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cGKI signaling in cardiac hypertrophy

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The atrial natriuretic peptide (ANP) has been shown to modulate hypertrophy of the heart via the cardiac NP receptor guanylyl cyclase-A (GC-A) [1]. Also, analysis of transgenic mice with a cardiomyocyte (cM) specific overexpression of GC-A and the chronic inhibition of the cGMP-degrading phosphodiesterase-5 by sildenafil indicated that the second messenger cGMP can blunt hypertrophic signals from pressure load and neurohormonal stress perhaps by activation of a cardiac cGMP kinase I (cGKI) pathway [2-4]. To test whether the predicted hypertrophic phenotype of transgenic animals carrying a genetic disruption of cGKI in the heart can be confirmed, we analyzed the recently established cGKI rescue mice (RM) [5]. We provide strong evidence that the cGKI protein is not present in cM of RM, whereas it is detectable in the myocardium of control mice. We studied hypertrophy in response to chronic β-adrenoreceptor stimulation by isoproterenol (ISO) and identified significantly reduced expression levels of the β_1-adrenergic receptor in the hearts of gene-targeted RM as compared to littermate controls. However, the heart/body weight ratios (HW/BW) and the mean cM cross-section area were increased to a similar extent in both genotypes after the 7 days of ISO (30 mg/kg/d). Up-regulation of fetal gene markers (*NPPA*, *Myh7*, *PI-16*) and down-regulation of genes which are normally expressed in the adult heart (*Myh6*, *Serca2*), both indicative for pathological hypertrophy, were as well not altered by the lack of cGKI in cM.

In summary, the presented data indicates that cGKI signaling in cM does not protect the heart from the maladaptive hypertrophy program induced by chronic β-adrenergic stimulation that activates G_s protein-coupled receptor pathways.

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