Contribution of Bradykinin to the Cardioprotective Action of Angiotensin Converting Enzyme Inhibition in Hypertension and After Myocardial Infarction

Katsuhiko Ito, Yi-Zhun Zhu, Yi-Chun Zhu, Peter Gohlke and Thomas Unger

Department of Pharmacology, Christian-Albrechts University of Kiel, Hospitalstrafie 4, 24105 Kiel, and German Institute for High Blood Pressure Research, Heidelberg, Germany

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ABSTRACT—Angiotensin converting enzyme (ACE) is identical with kininase II. Besides reducing the production of angiotensin II, inhibition of ACE potentiates the biological actions of endogenous kinins. In hypertension-induced left ventricular hypertrophy, potentiation of endogenous kinins contributes to the improvement of cardiac function and energy metabolism and to capillary proliferation effected by ACE inhibitors. In myocardial infarction (MI), the potentiation of kinins has been shown to be involved in the reduction of infarct size and improvement of cardiac function by ACE inhibition. The cardioprotective actions of ACE inhibition in MI seem to be, in part, mediated by the augmentation of myocardial blood flow, especially in the ischemic region of the heart.

Keywords: Bradykinin, Angiotensin converting enzyme, Angiotensin II receptor antagonist, B2 receptor antagonist, Myocardial infarction, Cardioprotective action

1. Introduction

The renin angiotensin system is generally known to play a major pathophysiological role in the development of hypertension and cardiovascular diseases such as left ventricular hypertrophy (LVH), congestive heart failure and cardiac remodeling post myocardial infarction (MI). The clinical success of angiotensin converting enzyme (ACE) inhibitors has proven the pathophysiological significance of the renin angiotensin system (RAS) in cardiovascular diseases. Experimental and clinical results obtained with the newly discovered angiotensin II (ANG II) receptor antagonists such as losartan, vraslant, irbesartan and candesartan underline the importance of the RAS. Although many of the actions of ACE inhibitors can be explained by the inhibition of ANG II production in circulating blood and various organs, the ACE inhibitor-induced potentiation of kinins may also contribute to the clinical benefits of these drugs.

ACE is a metalloprotease with two homologous domains, i.e., two binding sites as active centers containing a zinc atom each (1). ACE is also known to be identical with kininase II, a bradykinin (BK) degrading enzyme (2). ACE converts the inactive decapeptide angiotensin I into the biologically active octapeptide ANG II by removing the dipeptide, His-Leu, from the C-terminal end of the angiotensin I molecule. On the other hand, ACE inactivates BK by sequential removal of dipeptides
Phe-Arg and Ser-Pro from the C-terminal end of the peptide. The inhibition of ACE potentiates the biological actions of BK as well as attenuates the actions of ANG II, allowing for the possibility that kinins contribute to the effects of ACE inhibitors. In the present short review, we will focus on the contribution of kinins to cardioprotective actions of ACE inhibitors in hypertension and after MI on the basis of our recent findings.

2. Biological action of kinins

Several kinins such as the nonapeptide BK, the decapeptide Lys-BK (kallidin), the undecapeptides Met-Lys-BK and Ile-Ser-BK (T-kinin), Met-T-kinin and T-kinin-Leu have been identified in mammalian species (3). All kinins share the common amino acid sequence of BK (-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH) at the C-terminal (4–6).

Kininogens, which belong to the a2-globulin fraction, are mainly synthesized in the liver. Three types of kininogens exist in the rat, i.e., high- and low-molecular weight kininogens and T-kininogen (7, 8). Kininogens are cleaved by enzymes (kininogenases) such as plasma kallikrein in the liver and glandular- or tissue kallikrein in exocrine glands or the kidney, resulting in the production of kinins (9).

Kinins exert several biological actions. Intravenous injection of BK produces a short lasting decrease in blood pressure via arterial vasodilation (10, 11). The latter is due to the stimulation of nitric oxide as well as the prostacyclin production in the endothelium (12, 13). In addition to vasodilation, several other biological actions of kinins have been demonstrated. Kinins are involved in nociception (14) as well as in inflammation and capillary permeability (15). Kinins also mediate reactive hyperemia (16) and stimulate cellular glucose uptake (17). In the kidney, kinins affect the renal vascular resistance and produce diuresis and natriuresis (18, 19).

