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Evaluation of ODQ as specific inhibitor of NO-sensitive guanylyl cyclase using mice deficient for the enzyme

Dieter Groneberg*, Doris Koesling and Andreas Friebe

Address: Institut für Pharmakologie und Toxikologie, Ruhr-Universität-Bochum, Germany

Email: Dieter Groneberg* - dieter.groneberg@rub.de

* Corresponding author

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The NO/cGMP signal transduction is involved in the regulation of a variety of physiological processes e.g. smooth muscle relaxation and platelet aggregation. As signalling molecule, NO has diverse effects with NO-sensitive guanylyl cyclase (NO-GC) being accepted as the most important NO receptor. To differentiate between cGMP-dependent and -independent effects of NO inhibitors for the NO-GC are broadly used. The commonly used inhibitor for NO-GC is ODQ (1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one). The precise mechanism of NO-GC inhibition by ODQ remains unclear.

Recently, we have generated mice deficient in NO-GC (GC-KO). GC-KO mice show a pronounced increase in blood pressure, underlining the importance of NO in the regulation of smooth muscle tone in vivo. We showed a total lack of NO affecting smooth muscle tone and platelet aggregation which confirms NO-GC as the only NO target regulating these two functions in mice.

Using these KO mice we can evaluate the specificity of ODQ as inhibitor of NO-GC. In fact, ODQ used at low μM concentrations is a good inhibitor of cGMP signalling, allowing its use to investigate the cGMP dependence of NO effects. However, high NO concentrations elicited relaxation responses in ODQ-treated WT smooth muscle via NO-GC as they were absent in GC-KO tissue. This shows that NO-induced effects in the presence of ODQ do not necessarily indicate cGMP independence.