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Poster presentation

Opposite effects of cGMP-dependent protein kinase on cGMP production by soluble and particular guanylyl cyclase in adult ventricular myocytes

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Background

Both particulate (pGC) and soluble guanylyl cyclases (sGC) synthesize cGMP. While sGC is activated by nitric oxide (NO), pGC is activated by natriuretic peptides (NPs) such as ANP or BNP. Physiological effects of cGMP are mainly mediated by cGMP-dependent protein kinase (PKG) and cGMP phosphodiesterases (PDEs), namely PDE2 and PDE5. We hypothesised that PKG may underlie regulatory feedback in cGMP signals produced by pGC and sGC activation in adult rat ventricular myocytes (ARVMs).

Materials and methods

To test this hypothesis, subsarcolemmal cGMP signals elicited by NO-donors or NPs in the presence of the PKG inhibitor, KT5823 (KT, 50 nM) were monitored in ARVMs. Myocytes were infected by an adenovirus expressing the WT rat olfactory cyclic nucleotide-gated channel CNGA2 and the cGMP-gated current (I_{CNG}) was recorded by the whole-cell patch-clamp technique.

Results

Application of the membrane permeant cGMP analog Sp-8-pCPT-cGMPS (Sp-8, 100 μM) induced a large I_{CNG} current in myocytes infected by CNGA2 adenovirus, but not in control cells. KT increased 3-fold the I_{CNG} current followed by activation of sGC by *S*-nitroso-*N*-acetyl-penicillamine (SNAP, 100 μM). This effect was abolished in the presence of the non selective PDE inhibitor IBMX (100 μM) or a selective PDE5 inhibitor (sildenafil, 100 nM). Surprisingly, KT decreased (by 50%) the I_{CNG} current stimulated by ANP (10 nM and 100 nM) in a PDE-independent manner, but had no effect on total cGMP content measured by radioimmunoassay, which is controlled by PDE2 and PDE5 subtypes.

Conclusion

Our results suggest that in ARVMs the subsarcolemmal cGMP pools generated by sGC or pGC are differentially regulated by PKG. In the sGC pool, PDE5 mediates the effects of PKG, while in the pGC pool, the PKG effect is independent of PDE activity. These differential regulations of cGMP signals may underlie the specific effects of NPs and NO-donors on cardiac function.