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The ANP/cGMP/cGMP-dependent protein kinase pathway counteracts Angiotensin II-stimulated calcium mobilization in cardiac myocytes

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Background

The cardiac hormone atrial natriuretic peptide (ANP) exerts local, Guanylyl Cyclase-A (GC-A) – mediated myocardial effects to antagonize the Ca^{2+}_i-dependent hypertrophic growth response to Angiotensin II (Ang II). The present study aimed to characterize the specific molecular mechanisms mediating the reciprocal interactions between the ANP/GC-A and the Ang II/AT1 systems in the heart.

Results

Ca^{2+}_i-transients and cell shortening were monitored in Indo-1 loaded isolated, electrically paced adult murine cardiomyocytes. Ang II (1–100 nM) acutely enhanced the amplitude of Ca^{2+}_i-transients, accelerated Ca^{2+}_i-decay and stimulated cell shortening. These effects were completely prevented by ANP (100 nM). In contrast, the myocyte calcium responses to β-adrenergic stimulation (10 nM isoprenaline) were not affected by ANP. To study the role of cGMP-dependent protein kinase I (PKG I), we evaluated the ANP effects on calcium regulation in myocytes from transgenic mice with cardiac deletion of PKG I. The inhibitory effects of ANP on Ang II signaling were totally abolished in PKG I-deficient myocytes. Rp-8-pCPT-cGMPs, a membrane-permeable PKG inhibitor, mimicked the effects of genetic PKG I deletion. One downstream target of PKG I in the heart is regulator of G-protein signaling (RGS)-2, which attenuates Ang II – Gαq protein signaling. In RGS2 – deficient myocytes Ang II – induced Ca^{2+}_i-mobilization was enhanced. Moreover, the inhibitory effect of ANP was totally abolished.

Conclusion

Taken together, our data indicate that PKG I is a downstream target activated by the ANP/GC-A/cGMP-signaling pathway in cardiac myocytes. cGMP/PKG I-stimulated phosphorylation of RGS2 and subsequent inhibition of AT1/Gq-signaling appear to mediate the counterregulation of the cardiac effects of Ang II by ANP.

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