Kinins exert their biological effects via the stimulation of kinin receptors. Two subtypes of kinin receptors, designated B1 and B2, have been characterized (20, 21). The B1-receptor has a high affinity to kininase I metabolites such as Des-Arg8-BK and Des-Arg9-kallidin, whereas the B2-receptor recognizes BK and kallidin. The B1-receptor is not present in normal tissues but is induced under certain pathophysiological conditions such as tissue injury and stress. In contrast, B2-receptors mediate most of the biological actions of BK.

Kinin receptor antagonists have been widely used as tools to clarify the physiological and pathophysiological role of kinins. Icatibant (Hoe 140) is one of the potent and selective antagonists for the B2-receptor (22–24).

3. Contribution of kinins to the cardioprotective actions of ACE inhibitors in hypertension

Arterial hypertension is known to be accompanied by an adaptive LVH. Cardiac hypertrophy can also be seen in well-trained athletes; however, the physiologically hypertrophied heart contracts forcefully with much less risk for cardiovascular events. Capillaries of physiologically hypertrophied hearts grow in proportion to the enlargement of myocytes (25). On the other hand, hypertension-induced LVH is a prominent cardiovascular risk factor closely related to ischemia, lethal arrhythmias and cardiac failure (26). Adaptive LVH in hypertension is induced in order to overcome the chronically increased afterload imposed on the heart. In contrast to the physiologically hypertrophied heart, the rate of capillary growth of the hypertension-induced hypertrophied heart does not keep pace with the increase in muscular mass (27). The reduced capillary supply may eventually lead to cardiac ischemia followed by arrhythmias and cardiac failure. In addition, LVH is often accompanied by perivascular fibrosis of intramyocardial coronary arteries and by interstitial fibrosis (28, 29).

Clinical studies in patients with essential hypertension accompanied by LVH have shown that ACE inhibitors can regress LVH in addition to their antihypertensive effect (30–33). While part of the regressive effect of ACE inhibitors on LVH can be explained by blood pressure reduction, there is evidence for an additional mechanism in experimental models of hypertension.

Aortic banding between the renal arteries is known as an experimental model of renal hypertension in which LVH is induced by pressure overload to the heart. In rats with aortic banding, an antihypertensive dose of the ACE inhibitor ramipril prevented and regressed LVH, respectively, whereas equipotent doses of the calcium antagonist nifedipine and the arterial vasodilator dihydralazine had no effect on LVH in spite of their antihypertensive actions (34). Interestingly, a sub-antihypertensive dose of ramipril also prevented LVH, demonstrating that the ACE inhibitor exerted preventive effects of LVH independently of its antihypertensive actions in this model of hypertension.

When the ramipril treatment was begun prior to the establishment of LVH (just after the aortic constriction), the antihypertrophic effect was abolished by co-treatment with the B2-receptor antagonist, icatibant. On the other hand, co-treatment with icatibant was not able to reverse the antihypertrophic effect of ramipril when ramipril treatment was begun after the establishment of LVH (6 weeks after aortic constriction). Chronic infusion of BK at a dose that did not affect systemic blood pressure also prevented the development of LVH, whereas it had no
regressive effect on LVH (35). These findings indicate that potentiation of endogenous kinins contributed to the beneficial effect of ACE inhibitor on the development of LVH but was not involved in the regressive effect of the agent under these experimental conditions.

In spontaneous hypertensive rats (SHR) and stroke-prone spontaneous hypertensive rat (SHRSP), an animal model for essential hypertension, antihypertensive doses of the ACE inhibitors ramipril, zabicapril and perindopril prevented LVH when treatment was begun before the development of hypertension (36–39). Sub-antihypertensive doses of these ACE inhibitors had no effect on LVH. Therefore, in these genetically hypertensive animals, the anti-hypertrophic effects of ACE inhibitors seem to be due to their antihypertensive actions, i.e., reduction of afterload imposed on the heart. In addition, co-treatment with icatibant did not affect the antihypertensive or anti-hypertrophic actions of ACE inhibitors in SHR and SHRSP, suggesting that kinins do not contribute to the antihypertrophic effects of ACE inhibitors in rats with genetic hypertension.

