

ORAL PRESENTATION

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# A novel pathway of cGMP

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## 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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