BMC Pharmacology

Oral presentation

Signaling of NO/cGMP via IRAG

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from 3rd International Conference on cGMP Generators, Effectors and Therapeutic Implications
Dresden, Germany. 15–17 June 2007

Published: 25 July 2007

BMC Pharmacology 2007, **7**(Suppl 1):S49 doi:10.1186/1471-2210-7-S1-S49

This abstract is available from: http://www.biomedcentral.com/1471-2210/7/S1/S49

Signaling by NO/cGMP/cGMP-dependent kinase I (cGKI) is important for a variety of physiological functions comprising relaxation of smooth muscle and inhibition of platelet aggregation. An important pathway of this signaling cascade includes the inositol 1,4,5-trisphosphate receptor I (IP_3RI) associated protein cGMP kinase substrate (IRAG). This protein interacts in a trimeric macrocomplex with cGKIβ and the IP_3RI. To get insight into the physiological function of IRAG two different mice strains were generated by targeted deletion: (1) $IRAG^{\Delta 12/\Delta 12}$ with an exon 12 deletion disrupting the IRAG/IP_3RI interaction. (2) $IRAG^{-/-}$ with an exon 3 deletion generating an IRAG knockout mutant.

Analysis of $IRAG^{\Delta 12/\Delta 12}$ platelet aggregation in vitro using collagen and thrombin as agonists and Fura2 calcium measurements revealed that IP_3RI/IRAG interaction is essential for NO/cGMP signaling mediating inhibition of platelet aggregation. Furthermore, it was shown that IP_3RI/IRAG interaction is essential for the NO-dependent prevention of thrombus formation.

Relaxation of hormone-contracted aortic and longitudinal colonic smooth muscle by cGMP was abolished in $IRAG^{\Delta 12/\Delta 12}$ mice and IRAG knockout mice indicating an essential role of IRAG for NO/cGMP-dependent smooth muscle relaxation. The vascular function of IRAG was underlined by a lack of NO-dependent blood pressure reduction in $IRAG^{\Delta 12/\Delta 12}$ mice. These studies suggest that cGKI/IRAG/IP_3RI is an essential signaling pathway modulating cardiovascular functions.