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Structural and Functional Interactions of NO-Sensitive Guanylyl Cyclase

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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. NO-sensitive GC consists of two different subunits, α and β; two functionally indistinguishable isoforms have been shown to exist ($\alpha_1\beta_1$, $\alpha_2\beta_1$). The C-terminal peptide of the α_2 subunit is able to bind to PDZ domains. Indeed, interaction of the $\alpha_2\beta_1$ isoform with the PDZ-containing protein PSD-95 has been demonstrated targeting this GC to synaptic membranes. Moreover, as this α_2 isoform mainly occurs in brain the finding suggest a role of this isoform in synaptic transmission.

Desensitisation/sensitisation occurring within NO/cGMP signalling has been reported for a long time. In numerous reports, a relative shortage of NO caused either by endothelium removal, gene-disruption or inhibition of the endothelial NO synthase has been shown to result in an increased NO sensitivity. Inverse to the increase in sensitivity, we and others have been able to show that NO by itself leads to immediate desensitisation of the cGMP response. By monitoring the activity of the enzymes responsible for the NO-induced cGMP response in platelets, we found that the desensitisation does not occur on the level of NO-sensitive GC as the enzyme stayed activated during the entire cGMP response. Instead, we propose cGMP-induced long-term activation of the cGMP-degrading PDE5 as the mechanism responsible for the desensitisation of the NO-induced cGMP response in platelets and possibly in other tissues as well. This cGMP-mediated activation of PDE5 may be partly responsible for the phenomenon of NO tolerance.