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Oral presentation

NO/cGMP signalling

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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. In addition to the physiological activator NO, NO-sensitisers like the substance YC-1 sensitise the enzyme towards NO and may therefore have important pharmacological implications. 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 and the $\alpha_2\beta_1$ isoform mainly expressed in brain. Knock-out mice in which either one the GC subunits is deleted will provide information about the functional roles of GC and the isoforms.

In intact cells, NO-induced cGMP signalling not only depends on cGMP formation but is also critically determined by the activity of the enzyme responsible for cGMP degradation i.e. phosphodiesterase 5 (PDE5). Recently, direct activation of PDE5 by cGMP was demonstrated which is limiting the cGMP increase and therefore is functioning as a negative feedback. As the cGMP-induced PDE5 activation turned out to be sustained, in the range of hours, it is probably responsible for the NO-induced desensitisation observed within NO/cGMP signalling.