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Poster presentation

Cardiac natriuretic peptides inhibit TRPC6-mediated prohypertrophic signaling through cGMP-PKG pathway

Hideyuki Kinoshita*[1], Koichiro Kuwahara[1], Ryuji Inoue[2], Motohiro Nishida[3], Hitoshi Kurose[3], Shigeki Kiyonaka[4], Yasuo Mori[4], Masaki Harada[1], Masao Murakami[1], Yasuaki Nakagawa[1], Shinji Yasuno[1], Satoru Usami[1], Masataka Fujiwara[1], Yoshihiro Kuwabara[1], Takeya Minami[1], Yuko Yamada[1], Kenji Ueshima[5] and Kazuwa Nakao[1]

Address: [1]Department of Medicine and Clinical Science, Kyoto University Graduated School of Medicine, Kyoto, Japan, [2]Department of Physiology, Graduate School of Medical Sciences, Fukuoka University, Fukuoka, Japan, [3]Department of Pharmacology and Toxicology, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan, [4]Laboratory of Molecular Biology, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, Japan and [5]EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan

Email: Hideyuki Kinoshita* - kinos@kuhp.kyoto-u.ac.jp

* Corresponding author

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Background

Cardiac natriuretic peptides, atrial and brain natriuretic peptides (ANP and BNP, respectively) are known to have anti-cardiac hypertrophy effects. ANP and BNP bind to their common receptor, guanylyl cyclase-A, which subsequently activates cGMP-protein kinase G (PKG) pathway. Precise molecular mechanisms by which cardiac natriuretic peptides protect hearts against pathological cardiac hypertrophy still remain unclear, however. Transient receptor potential (TRP) C6, an ion channel responsible for the receptor-activated Ca2+ entry, has been shown to be a positive regulator of calcineurin-NFAT signaling pathway that drives pathologic cardiac remodeling [1]. In this study to elucidate the molecular pathways, by which cardiac natriuretic peptides negatively regulate pro-hypertrophic signaling, we investigated effects of ANP on TRPC6-calcineurin-NFAT signaling.

Results

In rat neonatal ventricular myocytes (NRVM), ANP significantly inhibited ET-1-induced Ca2+ entry and NFAT activation. The inhibitory effect of ANP on ET-1-induced Ca entry was abolished in the presence of BTP2, a TRPC inhibitor. In HEK293 cells expressing TRPC6, ANP dramatically inhibited TRPC6-mediated Ca2+ entry and cationic currents. The inhibitory effect of ANP on TRPC6 was abolished in the presence of specific PKG inhibitors or by the substitution of alanine for threonine at 69th amino acid of TRPC6, which has been shown to be phosphorylated by PKG.

Conclusion

All these results suggest that inhibition of TRPC6 is an important component, by which cardiac natriuretic peptides-GC-A-cGMP-PKG signaling pathway protects the hearts from pathological cardiac remodeling.

References

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