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Characterization of mice with a deletion of protein kinase G type I in cardiomyocytes and the effect on cardioprotection through either postconditioning or mitochondria-targeted *S*-nitrosothiol

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Background

Protein kinase G type I (PKGI/cGMP kinase I) plays a critical role in survival signalling of pre- and postconditioning. However, it is unclear whether cGKI exerts its protective effects in the cardiomyocyte or if other cardiac cell types are involved, and whether nitric oxide (NO) has cGKI-independent effects on cardiomyocytes mitochondria.

Objective

We developed mice with a cardiomyocyte-specific ablation of the cGKI gene (CMG-KO) and tested whether protection against reperfusion injury by ischemic postconditioning (IPost), soluble guanylyl cyclase (sGC) activation, the adenosine A_{2B} receptor ($A_{2B}AR$), or the mitochondria-targeted *S*-nitrosothiol (MitoSNO) was affected. MitoSNO accumulates within mitochondria, driven by the membrane potential, where it generates $NO^{\bullet}$ and *S*-nitrosated thiol proteins [1].

Methods and results

Conditional mice with floxed cGKI alleles were crossed to the MLC2a-Cre transgenic mice. Western Blot and immunohistochemistry confirmed that the Cre-mediated recombination produced the cGKI knock-out specifically in atrial and ventricular cardiomyocytes but not in other organs (Figure 1).

In situ hearts of underwent 30 min of regional ischemia followed by 2 h of reperfusion. As expected, in the control animals all interventions at early reperfusion

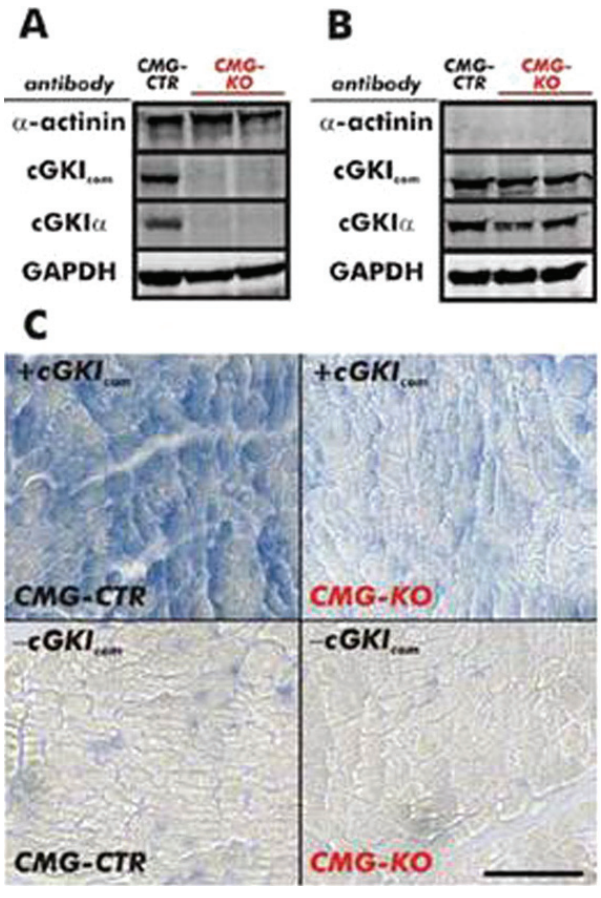

Figure 1 Representative Western Blots of **A** left ventricle and **B** cerebellum of CMG-KO and control mice from the same litters on a C57/Bl6N genetic background (CMG-CTR), clearly indicating the specific absence of cGKI in the heart. **C** Immunohistochemistry of cardiac tissue.

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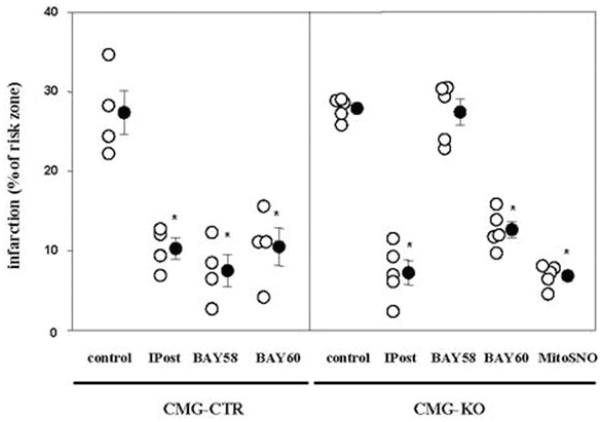

Figure 2 Results of open chest experiments. As expected, either IPost, activation of sGC with BAY58 or A_{2B}AR activation with BAY60 resulted in a profound decrease of infarct size in CMG-CTR. While BAY58 failed to protect in the CMG-KO animals, IPost, BAY60, and MitoSNO still afforded protection, suggesting a signaling independent on cGKI in the cardiomyocyte. *p<0.05 vs. control.

lead to profound infarct size reduction: IPost (six cycles of 10 sec reperfusion and 10 sec of coronary occlusion), treatment with the specific sGC activator BAY 58-2667 (BAY58), the selective A_{2B}AR agonist BAY 60-6583 (BAY60), as well as MitoSNO. In contrast, the hearts of CMG-KO animals were not protected by BAY58, whereas the protective effects of IPost, BAY60, and MitoSNO were unaffected by the lack of cGKI.

Conclusion

While cardiomyocyte cGKI is important for the protection afforded via cGMP-signalling, beneficial effects of IPost, activation of the A_{2B}AR, as well as direct NO effects via mitochondrial *S*-nitrosylation does not depend on cGKI in cardiomyocytes.

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