STUDIES ON THE IMPORTANCE OF SOLUBLE GUANYLYL CYCLASE (SGC) ISOFORMS IN ERECTILE FUNCTION USING TRANSGENIC MICE.

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The nitric oxide/cyclic guanosine monophosphate pathway plays a pivotal role in vasodilatation and as such in penile erection. Recently sGC-activating agents have been put forward as a novel therapeutical approach for treating erectile dysfunction. The finding that two physiologically active sGC isoforms ($sGC\alpha_1\beta_1$ and $sGC\alpha_2\beta_1$) exist in vivo might offer opportunities for a more selective approach. Therefore more information is required on the functional importance of these isoforms in the mechanism of erection. Both in vivo and in vitro studies have been performed using two different types of transgenic mice, namely the $sGC\alpha_1$ knockout mice and the $sGC\beta_1$ knockin mice. For the in vitro experiments corpora cavernosa were mounted in organ baths for isometric tension recording. For the in vivo studies, changes in intracavernosal pressure were recorded in anesthetized mice. sGC-dependent agents as well as cavernosal nerve stimulation induced corporal smooth muscle relaxation in vitro (agents examined: Ach, SNP, Spermine-NO and NO-gas) and increases in intracavernosal pressure in vivo (agents examined: SNP and Spermine-NO) in wild-type controle mice. These relaxations were however significantly reduced in $sGC\alpha_1$ knockout mice and even completely or almost completely abolished in $sGC\beta_1$ knockin mice. Responses to sGC-independent agents (8-pCPT-cGMP and forskolin) did not differ between wild-type control mice and transgenic mice. These studies clearly illustrate the importance of the predominantly expressed $sGC\alpha_1\beta_1$ isoform in the mechanism of penile erection, however a contribution of the lesser abundantly expressed $sGC\alpha_2\beta_1$ isoform cannot be ignored. The unaltered responses to sGC-independent agents confirm the specificity of the impaired sGC-related responses observed in both transgenic mice.