11. Bradykinin and Preconditioning Against Infarction

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Introduction

Bradykinin is a peptide consisting of nine amino acids, which is generated by the plasma kallikrein-kinin system as well as the glandular (tissue) kallikrein-kinin system and plasma aminopeptidase (Fig. 11-1). There are at least two classes of bradykinin receptors, i.e. B1 and B2 receptors, and bradykinin exerts its action on most of the cardiovascular system through B2 receptors. Although bradykinin production in ischemic myocardium was first reported almost 30 years ago, the significance of kinin in myocardial ischemic injury did not receive wide-spread attention for decades. Recently, a specific and potent B2 receptor antagonist Hoe 140 (icatibant) became available, and several important aspects of bradykinin in the pathophysiology of myocardial ischemia have been clarified in the past several years. Firstly, it has been suggested that activation of the B2 receptor before ischemia may protect the heart against ischemia/reperfusion injury, including arrhythmia, contractile dysfunction and necrosis. Secondly, bradykinin may play a role in an endogenous cardioprotective mechanism, ischemic preconditioning (i.e. cardioprotective effect of brief transient non-lethal ischemia). This article briefly reviews the involvement of bradykinin in the enhancement of myocardial tolerance against infarction by ischemic preconditioning.

Evidence for Involvement of Kallikrein-kinin System in Preconditioning

The first study suggesting the role of bradykinin in preconditioning was by Wall et al.1 They found that infarct size limitation by preconditioning was blocked by...
III. CELLULAR MECHANISMS OF CARDIOPROTECTION IN ISCHEMIC PRECONDITIONING

Hoe 140 administered before the preconditioning, and this observation was also confirmed in our laboratory (Fig. 11-2A). We also found that Hoe 140 does not modify preconditioning when administered after preconditioning, which suggests that the B2 receptor is important for triggering preconditioning, but its activation is not necessary during sustained ischemia for cardioprotection. Another line of evidence supporting the importance of bradykinin in preconditioning was obtained from experiments using aprotinin, an inhibitor of kallikrein. When rabbits were pretreated with aprotinin (2000 units/kg/min for 20 min plus 500 units/kg/min for 30 min), infarct size limitation by preconditioning was significantly attenuated as shown in Figure 11-2B. Aprotinin is a serine protease inhibitor, which is not very selective to kallikrein, and the inhibitory effect of aprotinin on preconditioning was not as potent as Hoe 140. Nevertheless, the attenuation of preconditioning by aprotinin supports the importance of bradykinin in the mechanism of preconditioning.

These results using Hoe 140 and aprotinin (Figs. 11-2A,B) suggest that the production of bradykinin and activation of B2 receptors play a crucial role in preconditioning. However, this does not necessarily mean that bradykinin is