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

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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 (100μM) increased basal $I_{Ca,L}$ from 5.93±0.23 pA/pF to 9.10±0.45pA/pF (p<0.001, n/N=117/62). The effect was abolished by inhibition of soluble guanylate cyclase (sGC) with ODQ (30μM), suggesting involvement of cGMP. Stimulator of sGC (BAY 41-2272, 10nM–10μM) 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 μM, 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 (10μM) did not affect basal or SNAP-stimulated $I_{Ca,L}$, therefore PDE2 does not regulate basal cAMP level. In contrast, PDE3 inhibition with cilostamide (1μM) 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 (1μM; 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.

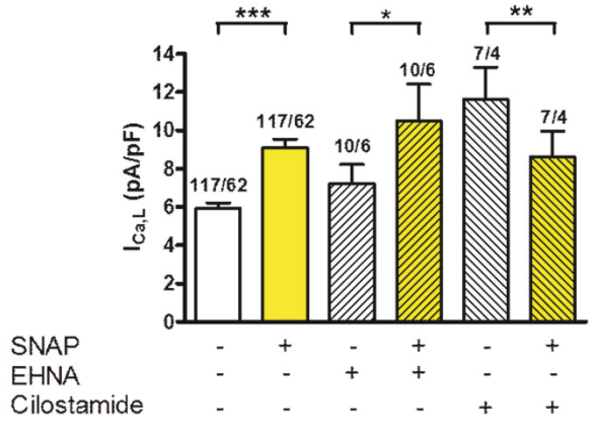

Figure 1 Effect of SNAP (100μM), PDE2 inhibitor (EHNA, 10μM) and PDE3 inhibitor (Cilostamide, 1μM) on $I_{Ca,L}$. SNAP effect in the presence of cilostamide.

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Conclusion

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

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