Introduction

Over 30 years ago, Ferreira et al.[1] isolated a bradykinin-potentiating peptide from the venom of a Central American viper. Shortly thereafter, Ondetti et al.[2] reported the isolation of an angiotensin-converting enzyme (ACE) inhibitor from the venom of the same snake. Erdös subsequently demonstrated that ACE and kininase II, which degrades bradykinin to inactive metabolites, are the same enzyme[3], thus linking the renin-angiotensin system (RAS) and the kallikrein-kinin system (KKS).

Overview of the RAS and KKS

The major components and actions of the RAS and the KKS are illustrated in Fig. 1. Both the RAS and KKS have been localised to the vasculature[4,5], where the effects of bradykinin oppose many of the actions of angiotensin II (Ang II).

Bradykinin: Key component of the KKS

The KKS is activated on the surface of endothelial cells[5]. Plasma kallikrein cleaves high-molecular-weight kininogen, to release bradykinin, which acts in a paracrine manner via bradykinin B₂ receptors. Tissue kallikrein, a distinct enzyme activated by different mechanisms, releases lysl-bradykinin (kallidin), which also acts through the B₂ receptor.

Bradykinin exerts a number of vascular effects (Fig. 2). By stimulating synthesis and release of nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF), bradykinin causes vasodilation and also inhibits platelet adhesion and smooth muscle cell proliferation[6]. Bradykinin is also one of the most potent stimuli for endothelial release of tissue plasminogen activator (tPA) in vivo[7].

Ang II: Key component of the RAS

ACE, a bivalent dipeptidyl carboxyl metallopeptidase, is present in endothelial, epithelial or neuroepithelial cells as a membrane-bound form, and as a soluble form in the brain, blood and numerous body fluids[8]. ACE converts angiotensin I (Ang I) to Ang II, the principal effector molecule of the RAS. Four receptor subtypes have been identified for Ang II[9]: the AT₁ receptor mediates vasoconstriction, vascular smooth muscle cell proliferation, and production of superoxide ions; the AT₂ receptor, which is normally expressed at very low levels in adults, may be upregulated during AT₁ receptor blockade and counteracts many AT₁-mediated effects (see below)[10,11]; the role of the AT₃ receptor is not known at present; and AT₄ influences local blood flow[12] and stimulates synthesis of plasminogen activator inhibitor I (PAI-1), the major physiological inhibitor of fibrinolysis, in endothelial cells[13].

Contribution of bradykinin to the cardioprotective effects of ACE inhibitors

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Bradykinin, through its B₂ receptor, stimulates endothelial release of a number of vasodilators, such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF). Angiotensin-converting enzyme (ACE) inhibitors enhance the effects of local bradykinin by decreasing its degradation and by increasing B₂ receptor sensitivity. Clinical and experimental studies demonstrate that blockade of the B₂ receptor attenuates the antihypertensive, antihypertrophic, and antiatherosclerotic effects of ACE inhibitors. Thus, the evidence strongly supports a role for bradykinin in mediating the cardiovascular benefits of ACE inhibitors.

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RAS / KKS linkages

The RAS and KKS are linked at a number of levels. ACE not only converts Ang I to Ang II but also bradykinin to inactive metabolites; hence, ACE inhibitors increase circulating concentrations of bradykinin [14]. Recent evidence suggests that ACE inhibitors also potentiate the effects of bradykinin via direct effects at the bradykinin B2 receptor [16,17]. For example, Benzing et al. [18] demonstrated that ramiprilat, a tissue-specific ACE inhibitor, inhibited the desensitization of the B2 receptor via sequestration within caveolae, lipid-rich pockets on the surface of endothelial cells. Similarly, Marcic et al. demonstrated that ACE inhibitors enhance the effect of bradykinin at its B2 receptor by inducing 'crosstalk' between ACE and the receptor [19].

In vitro and animal studies suggest that the AT2 receptor provides an additional connection between the RAS and the KKS. During AT1 receptor blockade, unopposed activation of the AT2 receptor leads to increased bradykinin, NO and cyclic (c)GMP [11,20]. Although acute AT1 receptor blockade does not potentiate the effects of exogenous bradykinin [21], these data potentially implicate endogenous bradykinin in the beneficial effects of chronic AT1 receptor blockade [22].

Bradykinin and antihypertensive effects of ACE inhibitors

The availability of a specific bradykinin B2 receptor antagonist, icatibant acetate (HOE 140), has allowed investigators to determine the contribution of bradykinin to the effects of ACE inhibitors in vivo. Bradykinin receptor blockade attenuates the hypotensive response to ACE inhibition in rats and dogs [23-25]. In humans, ACE inhibition enhances whereas B2 receptor blockade decreases the vasodilator effects of exogenous bradykinin. Studies using icatibant further indicate that endogenous bradykinin contributes to the acute hemodynamic effects of ACE inhibitors in humans. For example, bradykinin receptor blockade decreases the potentiation of endothelium-mediated, flow-dependent vasodilation by ACE inhibition in healthy individuals [28]. Similarly, co-administration of icatibant attenuates the acute hypotensive effects of oral captopril in both normotensive and hypertensive subjects [29].

