVMs in the ACE inhibitor-treated groups were significantly smaller than that in the control group (P<0.0001, Fig. 2). Icatibant did not influence the regressive effect of imidapril on LVH (2.32±0.03 g/kg in the imidapril-treated group vs 2.31±0.03 g/kg in the imidapril and icatibant-
cotentreated group, P > 0.5). Coadministration of icatibant tended to increase LVM slightly in the ramipril-treated rats (2.32 ± 0.03 g/kg in the ramipril-treated group vs 2.40 ± 0.03 g/kg in the ramipril and icatibant-cotentreated group, P > 0.05). The changes of LVM induced by cotreatment with icatibant were significantly different between the ramipril- and the imidapril-treated group (+3.7 ± 1.5% vs -0.7 ± 1.1% in the respective group, P < 0.05).

In the present study, chronic treatment with ramipril (3 mg/kg/day) and imidapril (10 mg/kg/day) similarly prevented the development of hypertension in SHR. The BP-lowering effects of ramipril and imidapril were not attenuated by chronic bradykinin B₂-receptor blockade with icatibant. Our results confirm the earlier findings that chronic treatment with icatibant did not attenuate the hypotensive action of ramipril in SHR (5) and in stroke-prone SHR (6). These results including ours suggest that BK does not seem to contribute to the antihypertensive action of ACE inhibitors in such genetically hypertensive models with normal to low plasma renin levels.

Because the capacity for inhibition of the degradation of BK relative to the inhibition of Ang II formation has been shown to be greater with ramipril than with imidapril (3), we speculated that the contribution of BK in the cardiovascular actions of ramipril is much more than that of imidapril. In the present study, we observed that chronic treatment with icatibant exerts a significantly different effect on the reduction of LVH induced by ramipril and imidapril. Icatibant tended to attenuate the antihypertrophic effect of ramipril, but not that of imidapril in SHR. These results suggest that BK might partly be involved in the antihypertrophic effect of ramipril, but not that of imidapril. In contrast to the present findings, Gohlke et al. have reported that icatibant did not alter the preventive effects of ramipril on the development of cardiac LVH in genetically hypertensive rats (6). The source of discrepancies between their results and ours is not obvious; however, it could reside in a different experimental protocol.

Our results showed a possibility that the contribution of BK to the antihypertrophic actions is different between ramipril and imidapril. However, the mechanisms by which the inhibitory effects in Ang II formation and BK degradation are different between imidapril and ramipril remain to be determined. ACE possesses two active domains that hydrolyze BK, substance P or Ang I. If the substrate specificity and the capacities to bind ACE inhibitors were different between the two active sites, the relative potencies in the hydrolysis of Ang I and BK might be different among ACE inhibitors. It has been reported that both the two active sites of ACE similarly hydrolyze BK and Ang I (7). This finding suggests that it would not be possible to dissociate the inhibition of Ang I conversion from the degradation of BK by an ACE inhibitor, even if it is specifically bound to one active site. It is considered that ACE inhibitors allow kinins to accumulate by inhibition of ACE activities in vascular endothelial cells and in the bloodstream. However, it has been implicated that several enzymes such as carboxypeptidase N, neutral endopeptidase 24.11 (8) or aminopeptidase P (9) are involved in kinin degradation in addition to ACE. In an endothelium-denuded aorta, the ACE inhibitor reduced BK breakdown by vascular smooth muscle cell enzymes, despite the activity of ACE was absent in this preparation (10). These findings suggest that the ACE inhibitor attenuates BK breakdown by inhibiting BK degrading enzymes other than ACE. As far as BK accumulation by ACE inhibitors is concerned, ramipril may inhibit these BK degrading enzymes more effectively than imidapril does.

In conclusion, our results suggest that kinins do not play a major role in the antihypertensive action of ramipril and imidapril in SHR. Our data, however, showed that chronic B₂-receptor blockade induced a different antihypertrophic action in between those of ramipril and imidapril. BK thus might contribute, at least in part, to the antihypertrophic action of ramipril but not to that of imidapril in SHR. Further studies will be needed to clarify the possibilities that the involvement of BK in the protective effects against hypertensive organ damages and adverse reactions could be different among ACE inhibitors.

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