BMC Pharmacology

ORAL PRESENTATION Open Access

A novel pathway of cGMP

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From 5th International Conference on cGMP: Generators, Effectors and Therapeutic Implications
Halle, Germany. 24-26 June 2011

Background

Cardiac atrial natriuretic peptide (ANP) regulates arterial blood pressure, moderates cardiomyocyte growth, and stimulates angiogenesis and metabolism. ANP binds to the transmembrane guanylyl cyclase (GC) receptor, GC-A to exert its diverse functions. This involves a cGMP-dependent signaling pathway preventing pathological $[Ca^{2+}]_i$ raises in myocytes. In chronic cardiac hypertrophy, however, ANP levels are markedly increased and GC-A/cGMP responses to ANP are blunted due to receptor desensitization.

Results

Here we show that in this situation ANP binding to GC-A stimulates a novel cGMP-independent signaling pathway in cardiac myocytes, resulting in pathologically elevated intracellular Ca^{2+} levels ($[Ca^{2+}_i]$). This pathway involves the activation of TRPC3/C6 Ca^{2+} channels (transient receptor potential canonical channel 3/6) by GC-A which forms a stable complex with TRPC3/C6 channels. Our results indicate that the resulting TRPC3/C6-mediated Ca^{2+} entry then stimulates Calmodulin Kinase II (CaMKII) to phosphorylate L-type Ca^{2+} channels leading to increased L-type Ca^{2+} channel mediated Ca^{2+} current and a rise in intracellular Ca^{2+} levels.

Conclusion

These observations reveal a dual role of the ANP/GC-A signaling pathway in the regulation of cardiac myocyte Ca^{2+}_i-homeostasis. Under physiological conditions, activation of a cGMP-dependent pathway moderates the Ca^{2+}_i-enhancing action of hypertrophic factors such as Angiotensin II. By contrast, a cGMP-independent pathway predominates under pathophysiological conditions, when GC-A is desensitized by high ANP levels. The concomitant rise in $[Ca^{2+}_i]$ is likely to increase the propensity to cardiac hypertrophy and arrhythmias.

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Published: 1 August 2011

doi:10.1186/1471-2210-11-S1-O28
Cite this article as: Kuhn *et al.*: A novel pathway of cGMP. *BMC Pharmacology* 2011 **11**(Suppl 1):O28.

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