# IN VIVO STUDIES ELUCIDATING THE FUNCTIONAL ROLE OF SOLUBLE GUANYLYL CYCLASE (SGC) AND ITS DIFFERENT ISOFORMS IN VASODILATATION AND PENILE ERECTION

Decaluwe´ K1, Nimmegeers S1, Thoonen R2,3, Brouckaert P2,3, Van de Voorde J1
1Department of Pharmacology, Ghent University, Ghent, Belgium, 2Department for Molecular Biomedical Research, VIB, Ghent, Belgium, 3Department of Biomedical Biology, Ghent University, Ghent, Belgium

The nitric oxide/cyclic guanosine phosphate (NO/cGMP) pathway plays a pivotal role in vasodilatation and as such also in penile erection. Recently sGC-activating agents have been put forward as novel therapeutical approaches for hypertension and erectile dysfunction. The existence of 2 physiologically active sGC isoforms (sGCα1β1 and sGCα2β1) offers a potentially more selective approach. However more knowledge is required on the functional importance of the different isoforms in vasodilatation. To investigate this we performed in vivo studies using 2 types of transgenic mice, sGCα1 knockout ($sGC\alpha1^{-/-}$) mice and sGCβ1 knockin ($sGC\beta1^{ki/ki}$) mice. Different agents were injected intravenously or intracavernosally and changes in mean arterial pressure (MAP) and intracavernosal pressure (ICP) were recorded. Injection of exogenous NO (SNP –Spermine/NO) induced a decrease in MAP or an increase in ICP in wild-type mice. These responses were significantly reduced in $sGC\alpha1^{-/-}$ mice and completely abolished in $sGC\beta1^{ki/ki}$ mice. While intravenous administration of L-NAME induced an increase in MAP in wild-type mice, this increase was significantly reduced in $sGC\alpha1^{-/-}$ mice and abolished in $sGC\beta1^{ki/ki}$ mice. Stimulation of cavernosal nerves resulted in frequency-dependent increases in ICP in control mice which were strongly reduced in $sGC\alpha1^{-/-}$ mice and abolished in $sGC\beta1^{ki/ki}$ mice. Equal responses to sGC-independent agents in transgenic mice and their wild-type controls confirmed the specificity of the impaired sGC-related responses. These studies illustrate that NO-induced vasodilatation and penile erection is completely sGC-dependent. While the sGCα1β1 isoform plays a pivotal role, a contribution of the sGCα2β1 isoform cannot be ignored.