Roles of cGMP-dependent protein kinase I (cGKI) and PDE5 in the regulation of Ang II-induced cardiac hypertrophy and fibrosis.

Abstract:
Conflicting results have been reported for the roles of cGMP and cGMP-dependent protein kinase I (cGKI) in various pathological conditions leading to cardiac hypertrophy and fibrosis. A cardioprotective effect of cGMP/cGKI has been reported in whole animals and isolated cardiomyocytes, but recent evidence from a mouse model expressing cGKI? only in smooth muscle (?RM) but not in cardiomyocytes, endothelial cells, or fibroblasts has forced a reevaluation of the requirement for cGKI activity in the cardiomyocyte antihypertrophic effects of cGMP. In particular, ?RM mice developed the same hypertrophy as WT controls when subjected to thoracic aortic constriction or isoproterenol infusion. Here, we challenged ?RM and WT (Ctr) littermate control mice with angiotensin II (All) infusion (7 d; 2 mg ? kg(-1) ? d(-1)) to induce hypertrophy. Both genotypes developed cardiac hypertrophy, which was more pronounced in Ctr animals. Cardiomyocyte size and interstitial fibrosis were increased equally in both genotypes. Addition of sildenafil, a phosphodiesterase 5 (PDE5) inhibitor, in the drinking water had a small effect in reducing myocyte hypertrophy in WT mice and no effect in ?RM mice. However, sildenafil substantially blocked the increase in collagen I,
fibronectin 1, TGFβ, and CTGF mRNA in Ctr but not in ?RM hearts. These data indicate that, for the initial phase of AII-induced cardiac hypertrophy, lack of cardiomyocyte cGKI activity does not worsen hypertrophic growth. However, expression of cGKI in one or more cell types other than smooth muscle is necessary to allow the antifibrotic effect of sildenafil.