BMC Pharmacology

Oral presentation

Open Access

Function of IRAG for cGMP kinase signalling in smooth muscle and platelets

Jens Schlossmann*

Address: Institut für Pharmakologie und Toxikologie der Technischen Universität München, Germany

Email: Jens Schlossmann* - Schlossmann@ipt.med.tu-muenchen.de

* 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):S13 doi:10.1186/1471-2210-5-S1-S13

Intracellular signalling by NO/cGMP/cGMP-dependent protein kinase type I (cGKI) regulates various physiological processes including smooth muscle contractility and platelet aggregation. An important mediator of this signalling cascade is the inositol 1,4,5-trisphosphate receptor I (IP_3RI) associated protein cGMP kinase substrate (IRAG). This protein forms a trimeric complex together with the cGMP kinase Iβ (cGKIβ) and the IP_3RI. Targeted deletion of exon 12 of IRAG coding for the N-terminal part of the coiled-coil domain disrupted *in vivo* the IRAG-IP_3RI interaction. The resulting $IRAG^{\Delta 12/\Delta 12}$ mice showed an increased mortality and a severely reduced gastrointestinal motility. The relaxation of hormone-contracted aortic and longitudinal colonic smooth muscle by cGMP was abolished in $IRAG^{\Delta 12/\Delta 12}$ mice, whereas cAMP-mediated relaxation was not altered. In contrast to WT mice, norepinephrine-induced increases in $[Ca^{2+}]_i$ were not reduced by cGMP in aortic smooth muscle cells from $IRAG^{\Delta 12/\Delta 12}$ mice. These data suggest, that IRAG is involved in the cGMP-dependent decrease of $[Ca^{2+}]_i$ *in vivo* and is essential for cGMP-dependent relaxation of hormone-induced vascular and colonic muscle contraction. However, cGMP-mediated relaxation of small intestinal smooth muscles was only partially affected in $IRAG^{\Delta 12/\Delta 12}$ mice suggesting tissue specific selectivity of cGKI mechanisms.

In addition, IRAG is highly expressed in platelets. To study the effect of IRAG signalling in platelets, we analysed the aggregation of $IRAG^{\Delta 12/\Delta 12}$ platelets. Nitric oxide and the cGMP analogue 8-pCPT-cGMP did not inhibit the aggregation of $IRAG^{\Delta 12/\Delta 12}$ platelets in contrast to wild type platelets, whereas the shape change of platelets was not affected in both mutant and wild type platelets. Furthermore, tail bleeding was abbreviated in $IRAG^{\Delta 12/\Delta 12}$ mice suggesting a defect in the regulation of coagulation *in vivo*. Therefore, cGKI/IRAG/IP_3RI signalling might be crucial for the NO/cGMP-dependent inhibition of platelet aggregation.