Protection through postconditioning or a mitochondria-targeted S-nitrosothiol is unaffected by cardiomyocyte-selective ablation of protein kinase G.

Abstract:
Protein kinase G type I (PKG1) plays a critical role in survival signaling of pre- and postconditioning downstream of cardiac cGMP. However, it is unclear whether PKG1 exerts its protective effects in the cardiomyocyte or if other cardiac cell types are involved, and whether nitric oxide (NO) metabolism can target cardiomyocyte mitochondria independently of cGMP/PKG1. We tested whether protection against reperfusion injury by ischemic postconditioning (IPost), soluble guanylyl cyclase (sGC) activation and inhibition, adenosine A(2B) receptor (A(2B)AR) agonist, phosphodiesterase type-5 (PDE-5) inhibitor, or mitochondria-targeted S-nitrosothiol (MitoSNO) was affected by a cardiomyocyte-specific ablation of the PKGI gene in the mouse (CMG-KO). In situ hearts underwent 30 min of regional ischemia followed by 2 h of reperfusion. As expected, in CMG-CTRs all interventions at early reperfusion lead to profound infarct size reduction: IPost (six cycles of 10-s reperfusion and 10-s coronary occlusion) with or without treatment with the sGC inhibitor ODQ, treatment with the specific sGC activator BAY58-2667 (BAY58), the selective A(2B)AR agonist BAY60-6583 (BAY60), PDE-5 inhibitor sildenafil, and MitoSNO. MitoSNO accumulates within mitochondria, driven by the membrane potential, where it
generates NO- and S-nitrosates thiol proteins. In contrast, the hearts of CMG-KO animals were not protected by BAY58 and sildenafil, whereas the protective effects of IPost, IPost with ODQ, BAY60, and MitoSNO were unaffected by the lack of PKGI. Taken together, PKGI is important for the protection against ischemia reperfusion injury afforded by sGC activation or PDE-5 inhibition. However, the beneficial effects of IPost, activation of the A(2B)AR, as well as the direct effects via mitochondrial S-nitrosation do not depend on PKGI in cardiomyocytes.