The discrepancy between findings from rats with genetic hypertension, on one hand, and with aortic banding, on the other hand, could be explained by differences in the pathogenic mechanisms between these experimental models of hypertension. Rats with renal hypertension respond to ACE inhibition more drastically than rats with genetic hypertension because they are highly dependent on the RAS and appear to feature a compensatory stimulation of the kinin system. In contrast, SHR or SHRSP seem to be dependent to a lesser degree on both hormonal systems (40, 41).

However, we can not rule out the involvement of kinins in the beneficial effect of ACE inhibitor even in rats with genetic hypertension. For instance, Gohlke et al. (38, 39) demonstrated a contribution of kinins to the improvement of cardiac function by ACE inhibitors in SHRSP. Chronic treatment with ramipril improved cardiac function, as demonstrated by increases in left ventricular pressure, dp/dt max and coronary flow. These effects of ramipril were accompanied by reduced activities of lactate dehydrogenase and creatine kinase in the venous effluent of the heart and by increased myocardial high-energy phosphates and glycogen, whereas tissue lactate was reduced (Table 1). The beneficial effects of ramipril were abolished by co-treatment with icatibant. These findings demonstrate that the potentiation of endogenous kinins contributed to the improvement of cardiac function by the ACE inhibitor in rats with genetic hypertension. The development of LVH in rats with genetic hypertension is associated with a diminished capillary density. Chronic, early-onset treatment with an anti-hypertensive dose of ramipril and perindopril increased capillary density in the left ventricle (37, 42). Even a sub-antihypertensive dose of the ACE inhibitor ramipril improved myocardial density (37, 42). The beneficial action of ACE inhibition on capillary proliferation seems to be independent of the antihypertensive and antihypertrophic effects; however, the mechanism has not yet been fully clarified. It may be, in part, explained by the inhibitory effect of ACE inhibitors on ANG II production, because ANG II inhibits the serum- and basic fibroblast growth factor (bFGF)-stimulated proliferation of coronary endothelial cells through the AT2-receptor (43, 44).

However, we can not rule out the involvement of kinins since B2-receptor blockade prevented the increase in myocardial density induced by ACE inhibitor treatment (42). The perfusion of BK has been shown to improve myocardial blood flow in the ischemic heart (45). ACE inhibitor-induced augmentation of coronary flow was abolished by icatibant (38, 39, 45). Therefore, kinin-mediated vasodilation and augmentation of myocardial blood flow may contribute to the capillary proliferation, because it has been shown that the mechanical shear stress on the surface of the endothelial cells following vasodilation and increased blood flow was a trigger for capillary growth (46). It could be considered that potentiation of endogenous kinins contributed to the capillary proliferative action of ACE inhibitor.

### Table 1. Effect of chronic treatment with ramipril on cardiac parameters of isolated heart from stroke-prone spontaneous hypertensive rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>0.01 mg/kg Ramipril</th>
<th>1 mg/kg Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVP (mmHg)</td>
<td>67.3±3.0</td>
<td>82±3</td>
<td>87±4</td>
</tr>
<tr>
<td>dp/dt max (mmHg/sec)</td>
<td>2129±198</td>
<td>2931±207</td>
<td>2873±222</td>
</tr>
<tr>
<td>CF (ml/g/min)</td>
<td>11.3±0.9</td>
<td>14.1±1.3</td>
<td>13.8±0.9</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>190±4</td>
<td>193±5</td>
<td>185±5</td>
</tr>
<tr>
<td>Venous effluent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH (mU/min/g wet wt.)</td>
<td>28±3</td>
<td>16±2</td>
<td>17±3</td>
</tr>
<tr>
<td>CK (mU/min/g wet wt.)</td>
<td>36±4</td>
<td>21±3</td>
<td>16±2</td>
</tr>
<tr>
<td>Lactate (mol/min/g wet wt.)</td>
<td>0.33±0.03</td>
<td>0.14±0.02</td>
<td>0.11±0.01</td>
</tr>
<tr>
<td>Myocardial tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate (mol/g dry wt.)</td>
<td>22.1±1.5</td>
<td>17.2±1.3</td>
<td>17.5±1.8</td>
</tr>
<tr>
<td>Glycogen (mol/g dry wt.)</td>
<td>113.8±5.2</td>
<td>147.3±5.7</td>
<td>149.4±6.4</td>
</tr>
<tr>
<td>ATP (mol/g dry wt.)</td>
<td>14.8±1.7</td>
<td>19.8±1.9</td>
<td>20.7±2.2</td>
</tr>
<tr>
<td>CP (mol/g dry wt.)</td>
<td>9.9±1.2</td>
<td>18.1±1.4</td>
<td>17.2±1.9</td>
</tr>
</tbody>
</table>

