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

H. Brinks, Matthieu Boucher, S. Pesant, Erhe Gao, K. Chuprun, Philip Raake, Leif Vinge, David Harris, Patrick Most, Andrea D. Eckhart, Walter J. Koch

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

Brinks H[1,2], Boucher M[3], Pesant S[2], Gao E[2], Chuprun K[2], Raake P[4], Vinge LE[2], Harris DM[2], Most P[4], Eckhart AD[2], Koch WJ[2]

[1]Inselspital Bern, Universitätsspital, Herz- und Gefäßchirurgie, Bern, Switzerland, [2]Thomas Jefferson University, Center for Translational Medicine, Philadelphia, United States, [3]Pfizer Canada Inc., Cardiovascular & Metabolic/Medical Division, Kirkland (Québec), Canada, [4]Universitaet Heidelberg, Kardiologie, Angiologie und Pneumologie, Heidelberg, Germany

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 (βARKct) 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 βARKct-transgenic mice were subjected to I/R. Infarct size was enlarged in GRK2 overexpressing mice (45.0 ± 2.8%) compared to controls (31.3 ± 2.3%), βARKct expression reduced it to 16.8 ± 1.3% ($p < 0.05$). Additionally, adenoviral delivery of the βARKct gene in rabbits subjected to I/R was achieved via intracoronary delivery, decreasing infarct size from 30.0 ± 3.0% (Control) to 16.8 ± 2.1% (βARKct). Infarct sizes were measured by triphenyltetrazoliumchloride staining and myocardial apoptosis was assessed. Apoptotic index was significantly decreased in the hearts expressing βARKct 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 bARKct-group compared to the GRK2-overexpressing group. **Conclusion:** GRK2 overexpression was deleterious in ischemic myocardium whereas inhibition via βARKct 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.