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JOURNAL ARTICLE

Intracavernosal sildenafil facilitates penile erection independent of the nitric oxide pathway

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Sildenafil, in nanomolar serum levels, is an effective phosphodiesterase type 5 inhibitor, and facilitates penile erection only during sexual stimulation. However, there is limited information on the pharmacological activity of this agent when tissue levels approach millimolar concentrations following intracavernosal injection. The aim of this study was to investigate whether sildenafil causes penile erection in the absence of active neurogenic input. Organ bath preparations of rabbit penile cavernosal tissue strips were contracted with 1 microM phenylephrine and exposed to increasing concentrations of sildenafil in the absence or presence of the nitric oxide (NO) synthase inhibitor, Nomega-nitro-L-arginine methyl ester (L-NAME; 0.6 mM). Sildenafil caused dose-dependent relaxation of rabbit cavernosal smooth muscle at high concentrations (>0.1 microM) with little or no effect at concentrations below 0.1 microM. The addition of L-NAME did not affect this response. In a separate protocol, sildenafil dose response determinations were performed in the presence of the guanylyl cyclase inhibitor, 1H-[1,2,4]-oxadiazolo-[4,3-a]-quinoxalin-1-one (ODQ; 3 microM) or vehicle (50% dimethyl sulfoxide [DMSO]). Relaxation to sildenafil in the presence of DMSO was significantly enhanced relative to sildenafil alone. ODQ treatment partially attenuated relaxation to sildenafil, but failed to completely inhibit the response. In cavernosal tissue strips, sildenafil elevated basal cyclic guanosine monophosphate (cGMP) levels twofold (0.54 vs. 1.10 pmol/mg prot). To further investigate these observations, anesthetized rabbits were injected intracavernosally with sildenafil (0.3-1.3 mg). In the absence of pelvic nerve stimulation, the magnitude and duration of the intracavernosal pressure increased in a dose-dependent fashion in response to sildenafil, approaching the systemic arterial pressure at higher doses. Intracavernosal administration of L-NAME, at doses that inhibited pelvic nerve stimulated penile erection, did not alter the response to intracavernosal sildenafil at 1.3 mg. Sildenafil, at the doses tested, did not significantly change the systemic arterial pressure. These data suggest that intracavernosal sildenafil, at tissue levels approaching millimolar concentrations, can cause relaxation of vascular smooth muscle and penile erection by a novel mechanism independent of the classical NO/cGMP pathway.

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