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Cardiovascular and gastrointestinal function of IRAG

Matthias Desch*[1], Katja Sigl[4], Jörg Wegener[2], Robert Feil[3], Susi Feil[3], Franz Hofmann[2] and Jens Schlossmann[1]

Address: [1]Lehrstuhl für Pharmakologie & Toxikologie, Universität Regensburg, Germany, [2]Institut für Pharmakologie & Toxikologie, Technische Universität München, Germany, [3]Interfakultäres Institut für Biochemie, Universität Tübingen, Germany and [4]Urologische Klinik & Poliklinik, Klinikum Großhadern, LMU München, Germany

Email: Matthias Desch* - matthias.desch@chemie.uni-regensburg.de

* Corresponding author

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Background

Signalling by NO/cGMP is very important for regulation of vascular tone and gastrointestinal motility. One important signalling pathway of cGMP-dependent protein kinase type I (cGKI) is mediated by IRAG (IP_3 **R**eceptor **A**ssociated c**G**KI substrate) which is highly expressed in smooth muscle of cardiovascular and gastrointestinal tissue. In order to elucidate the physiological role of IRAG we generated IRAG knockout mice by targeted deletion of exon 3. These mice show an enlarged gastrointestinal tract including pylorus stenosis.

Results

Exogenous and endogenous NO and cGMP stimulation relaxes hormone induced contraction of wild type aortic vessels as well as gastrointestinal tissues of colon and jejunum. This effect is significantly reduced in IRAG – deficient animals. Furthermore, activation of particular guanylyl cyclase by atrial natriuretic peptide (ANP) shows a reduced relaxing effect in IRAG knockout tissue strips. The expression levels of other cGKI substrates and the NO-induced cGMP synthesis are not affected in these tissues from IRAG KO mice.

Conclusion

These results indicate that IRAG signalling is essentiaI for smooth muscle relaxation by NO/cGMP and ANP/cGMP.