Bradykinin and anti-ischemic and antiatherosclerotic effects of ACE inhibitors

ACE inhibitors decrease cardiac hypertrophy in patients with hypertension [30]. Bradykinin receptor antagonism decreases the antihypertrophic effect of ACE inhibitors in hypertensive animals [23]. Conversely, genetic B2 receptor deficiency is associated with the development of cardiac hypertrophy [31]. In vitro, bradykinin prevents Ang II-induced hypertrophy of cultured cardiomyocytes by releasing nitric oxide (NO) from endothelial cells, thereby increasing cardiomyocyte guanosine 3′,5′-cyclic monophosphate (cGMP) [32].
well as in patients with normal left ventricular function who are at risk for coronary artery disease[35]. Again, studies in animals using icatibant implicate bradykinin in the mechanism of the anti-ischemic effects of ACE inhibitors. Thus ACE inhibition decreases infarct size following coronary artery occlusion in dogs or rabbits and this effect is abolished by either bradykinin receptor antagonism[36,37] or nitric oxide synthase inhibition with Nω-L-nitro-arginine methyl ester (L-NAME)[38].

Bradykinin, ACE inhibition, and fibrinolytic balance

One mechanism through which bradykinin may contribute to the anti-ischemic effects of ACE inhibitors involves the fibrinolytic system. The endogenous fibrinolytic system serves as one of the major defense mechanisms against intravascular thrombosis. Fibrinolytic activity is regulated by the balance between tPA and PAI-1 (Fig. 3)[39,40]. Bradykinin stimulates endothelial release of tPA,[8,42] whereas Ang II increases PAI-1 expression[13].

Brown et al.[7] have studied the mechanism of bradykinin-induced tPA release from the human vasculature. They demonstrated that bradykinin stimulates vascular tPA release in a dose-dependent manner, that this effect is independent of changes in flow, and that, like vasodilatation, this effect is mediated through the bradykinin B₂ receptor. However, following receptor activation, bradykinin appears to cause vasodilation and stimulate tPA release through distinct mechanisms. Thus, while administration of the nitric oxide synthase (NOS) inhibitor L-NG-monomethyl-L-arginine (L-NMMA) attenuates the forearm vasodilator response to bradykinin, indicating that NO contributes to bradykinin-induced vasodilation, L-NMMA alone or in combination with the cyclooxygenase inhibitor indomethacin did not affect the tPA response to bradykinin, suggesting that tPA release is mediated through a NOS- and cyclooxygenase-independent pathway.

ACE inhibitors improve endothelial function as measured by the vasodilator response to endothelium-dependent agonists[42]. ACE inhibition, but not AT₁ receptor blockade, potentiates the effect of exogenous bradykinin on tPA release in the peripheral[41] and coronary vasculature[43]. A recent study using icatibant indicates that ACE inhibition increases constitutive vascular tPA release in subjects at risk for coronary artery disease through effects on endogenous bradykinin[44].

The findings that bradykinin induces tPA expression and release while Ang II stimulates PAI-1 expression suggest that ACE inhibitors reduce risk of MI, in part, through effects on fibrinolytic balance. Indeed, activation of the renin-angiotensin-aldosterone system by salt depletion or diuretic use increases plasma PAI-1 concentrations, while ACE inhibition significantly decreases plasma PAI-1 without consistently decreasing tPA concentrations[40]. Hence, ACE inhibitors improve the molar ratio of PAI-1 to tPA. These effects have been observed in young normotensive subjects, healthy postmenopausal women, hypertensive subjects, and patients post-MI. For example, in the Healing and Early Afterload Reduction Therapy (HEART) study[45], ACE inhibition decreased PAI-1 antigen and activity in patients with acute anterior MI. Plasma tPA levels were similar in both the ramipril and control groups. The effect of ACE inhibition on PAI-1 antigen following thrombolysis for acute MI has also been described[46]. ACE inhibition was associated with a diminished rise in PAI-1 antigen following thrombolysis and an increased rate of patency of the infarct-related artery.

The observation that chronic ACE inhibition but not AT₁ receptor antagonism decreases circulating PAI-1 antigen concentrations[47] raises the possibility that bradykinin not only stimulates tPA release, but also contributes to the regulation of PAI-1. Because NO suppresses PAI-1 expression after stimulation by Ang II in aortic smooth muscle cells[48], it may be hypothesized that bradykinin could moderate PAI-1 expression by releasing NO. Further studies are needed to determine whether bradykinin opposes the effects of Ang II on PAI-1 expression.

Conclusion

Bradykinin favorably alters fibrinolytic balance and promotes release of vasoactive compounds that improve endothelial function. ACE inhibitors potentiate bradykinin by blocking (1) ACE-mediated breakdown of bradykinin, and (2) B₂ receptor desensitization. A substantial body of evidence points to increased local bradykinin action as an important contributing mechanism in the reduction of cardiovascular events[35].
References


