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Kinins Mediate the Cardioprotective Effects Induced by Ischemic Preconditioning and ACE Inhibitor Treatment in Rat Heart

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With the highly specific kinin RIAs, bradykinin (BK) and a kallidin-like peptide (KLP) were measured in the effluent of the isolated perfused hearts of SD and BNK rats. We also measured these kinins in the incubation medium of the isolated cardiomyocytes of SD rat hearts. Based on our previous work and theoretical considerations, we believe that KLP most likely is Arg^0-BK. This peptide is released from the LMW kininogen by cardiac kallikrein. These data strongly support the notion that a local tissue kallikrein kinins system (tKKS) exists in the rat hearts.
The release of KLP into the effluent of the perfused rat hearts is about 4-6 folds higher than that of BK. The concentration of KLP in the incubation medium of rat cardiomyocytes is also higher than those of BK (2-4 folds). These results indicate that KLP is the major kinin locally generated in the hearts. BK is most likely a secondary product of KLP, degraded by aminopeptidase in the hearts.

IPC significantly increased the kinin release into the effluent of the perfused SD rat hearts. The release of KLP is much higher than that of BK (7.5 folds). This result suggests that hypoxia activates the tissue kallikrein kinin system in the heart, which generates KLP as the predominant kinin. In contrast, in the heart of BNK rats, IPC had little effect on the release of kinins.

Infusions with the ACE inhibitor, Captopril (Cap), caused an obvious increase of KLP release in the effluent of the isolated perfused heart (SD and BNK rat), but it had little effects on the release of BK. Incubation of the cardiomyocytes with Cap also increases kinin concentration in the medium. But it is the KLP that is increased substantially, and to lower degree BK, suggesting that KLP is the major endogenous substrate for ACE.

IPC obtained with three 5-min cycles of ischemia and three 5-min cycles of reperfusion renders significant cardioprotection against the prolonged 30 min ischemia. This is shown by the improvement in cardiac functions, the attenuation of reperfusion arrhythmia, and a substantially lower CK release. Treatment with HOE140 and a specific KAL antiserum, respectively, abolish the cardioprotective effect in CK release of the preconditioned hearts but can not abolish the improving effect of IPC on cardiac function. These results indicate that KLP mediates the cardioprotection of IPC in CK release via B_2 receptors in this model. However other agents or mechanisms are also involved in the improvement of the cardiac function by IPC.

Pharmacological preconditioning in SD rat hearts with three 5-min Cap infusions (10μM) followed by 5-min drug free infusions mimics the cardioprotection of IPC. This beneficial effect includes cardiac function recovery, alleviation of reperfusion arrhythmia and a substantial lower release of CK. Additional treatment with HOE140 and a specific KAL antiserum respectively completely abolish the cardioprotection of Cap, while additional treatment with L-NAME has no significant effect. These results indicate that KLP mediates the cardioprotection of Cap via B_2 receptor, while NO is of minor importance.

In BNK rat hearts, IPC with three 5-min ischemia and three 5-min reperfusion cycles rendered significant cardioprotection against the prolonged 30 min ischemia indicated by cardiac function and CK release. Pretreatment with the adenosine receptor antagonist, 8-PT, completely abolish the cardioprotective effect of IPC. These results indicate the adenosine via A_1 receptor is involved in the cardioprotection of IPC in BNK rat heats.

Pharmacological preconditioning in BNK rat hearts with three 5-min Cap infusions (10μM) followed by 5-min drug free infusions did not mimic the cardioprotection of IPC. Preconditioning with Diazoxide (Dia) rendered improvement in cardiac function during reperfusion, but did not alter the CK release. These results indicate that the deficiency in cardioprotection of BNK rat hearts is related with the local kinin system in the heart. The mechanism of this phenomenon is currently under investigation.