BMC Pharmacology

Poster presentation

The novel NO redox sibling, nitroxyl (HNO), prevents cardiomyocyte hypertrophy and superoxide generation via cGMP

Rebecca Ritchie*[1], Jennifer Irvine[1], Swati Gossain[1,2], Jane Love[1], John Horowitz[3] and Barbara Kemp-Harper[2]

Address: [1]Heart Failure Pharmacology, Baker IDI Heart & Diabetes Institute, Melbourne, Vic 8008, Australia, [2]Department of Pharmacology, Monash University, Clayton, Vic 3800, Australia and [3]Cardiology Unit, The Queen Elizabeth Hospital, Woodville, SA 5011, Australia

Email: Rebecca Ritchie* - rebecca.ritchie@bakeridi.edu.au

* Corresponding author

from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P58 doi:10.1186/1471-2210-9-S1-P58

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P58

We have previously shown that NO•/cGMP signalling is an important antihyper-trophic mechanism in the heart [1-3]. HNO is the one electron reduction of NO•, thought to elicit cardiovascular actions via cGMP and/or calcitonin gene-related peptide (CGRP) [4]; we have recently shown that the HNO donor Angeli's salt inhibits cardiomyocyte hypertrophy and superoxide generation [5]. We now test the hypothesis that isopropylamine/NO (IPA/NO) elicits concentration-dependent anti-hypertrophic and antioxidant actions via HNO/sGC/cGMP-dependent signalling. IPA/NO (0.1–3 μM, replenished 3×/day over 48 h) elicited concentration-dependent inhibition of endothelin-1 (ET_1, 60 nM)-stimulated neonatal rat cardiomyocyte (NRCM) hypertrophy (on two dimensional area of live cells). At 3 μM, IPA/NO decreased cell size from 255 ± 28% to 96 ± 27% of paired control (n = 4, $p < 0.001$). This antihypertrophic action of IPA/NO was significantly attenuated in the presence of the HNO scavenger L-cysteine (3 mM) or the cGMP-dependent protein kinase inhibitor Rp-8 PCTP cGMPS (10 μM, both n = 4, $p < 0.05$), but was unaffected by the NO scavenger carboxy-PTIO (200 μM) or the CGRP antagonist, $CGRP_{8-37}$ (1 μM, both n = 4). For comparison, the NO• donor DEA/NO elicited similar concentration-dependent inhibition of ET_1-induced cardiomyocyte hypertrophy; this was inhibited by carboxy-PTIO and Rp-8 PCTP cGMPS (10 μM, both n = 4, $p < 0.05$), but was unaffected by L-cysteine. Both IPA/NO and DEA/NO also blocked ET_1-induced cardiomyocyte superoxide generation (both n = 4, $p < 0.001$, on NADPH-driven lucigenin-enhanced chemiluminescence), a key trigger of hypertrophy [3]. IPA-NO stimulated purified cell-free sGC activity by 3.2 ± 0.6-fold, and elevated NRCM cGMP content by 3.5 ± 0.4-fold (both n = 5, $p < 0.05$ via cGMP ELISA, as previously described [2,3]. None of these agents alone, or their respective vehicles, elicited any effect on NRCM. Finally, using an NO•-sensing electrode, we demonstrated that IPA/NO (in contrast to DEA/NO), does not release NO• under these conditions, even at supra-pharmacological concentrations. In conclusion, these results provide convincing evidence that IPA/NO prevents cardiomyocyte hypertrophy via HNO activation of sGC. Although the antihypertrophic and antioxidant efficacy of IPA/NO was comparable to NO•, there is no role for extracellular oxidation of HNO to NO• or CGRP-mediated signalling in these IPA/NO actions. These studies may ultimately facilitate the development of HNO donors such as IPA/NO as novel antihypertrophic therapy for patients at risk of heart failure.

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