MEETING ABSTRACT



Investigation of the role of multidrug resistance proteins (MRPs) in vascular homeostasis

Robert M H Allen^{*}, Aniruthan Renukanthan, Kristen J Bubb, Inmaculada C Villar, Amie J Moyes, Reshma S Baliga, Adrian J Hobbs

From 7th International Conference on cGMP Generators, Effectors and Therapeutic Implications Trier, Germany. 19-21 June 2015

Background

Cellular levels of cyclic GMP (cGMP) are tightly controlled by synthetic and degradative mechanisms. Pharmacological manipulation of these processes (e.g. soluble guanylate cyclase stimulators, phosphodiesterase 5 inhibitors) augments cGMP-dependent signalling and is beneficial in treating cardiovascular disease (e.g. pulmonary hypertension). An additional mechanism potentially important in regulating cGMP signalling is cellular extrusion, driven by a family of multidrug resistance proteins (MRPs). Herein, we investigated if inhibition of MRPs modulates vascular reactivity, smooth muscle cell proliferation, and systemic hemodynamics.

Methods and main findings

The functional reactivity of murine aortic rings and proliferation of human pulmonary artery smooth muscle cells (PASMC) were determined in the absence and presence of the MRP inhibitor MK571. Hemodynamic changes in vivo in response to MK571 were analysed acutely by bolus dosing and chronically by radiotelemetry.

MK571 (1nM-50 μ M) caused a concentration-dependent relaxation of mouse aortic rings. In the presence of a threshold concentration of MK571 (3 μ M), vasorelaxant responses to NO and atrial natriuretic peptide (ANP) were significantly augmented. MK571 (3 μ M) also significantly inhibited PASMC proliferation and enhanced the antimitogenic properties of ANP (1 μ M) and NO. *In vivo*, MK571 (0.001-10mg/kg; i.v.) elicited an acute, dosedependent hypotensive activity and when delivered via the drinking water caused a more sustained drop in mean arterial pressure (~5 mmHg).

* Correspondence: r.m.h.allen@qmul.ac.uk

William Harvey Research Institute, Barts & The London Medical School, Queen Mary University of London, London, UK

Conclusion

These data suggest that extrusion by MRPs contributes to the dynamic equilibrium regulating intracellular levels of cGMP, and may represent a further target amenable to drug intervention for the treatment of cardiovascular disease.

Published: 2 September 2015

doi:10.1186/2050-6511-16-S1-A33 Cite this article as: Allen *et al.*: Investigation of the role of multidrug resistance proteins (MRPs) in vascular homeostasis. *BMC Pharmacology and Toxicology* 2015 16(Suppl 1):A33.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

BioMed Central

Submit your manuscript at www.biomedcentral.com/submit



© 2015 Allen et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http:// creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/ zero/1.0/) applies to the data made available in this article, unless otherwise stated.