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Oral presentation

Functional roles of isoforms of NO-sensitive guanylyl cyclase

Doris Koesling*[1], Evanthia Mergia[1], Feras Taqatqeh[2], Thomas Mittmann[2], Axel Becker[3], Volker Hoellt[3] and Gisela Grecksch[3]

Address: [1]Institut für Pharmakologie und Toxikologie, Ruhr-Universität Bochum, 44780 Bochum, Germany, [2]Institut für Physiologie, Abteilung für Neurophysiologie, Ruhr-Universität Bochum, 44780 Bochum, Germany and [3]Institut für Pharmakologie und Toxikologie, Otto von Guericke Universität Magdeburg, 39120 Magdeburg, Germany

Email: Doris Koesling* - koesling@iname.com

* Corresponding author

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Most of the effects of the signalling molecule nitric oxide (NO) are mediated by the stimulation of the NO-sensitive guanylyl cyclase (GC) and the subsequent increase in cGMP formation. The enzyme contains a prosthetic heme group which mediates NO stimulation. NO/cGMP signalling plays an important role in the vascular system and has been proposed to participate in synaptic plasticity in brain.

Two isoforms of NO-sensitive GC have been identified to date that share regulatory properties but differ in the subcellular localization; the more ubiquitously expressed $\alpha_1\beta_1$ heterodimer (α_1-GC) and the $\alpha_2\beta_1$ isoform (α_2-GC) mainly expressed in brain. Knock-out mice in which either one the α subunits is deleted reveal a loss of the respective GC isoform. The α_1-GC and α_2-GC KO mice do not show up-regulation of the remaining non-deleted isoform and therefore provide information about the functional roles of the isoforms.

In the vascular system, α_1-GC was shown to represent the major GC isoform with α_2-GC amounting only to about 6% of WT enzyme in aorta. Surprisingly, α_2-GC was able to mediate full relaxation in response to NO showing that small cGMP increase are sufficient to induce the physiological response and that α_2-GC functionally is able to substitute for α_1-GC in α_1-deficient rings.

To obtain information about the neuronal function of the isoforms, long term potentiation (LTP) was measured in the visual cortex. NO-dependent LTP was absent in either one of isoform deficient KO mice but was reconstituted with a cGMP analogue in both strains. The results suggest that the GC isoforms play distinct roles in LTP and cannot substitute for each other. Further experiments have to show whether both GC isoforms are also required for LTP in other brain regions i.e. for hippocampal LTP and whether the KO mice show any behavioural alterations.