

POSTER PRESENTATION

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NO-donors induce cross talk between cGMP and cAMP in signalling to human atrial L-type Ca^{2+} current

Nadiia Rozmaritsa*, Torsten Christ, Erich Wettwer, Ursula Ravens

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

Background

Cardiac NO-activated pathways are discussed to involve cross-talk between cGMP and cAMP signalling [1,2]. Here we have investigated the signalling pathways relating to NO-donor S-nitroso-N-acetylpenicillamine (SNAP) modulation of L-type Ca^{2+} current ($I_{Ca,L}$) in human right atrial cardiomyocytes.

Material and methods

Experiments were performed on human biopsy tissue from 62 patients in sinus rhythm. $I_{Ca,L}$ was measured with whole-cell voltage-clamp technique.

Results

Application of SNAP (100 μ M) increased basal $I_{Ca,L}$ from 5.93 ± 0.23 pA/pF to 9.10 ± 0.45 pA/pF ($p < 0.001$, $n/N = 117/62$). The effect was abolished by inhibition of soluble guanylate cyclase (sGC) with ODQ (30 μ M), suggesting involvement of cGMP. Stimulator of sGC (BAY 41-2272, 10nM–10 μ M) also increased $I_{Ca,L}$ and this effect was potentiated in the presence of SNAP. Direct activation of protein kinase G (PKG) with 8-Br-cGMP (100 μ M, intracellular application) increased basal $I_{Ca,L}$. However, not only cGMP but also cAMP was involved, because, the effect of SNAP on $I_{Ca,L}$ was prevented with the protein kinase A blocker (Rp-8-Br-cAMP 1 mM, intracellular). Thus, cGMP may activate $I_{Ca,L}$ via direct activation of PKG and indirect activation of PKA at the same time. It is known, that cAMP-mediated activation of PKA is regulated by cGMP via modulation of phosphodiesterases (PDEs). The selective PDE2 inhibitor EHNA (10 μ M) did

not affect basal or SNAP-stimulated $I_{Ca,L}$, therefore PDE2 does not regulate basal cAMP level. In contrast, PDE3 inhibition with cilostamide (1 μ M) increased basal $I_{Ca,L}$, suggesting that PDE3 is involved in basal cAMP level regulation. Interestingly, the cilostamide-induced increase in $I_{Ca,L}$ is blunted upon addition of SNAP, most probably via activation of PDE2 by SNAP-mediated cGMP increase (Figure 1). Similarly, SNAP blunted enhancement of $I_{Ca,L}$ by PKA activation with isoprenalin (1 μ M; 18.07 ± 1.12 pA/pF vs 23.06 ± 1.36 pA/pF, $p < 0.001$, $n/N = 21-39/18$), however, this effect was prevented by PDE2 inhibition with EHNA.

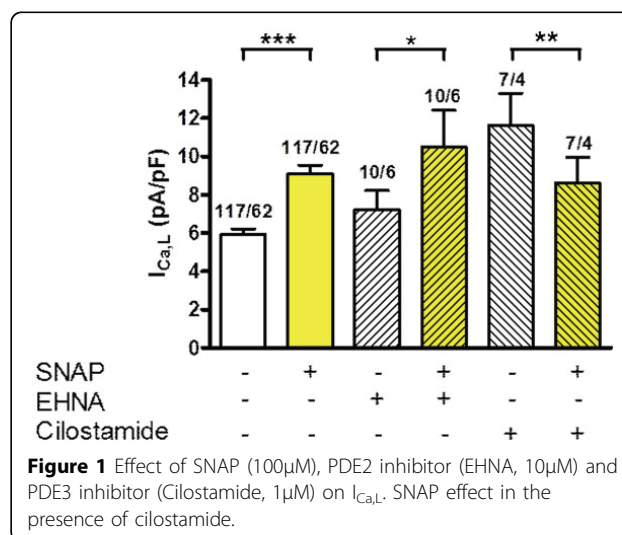


Figure 1 Effect of SNAP (100 μ M), PDE2 inhibitor (EHNA, 10 μ M) and PDE3 inhibitor (Cilostamide, 1 μ M) on $I_{Ca,L}$. SNAP effect in the presence of cilostamide.

* Correspondence: nadiia.rozmaritsa@tu-dresden.de
Department of Pharmacology and Toxicology, Dresden University of
Technology, Dresden, 01307, Germany

Conclusion

We conclude that in human atrial cardiomyocytes NO-donors stimulate production of cGMP with further cross-talk to cAMP via PDE2 and PDE3.

Published: 1 August 2011

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doi:10.1186/1471-2210-11-S1-P55

Cite this article as: Rozmaritsa *et al.*: NO-donors induce cross talk between cGMP and cAMP in signalling to human atrial L-type Ca²⁺ current. *BMC Pharmacology* 2011 **11**(Suppl 1):P55.

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