Activation of RISK signaling pathway is involved in age-dependent cardioprotective effect of remote ischemic preconditioning in SHR rats

Authors:
V Ledvenyiova-Farkasova¹, L Grieceva¹, M Murarikova¹, S Carnicka¹, M Ferko¹, T Rajtik², A Szobi², A Adameova², I Bernatova³, T Ravingerova¹, ¹Slovak Academy of Sciences, Institute for Heart Research - Bratislava - Slovak Republic, ²Comenius University, Faculty of pharmacy - Bratislava - Slovak Republic, ³Slovak Academy of Sciences, Institute of normal and pathological physiology - Bratislava - Slovak Republic.

Topic(s):
Ischemia, Infarction, Cardioprotection

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S127

Funding Acknowledgements:

Background: Remote ischemic preconditioning (RIPC) represents a form of innate cardioprotection conferred by short episodes of ischemia applied in a distant organ/tissue. However, the RIPC application in humans has not been always beneficial. To a major extent, the latter might be attributed to the presence of various comorbidities and/or confounders, such as the presence of hypertension, metabolic disorders, gender differences or middle age of the patients. Cardioprotective effect of RIPC has been shown to be mediated by activating intrinsic pro-survival signaling cascades, such as reperfusion injury salvage kinase (RISK) pathway in the healthy animals, however, there is no evidence of its involvement in the mechanisms of RIPC in the hearts of spontaneously hypertensive (SHR) rats.

Purpose: The aim of this study was to investigate the effectiveness of RIPC in SHR rats of different ages and to evaluate the role of RISK pathway in the effect of RIPC on cardiac ischemic tolerance in these animals.

Methods: Rats of age three, five and eight months were anesthetized and RIPC was performed on the right hind limb. Its protocol consisted of three cycles of 5 min non-invasive limb occlusion followed by 5 min reperfusion. Subsequently, hearts were excised, Langendorff-perfused and exposed to 30 min global ischemia and 2 h reperfusion for the evaluation of reperfusion-induced ventricular arrhythmias, infarct size and recovery of contractile function. Tissue samples for Western blot analysis were collected after 40 min of reperfusion.

Results: Enhanced resistance to lethal injury (myocardial infarction) compared to that in non-preconditioned animals was observed in all experimental groups. Moreover, in three and five months old animals, RIPC exhibited antiarrhythmic effect, while its impact on the severity of arrhythmias in eight months old SHR rats was negative. Additionally, RIPC enhanced recovery of contractile function only in five months old animals, with no effect on contractility in three and eight months old rats. Protective effect of RIPC was associated with an increased Akt, ERK and GSK-3β phosphorylation as well as decreased Bax/Bcl-2 ratio and caspase-3 activation only in the groups of three and five months old animals.

Conclusions: RIPC exhibited cardioprotective effects in SHR rats that were partially age-dependent. Whereas in older adult animals, RIPC decreased the extent of lethal injury, it did not attenuate myocardial stunning and aggravated arrhythmogenesis as compared to younger individuals. These effects of RIPC may be attributed to the differences in the activation of the components of RISK and appopptic pathway and a distinct influencing of various aspects of ischemia/reperfusion injury.