Lack of Mitochondrial Uncoupling Protein 3 Results in Decreased Postischemic Activation of p42/p44 Mitogen-Activated Protein Kinase after Ischemic Preconditioning

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Background: Ischemic heart disease is the number one cause of death in the United States with approximately 425,000 deaths per year in 2006. In the current era of reperfusion therapy, much of the mortality is due to myocardial injury during reperfusion. The uncoupling proteins (UCPs) are members of the mitochondrial anion transporter superfamily that reside in the inner mitochondrial membrane and are primarily responsible for the dissipation of the proton gradient between the mitochondrial matrix and the space between the inner and outer mitochondrial membranes that drives ATP synthesis by the F0F1-ATPase. The activation of p42/p44-MAPK has been implicated in the adaptive response of ischemic preconditioning (IPC) in the setting of ischemia-reperfusion (IR) injury. In a model of IPC, we have found that hearts of mice lacking UCP3 subjected to IR injury have poorer recovery of function and greater myocardial damage compared to wild-type (WT) mice.

Hypothesis: The loss of functional recovery in UCP3-/- hearts subjected to IPC followed by IR injury maybe a result of impaired p42/p44-MAPK signaling after preconditioning.

Methods: Hearts from male WT and UCP3-/- mice (n=4) were subjected to 3 cycles of 4 minutes no-flow ischemia followed by 4 minutes of reperfusion (simulating IPC) followed by 30 minutes of no-flow ischemia with 30 minutes reperfusion using the isolated perfused working mouse heart model. p42/44 MAPK phosphorylation status was determined after 30 minutes of IPC and after IPC with IR to determine if there is sustained activation of p42/p44-MAPK activation with IR injury.

Results: While both hearts from UCP3-/- and WT mice had similar levels of activation of p42/p44-MAPK immediately after IPC, the activation of p42/p44-MAPK was 17% lower (p<0.05) in UCP3-/- hearts after 30 minutes of reperfusion, which correlated with decreased post-ischemic contractile function and increased myocardial injury.

Conclusions: A decrease in the sustained postischemic activation of p42/p44-MAPK following IPC in hearts of UCP3-/- mice results in increased myocardial damage and functional decline after IR injury compared to WT hearts. This may represent dysregulated activation of p42/p44 MAPK in response to enhanced reactive oxygen species (ROS) generation in the UCP3-/- mouse heart. Future studies will investigate the role of other stress signalling responses to IPC in mice lacking UCP3.