BMC Pharmacology

Poster presentation

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PDE2 and PDE5 exert specific and distinct roles in regulating cGMP signals elicited by particulate or soluble guanylyl cyclases in rat cardiac myocytes

Liliana Castro*, Grégoire Vandecasteele and Rodolphe Fischmeister

Address: INSERM U-446, Laboratoire de Cardiologie Cellulaire et Moléculaire, Faculté de Pharmacie, Université Paris-Sud, Châtenay-Malabry, France

Email: Liliana Castro* - liliana.castro@cep.u-psud.fr

* Corresponding author

from 2nd International Conference of cGMP Generators, Effectors and Therapeutic Implications
Potsdam, Germany, 10–12 June, 2005

Published: 16 June 2005

BMC Pharmacology 2005, **5**(Suppl 1):P9 doi:10.1186/1471-2210-5-S1-P9

Background

Both particulate (pGC) and soluble guanylyl cyclases (sGC) are known to be involved in the regulation of cardiac function. While sGC is activated by nitric oxide (NO), pGC is activated by natriuretic peptides (NPs), such as ANP or BNP. Regulation of cGMP signals by cardiac phosphodiesterases (PDEs) subtypes may underlie a specific role of pGC or sGC activation in cardiac myocytes. To test this hypothesis, subsarcolemmal cGMP signals elicited by NO-donors or NPs were monitored in adult rat ventricular myocytes.

Materials and Methods

Myocytes were infected by an adenovirus expressing the WT rat olfactory cyclic nucleotide-gated (CNG) channels α-subunit (CNGA2) and subsequent recording of the cGMP-gated current (I_{CNG}) was achieved 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 the CNGA2 adenovirus, but had no effect in control cells. Specific stimulation of sGC by a direct agonist HMR1766 (10 μM) or by several NO-donors (SNAP, SNP, DEANO, SIN-1, spermine NO, all at 100 μM) induced only a small but detectable I_{CNG}. The current was potentiated by non-selective PDE inhibition with IBMX (100 μM) indicating that PDE activity limits the spread of cGMP at the membrane. Selective inhibition of either PDE2 with EHNA (10 μM) or PDE5 with sildenafil (100 nM) also increased I_{CNG} but to a lower degree than IBMX. However, a concomitant inhibition of both PDE2 and PDE5 exerted a similar effect to IBMX. Unlike NO donors, pGC activation by ANP or BNP (10 nM) induced a much larger I_{CNG}, which reached 15–25% of the maximal current elicited by Sp-8 (100 μM). The pGC I_{CNG} current increased further in the presence of IBMX, or in the presence of EHNA, but sildenafil had no effect. None of the PDE inhibitors tested alone had any effect on basal I_{CNG}.

Conclusions

These results indicate that, in rat ventricular myocytes: i) cGMP produced by pGC is readily accessible to plasma membrane, while that produced by sGC is not; ii) both PDE2 and PDE5 limit the spread of sGC-cGMP production to plasma membrane but only PDE2 regulates the level of cGMP following pGC activation. The differential spatio-temporal distribution of cGMP upon application of NPs or NO-donors may participate in their specificity of action on cardiac function.

Acknowledgement

We thank Dermot M.F. Cooper for providing Adenovirus encoding wild type CNGA2 channels.