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

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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 (sGCα1−/−) mice and sGCβ1 knockin (sGCβ1ki/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/N0) induced a decrease in MAP or an increase in ICP in wild-type mice. These responses were significantly reduced in sGCα1−/− mice and completely abolished in sGCβ1ki/ki mice. While intravenous administration of L-NAME induced an increase in MAP in wild-type mice, this increase was significantly reduced in sGCα1−/− mice and abolished in sGCβ1ki/ki mice. Stimulation of cavernosal nerves resulted in frequency-dependent increases in ICP in control mice which were strongly reduced in sGCα1−/− mice and abolished in sGCβ1ki/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.