BMC Pharmacology

Poster presentation

IRAG is involved in cGMP/cGK-mediated relaxation of contractions induced by calcium entry

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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):P60 doi:10.1186/1471-2210-5-S1-P60

Inhibition of hormone-induced Ca^{2+} release from intracellular stores by cGMP involves a protein complex which consists of at least 3 proteins, i.e. the inositol-1,3,4-phosphat receptor (IP_3R), the cGMP-dependent protein kinase (cGK), and, as a linker protein between both, the inositol-1,3,4-phosphat receptor associated G-kinase substrate (IRAG [1]). Recently, mutant mice were created which lack the part of the IRAG protein that is supposed to mediate the association between IRAG and the IP_3R. In these mice ($IRAG^{\Delta 12}$ mice), cGMP failed to attenuate both, hormone-induced Ca2+ signals and hormone-induced contractions in vascular preparations [2]. These result confirm the concept that IRAG is an essential mediator of relaxation mediated by cGMP/cGK signalling in vascular smooth muscle.

In the present study, we tested this hypothesis in two other smooth muscle types, i.e. from jejunum and colon. In line with the concept above, cGMP failed to relax hormone-induced contractions in colon muscle from $IRAG^{\Delta 12}$ mice. In contrast, cGMP clearly relaxed hormone-induced contractions in jejunum muscle from these mutant mice. Thus, Rho/Rho kinase rather than IRAG seems to be the key player in mediating cGMP/cGK signalling in this particular type of smooth muscle.

Next, we questioned whether the mutation of IRAG affects the relaxant effects of cGMP on hormone-independent contractions. For this purpose, muscles were contracted by activation of Ca^{2+} influx, either by depolarisation with high K^+ or by initiating capacitative Ca^{2+} entry with thapsigargin. Since IRAG is mainly associated with sarcoplasmatic membrane proteins, we expected that the IRAG mutation would not affect cell membrane Ca^{2+} signalling. Surprisingly, the relaxant effects of cGMP on these types of contraction were attenuated in intestinal muscles from $IRAG^{\Delta 12}$ mice.

The results suggests that (1) the association of IRAG/IP_3R determines cGMP/cGK-mediated relaxations only in distinct types of smooth muscle, and (2) IRAG participates in cGMP/cGK-mediated relaxation not only during hormone-induced Ca^{2+} release but also during hormone-independent Ca^{2+} entry. Thus, cGMP/cGK may target via IRAG, either alone or with the IP_3R, to, at present, unidentified elements of the Ca^{2+} entry machinery in certain types of smooth muscle.

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