LVP represents left ventricular pressure; dp/dt, differentiated left ventricular pressure; CF, coronary flow; HR, heart rate; LDH, lactate dehydrogenase; CK, creatine kinase; and CP, creatine phosphate.
4. Contribution of kinins to the cardioprotective actions of ACE inhibitors following myocardial infarction

ACE inhibitors have been advocated as therapeutic agents for patients with chronic heart failure after MI. In fact, clinical studies have provided evidence for the cardioprotective and mortality reducing effects of ACE inhibitors post MI (47–51).

The mechanism of the cardioprotective and life-saving actions of ACE inhibitors post MI can be explained, in part, by their lowering effect on afterload imposed on the damaged heart, resulting in a decrease in energy consumption of the myocardium. However, Martorana et al. (52) suggested other possibilities based on their observation that locally administered ramipril (intracoronary infusion) significantly reduced infarct size in dogs without affecting systemic blood pressure. They also reported that the intracoronary administration of BK had similar cardioprotective effects as ramipril and that the B₂-receptor antagonist icatibant prevented the effects of the ACE inhibitor. Therefore, the beneficial effects of ACE inhibitor in MI do not seem to be only due to the reduced afterload imposed on the heart but may depend also on BK potentiation.

Recent investigations from our group give further support to the possibility that kinins contribute to the cardioprotective effect of ACE inhibitors following MI (53). As shown in Fig. 1, the ACE inhibitor moexipril reduced infarct size and prevented the increase in end-diastolic pressure in rats with MI when the chronic treatment for 6 weeks post MI was begun one week prior to coronary ligation. Co-treatment with the B₂-receptor antagonist icatibant abolished these effects of moexipril. Interestingly, the AT₁-receptor antagonist losartan had no cardioprotective effects under these experimental conditions (53). In line with these findings, Hartman et al. (54) found that intracoronary infusion of ramipril, but not losartan, reduced infarct size when treatment was begun prior to the occlusion of the left coronary artery in rabbits. On the other hand, when treatment with ACE inhibi-

![Fig. 1. Cardioprotective effects of ACE inhibitor, angiotensin II receptor antagonist and the combination of ACE inhibitor and B₂ kinin receptor antagonist in myocardial infarction in rats. Upper and lower panels represent the effects of these agents on the infarct size and end-diastolic pressure (EDP), respectively. Moexipril and losartan were administered orally to rats at a dose of 10 mg/kg daily. Icatibant was co-administered with moexipril at a dose of 0.5 mg/kg (s.c.) daily. These treatments were begun 1 week prior to the left coronary artery ligation and were continued for 6 weeks. *P<0.05 vs control value.](image-url)
bitor was begun 6 weeks after coronary ligation, i.e., when congestive heart failure had developed, moexipril had no significant effects on infarct size or end-diastolic pressure, whereas losartan improved cardiac function as demonstrated by a significant reduction of end-diastolic pressure (55).

Based on these findings, one could speculate that in an earlier stage of MI, during the remodeling process of the damaged heart, the potentiation of endogenous kinins is closely related to cardioprotective effects of ACE inhibitors as demonstrated by the reduced infarct size and prevention of the increase in end-diastolic pressure. On the other hand, in a later stage of MI, the stage of development of congestive heart failure, the reduction of ANG II production gain more importance.

