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Investigating the Signal Transduction Pathways Underlying Remote Ischaemic Preconditioning in Pigs

Ioanna Andreadou[1], Efstathios K. Iliodromitis[2], Apostolos Papalois[2], George Gritsopoulos[2], Dimitra Karageorgiadi[1], Katerina Deli[1], Dimitrios Th. Kremastinos[2], Maria Anastasiou-Nana[2]

[1]Department of Pharmaceutical Chemistry, School of Pharmacy, University of Athens, Athens, Greece, [2]2nd University Department of Cardiology, Medical School, Attikon General Hospital, University of Athens, Athens, Greece

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INTRODUCTION

Applying brief ischaemia/reperfusion to a limb either prior to myocardial ischaemia (remote ischaemic preconditioning, RIPC) can reduce myocardial infarct size. We hypothesised that RIPC limits infarct size by activating the adenosine receptor and the PI3K-Akt pathway at the onset of myocardial reperfusion.

METHODS

Under general anaesthesia mini swines (25-30kg) were randomly divided into four groups and were subjected to 60min regional ischemia of the heart after ligation of a prominent coronary artery with the following additional interventions: *Control group* with no additional interventions, *RIPC group* subjected to four cycles of 5min ischemia/5min reperfusion of a lower limb prior to the onset of myocardial ischaemia, *RIPC+Wort group* and *RIPC+8-SPT groups* were subjected to the same intervention were treated with 20 μg/kg Wortmannin or 10 mg/kg 8-SPT respectively that were intravenously given 30 seconds before the end of prolonged ischemia. After the end of the long reperfusion period, the infarct size (I) was delineated by TTC staining, the area at risk (R) by fluorescent particles and the percent (%) I/R ratio was calculated. In a second series of experiments, three respective to the first series groups were subjected to the same protocol. Myocardial biopsies were taken from all studied groups, at three different time points: (A) baseline – healthy myocardial tissue – up and away from the ischemic region and the apex of the heart, (B) 5 min and (C) 15 min respectively after the onset of reperfusion from area at risk. PI3, phospho-PI3, Akt, phospho-Akt and total GSK-3β were assessed by Western blot.

RESULTS

RIPC significantly reduced myocardial infarct size (13.3±2.2% versus 48.8±4.2% in control: $P<0.05$:N>5/group). Wortmannin, the PI3K-Akt inhibitor, partially abolished the infarct-limiting effects of RIPC (33.2±6% with RIPC+Wort versus 13.3±2.2% with RIPC:$P<0.05$:N>5/group). 8-SPT, the adenosine receptor inhibitor, did not influence the infarct-limiting effects of RIPC (10.4±2.0% with RIPC+8-SPT versus 13.3±2.2% with RIPC: $P>0.05$:N>5/group). The phosphorylation of PI3 and Akt was significantly higher in the ischaemic regions of the heart, in the protected *RIPC group* compared to the *Control*, *RIPC+Wort* and *RIPC+8-SPT* groups. GSK-3β was inhibited only in the protected *RIPC* and *RIPC+SPT* groups and not in the *Control* and the non protected *RIPC+Wort* groups.

CONCLUSION

RIPC reduces myocardial infarct size by activating the PI3K-Akt pathway at reperfusion. RIPC

does not require activation of the adenosine receptor at the time of reperfusion for its infarct-limiting effects. The complete absence of PI3 and Akt does not abrogate the protective effect of RIPC if it is combined with simultaneous inhibition of GSK-3β. Total GSK-3β prevents the protection afforded by RIPC.