

Inhibition of G-protein coupled receptor kinase-2 protects from myocardial ischemia-reperfusion injury via an anti-apoptotic effect

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Objective: Morbidity and mortality of acute myocardial infarction remains significant, resultant left ventricular systolic function presenting a major determinant of clinical outcome. Activation of pro-survival kinases such as AKT have proven to pose powerful targets for cardioprotection in ischemia-reperfusion injury (I/R) models. G-protein-coupled receptors can confer cardioprotection by activating AKT signaling. The carboxyl-terminus of GRK2 (β ARKct) has been shown to have beneficial effects in heart failure by inhibiting G-protein coupled receptor kinase 2 (GRK2), leading to improved cardiac performance. **Methods/results:** Non-transgenic littermate controls (NLC) and myocardial-specific GRK2-overexpressing or β ARKct-transgenic mice were subjected to I/R. Infarct size was enlarged in GRK2 overexpressing mice ($45.0 \pm 2.8\%$) compared to controls ($31.3 \pm 2.3\%$), β ARKct expression reduced it to $16.8 \pm 1.3\%$ ($p < 0.05$). Additionally, adenoviral delivery of the β ARKct gene in rabbits subjected to I/R was achieved via intracoronary delivery, decreasing infarct size from $30.0 \pm 3.0\%$ (Control) to $16.8 \pm 2.1\%$ (β ARKct). Infarct sizes were measured by triphenyltetrazoliumchloride staining and myocardial apoptosis was assessed. Apoptotic index was significantly decreased in the hearts expressing β ARKct compared to increased cell death in GRK2 transgenic mice. AKT phosphorylation was measured in the ischemic area up to 24 hours after I/R and revealed a two-fold higher increase of pAKT protein in the β ARKct-group compared to the GRK2-overexpressing group. **Conclusion:** GRK2 overexpression was deleterious in ischemic myocardium whereas inhibition via β ARKct was cardioprotective resulting in reduced apoptosis and increased AKT signaling. GRK2 inhibition represents a therapeutic approach reducing acute ischemic injury in the myocardium, thus GRK2 inhibition appears a valuable strategy limiting acute myocardial ischemia.