Ertl (56) reported that ACE inhibitor treatment reduced the area at risk and the infarct size more effectively in dogs with coronary artery ligation. We measured tissue blood flow in the marginal zone of the area at risk 30 min before and after left coronary artery ligation in rats. In animals pretreated with ramipril, tissue blood flow in the marginal zone of the infarct area after the ligation was higher than that in non-treated animals. In addition, the infarct size 3 weeks after MI was found to be reduced even when the treatment was withdrawn after MI. Co-treatment with icatibant abolished these beneficial effects of ramipril. Losartan had no significant effects on blood flow and infarct size (57). These findings suggested that the ACE inhibitor improved collateral myocardial blood flow especially in the marginal zone of ischemia by potentiation of endogenous kinins. The mechanism have been responsible for the reduction of infarct size.

From these data, it appears that kinins contribute to the cardioprotective actions of ACE inhibitor especially in the acute ischemic phase of MI. Indeed in ischemic isolated working rat hearts submitted to reperfusion injury, perfusion with BK or ACE inhibitors improved cardiac function and coronary flow, reduced the release of lactate dehydrogenase and creatine kinase into the perfusate and preserved myocardial content of energy stores as demonstrated by maintained glycogen, ATP and creatine phosphate (58). In addition, posts ischemic reperfusion arrhythmias were distinctly attenuated by perfusion with BK or ACE inhibitor at doses that had no cardiodynamic actions (59). The effects of ACE inhibition were abolished by icatibant (45). Thus, the potentiation of endogenous kinins seems to contribute to the cardioprotective effects of ACE inhibition in myocardial ischemia not only by the improvement of myocardial blood flow but also by the improvement of energy metabolism in the ischemic heart.

5. Contribution of kinins to the action of ACE inhibitors on myocardial remodeling

As described above, myocardial remodeling is a consequence of MI. Left ventricular remodeling after MI is associated with morphological changes such as increase in left ventricular mass, chamber dilation and compensatory hypertrophy of the non-infarcted myocardium. In an earlier stage of MI, necrosis, edema and vascular congestion can be seen, and the left ventricle dilates as the result of expansion of the infarcted area by thinning and dilation of the necrotic region. In necrotic tissue, a thin scar is formed and a collagen network protects against further expansion. The compensatory hypertrophy of the residual viable myocardium takes place to overcome the decreased contractility of the damaged heart to maintain stroke volume. Even after the healing process is completed, the ventricular remodeling continues (60). ACE expression was markedly increased in the repairing scar after 3 weeks of MI (61). ACE was also expressed in macrophages and endothelial cells, but the enzyme could not be found in vascular smooth muscle cells, cardiomyocytes or fibroblasts (61). These findings suggest that ACE is closely related to tissue repair and remodeling after MI.

ACE inhibitors have been shown to reduce cardiac mass and volume while maintaining cardiac output post MI (62–65). The mechanism of the anti-remodeling effect of ACE inhibitors is still controversial. A reduction of afterload on the heart may contribute to the effect of the ACE inhibitors; however, hydralazine had no effect on remodeling in spite of its antihypertensive effect (66). AT₁-receptor antagonist have been reported to attenuate the structural change in myocardium after MI (64, 67). On the other hand, McDonald et al. (68) demonstrated that an AT₁-receptor antagonist was ineffective in dogs with transmyocardial direct current shock, a model for myocardial necrosis. Furthermore, the B₂ kinin receptor antagonist icatibant abolished the anti-remodeling effect of the ACE inhibitor (69). Together, these findings allow for the possibility that kinins contribute to the anti-remodeling effect of ACE inhibitors under certain conditions.

6. Conclusion

We have given several examples for the contribution of kinins to the cardioprotective actions of ACE inhibitors in hypertension, LVH and post MI. The potentiation of endogenous kinins appears to contribute to the anti-hypertrophic effect of ACE inhibitor, especially in the developmental stage of hypertension-induced LVH. Kinins also contribute to the improvement of cardiac function and energy metabolism by ACE inhibitors in LVH.
Furthermore, kinins are involved in capillary proliferation induced by ACE inhibitors in LVH.

In the early stage of MI, the remodeling process of damaged heart, the potentiation of endogenous kinins appear to contribute to beneficial effects of ACE inhibitors on infarct size and cardiac function, possibly by the augmentation of myocardial blood flow, especially in the ischemic region of the heart. Moreover, kinins can also contribute to the anti-remodeling effects of ACE inhibitor, although the mechanism is still controversial. Further studies will be needed to clarify how cardiac kinins protect the heart in LVH and MI.

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