Hypertension Research (2011) 34, 448–449

www.nature.com/hr

COMMENTARY

Angiotensin-converting enzyme inhibition and fibrinolytic balance

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Hypertension Research (2011) **34,** 448–449; doi:10.1038/hr.2011.3; published online 17 February 2011

Fibrinolytic activity is primarily determined by the balance between the levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1).[1] Impaired fibrinolytic function, characterized by increased PAI-1 level and decreased t-PA activity, has been found in patients with hypertension. The t-PA antigen concentration reflects both active t-PA and inactive t-PA complexed with PAI-1. The t-PA antigen concentration is determined in part by increased PAI-1 level. Free and unbound t-PA is physiologically active and leads to endogenous fibrinolysis.

Data from the literature indicate that different antihypertensive drugs may vary in their influence on fibrinolysis. Blood pressure reduction itself could improve the capacity for pharmacologically stimulated t-PA release.[2] There is a growing body of evidence that angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) improve endothelial dysfunction. Previous comparative studies have shown that ACE-I and ARB differ in their effects on fibrinolysis.[3,4] ACE-I have generally been shown to improve the fibrinolytic balance by reducing plasma PAI-1 level, and ARB seem to be neutral in their effect. The positive effect of ACE-I on the fibrinolytic system is related to (1) a decrease in the release of angiotensin II-mediated PAI-1; (2) an increase in the release of bradykinin-induced t-PA and (3) improvement of insulin sensitivity (Figure 1).

Tissue-PA is released from the endothelium both constitutively and in response to agonists, such as bradykinin and substance P. On the other hand, PAI-1 has been detected in endothelial cells, platelets and vascular smooth muscle cells. Many studies have shown an association between abdominal obesity, insulin resistance and increased level of PAI-1.[5] There is a relationship between obesity and elevated plasma PAI-1 concentration. It has been shown that adipose tissue, which is abundant in the insulin resistance syndrome, produces a substantial amount of PAI-1, and plasma level of PAI-1 strongly correlates with body mass index (BMI).[6,7]

In a homogenous population of normoweight ($BMI < 25\,kgm^{-2}$) hypertensive patients, the effects of ARB on fibrinolysis and insulin sensitivity in comparison with the effects of ACE-I have not yet been determined. Fogari *et al.*[8] compared the effects of 12-week treatment with the ACE-I imidapril and the ARB candesartan on plasma PAI-1 antigen and its activity, and on plasma t-PA activity in normoweight hypertensive patients. In this study, despite similar blood pressure reduction, imidapril but not candesartan improved the fibrinolytic balance, possibly through bradykinin-mediated effects on insulin sensitivity and endothelial function.

In Japanese patients with myocardial infarction, administration of imidapril for 1 month did not change the level of t-PA antigen, but decreased the level of PAI-1.[9] Previous studies have indicated that ACE-I increase bradykinin type 2 receptor functions as allosteric enhancers by inducing a conformational change in ACE.[10] Therefore, the mechanisms by which ACE inhibition enhances t-PA release may include not only reduced degradation of endogenous bradykinin but also enhanced sensitivity of the bradykinin type 2 receptor. However, as ARB increase angiotensin II concentration, it has been suggested that PAI-1 may increase through stimulation of the angiotensin II type 4 receptor (Figure 1).[1] Brown *et al.*[11] reported that bradykinin stimulates t-PA release from the forearm vascular endothelium through a bradykinin type 2 receptor-dependent, nitric oxide-synthase-independent and cyclooxygenase-independent pathway. They suggested that endothelium-derived hyperpolarizing factor may contribute to bradykinin-stimulated t-PA release. It is suggested that epoxyeicosatrienoic acids, which share many of the properties of endothelium-derived hyperpolarizing factor, possess fibrinolytic properties through the induction of t-PA expression without affecting PAI-1 in vascular endothelial cells.[12]

Coronary release of t-PA from the endothelium is an important defense against coronary thrombosis. It is possible that t-PA release may be a critical aspect of endothelial function in terms of preventing coronary thrombosis. We previously reported that intracoronary infusion of bradykinin stimulates the release of t-PA from the coronary vasculature in patients with hypertension, and this effect is potentiated by chronic ACE inhibition.[13] These effects are not seen with ARB. In addition, chronic inhibition of ACE has been shown to increase endogenous coronary release of t-PA without affecting PAI-1 level in hypertensive patients.[14] It has been suggested that ACE inhibition may have a more favorable effect on t-PA production beyond blood pressure-lowering effects.

Analyses by the Blood Pressure Lowering Treatment Trialists' Collaboration have shown blood pressure-dependent and -independent effects of ACE-I and ARB on major cardiovascular events in patients with coronary risk factors.[15] In this study, an ACE-I but not an ARB was suggested to have protective effects against coronary artery disease, even in the absence of any reduction in blood pressure. The positive effects of ACE-I on the coronary fibrinolytic balance may contribute

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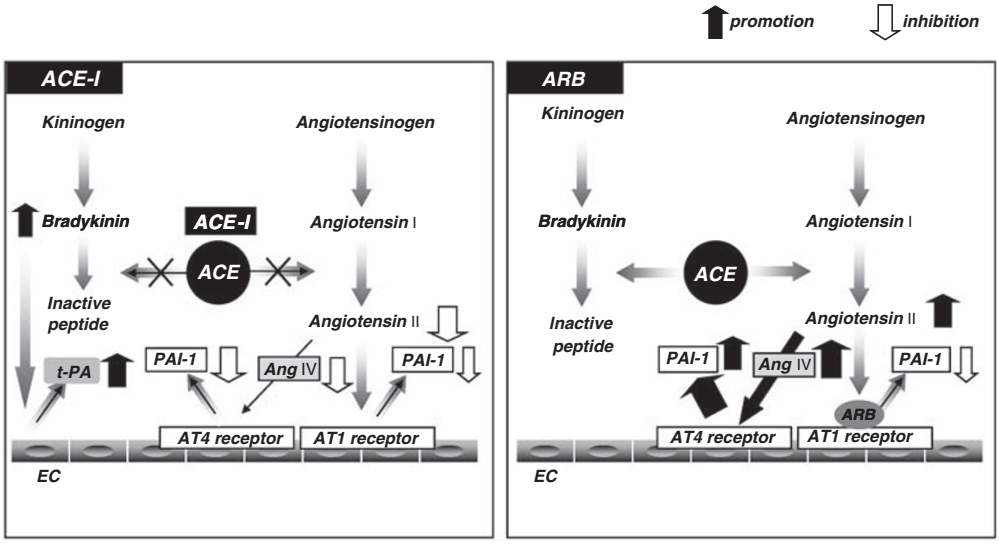

Figure 1 Comparative effects of ACE-I and ARB on fibrinolytic balance. ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; AT, angiotensin II type; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor type 1; EC, endothelial cell.

to the reduction in myocardial infarction rate achieved in clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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