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DUAL ACTIVATION OF AKT KINASE AND STAT-3 KINASE IS INVOLVED IN THE CARDIOPROTECTION BY REMOTE LIMB ISCHEMIC POSTCONDITIONIN IN RATS

Han Guan-ping, Song Jun-xian, Ren Jing-yi, Chen Hong *Department of Cardiology, Peking University, People´s Hospital, Beijing, China*

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Objective This study aimed at investigating whether reperfusion injury salvage kinases (RISK) pathway, which mainly includes phosphatidylinositol 3-kinase/Akt (PI3K/AKT), and survivor activating factor enhancement (SAFE) pathway, which mainly consists of Janus-activated kinase/signal transducer and activator of transcription-3 (JAK/STAT-3), are responsible for the cardioprotection by remote limb ischemic postconditioning (RIPostC) in heart during myocardial ischemia/reperfusion.

Methods Sprague–Dawley rats were subjected to 30 min of myocardial ischemia (ligation of left anterior descending coronary artery) followed by 3 h of reperfusion (release of the ligation). RIPostC was initiated by 3 cycles of 5 min of

ischemia and 5 min of reperfusion on both hind limbs immediately at the onset of myocardial reperfusion using a natural rubber tourniquet in the presence or absence of AKT inhibitor wortmannin or STAT3 inhibitor AG490. The protein and phosphorylation levels of AKT and STAT-3 in left ventricular were measured immediately after RIPostC. Moreover, infarct sise, serum creatine kinase (CK) and cardiac troponin I (TnI) levels, and cardiac function parameters including heart rate (HR), left ventricular end-diastolic pressure (LVEDP), left ventricular systolic pressure (LVSP) and maximum rise/fall rate of LV pressure (±dP/dtmax) were monitored at the end of 3 h of myocardial reperfusion.

Results RIPostC effectively protected hearts against ischemia/reperfusion injury by limiting infarct sise, lowering CK and cTnI release and improving cardiac function including decrease in LEVDP and increase in LVSP and ±dP/dtmax, which could be essentially prevented by wortmannin or AG490. RIPostC led to evident increase in phosphorylation levels of AKT and STAT-3 at the end of 30 min of myocardial reperfusion, which could be significantly inhibited by wortmannin and AG490, respectively.

Conclusions The beneficial effects of RIPostC against myocardial ischemia/reperfusion are associated with the activation of AKT and STAT3 kinases at reperfusion. These findings suggest that dual activation of AKT kinase in RISK pathway and STAT-3 kinase in SAFE pathway is required for the cardioprotection by RIPostC during myocardial ischemia/reperfusion.