Is relaxation of human detrusor by sildenafil relying on PDE 5 inhibition?

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OBJECTIVES

- Clinical studies have reported that phosphodiesterase 5 (PDE5) inhibitors including sildenafil could improve both voiding and storage lower urinary tract symptoms (LUTS) suggestive of benign prostate hyperplasia (BPH) (1-4).
- The mechanism(s) of action responsible for these effects, particularly on storage symptoms, could include a direct relaxing effect of PDE5 inhibitors on the detrusor.

MATERIALS & METHODS

- **Human detrusor strip preparation**
  - Human bladder samples were obtained from 20 different patients with no known OAB undergoing cystectomy for bladder cancer. Detrusor strips without urothelium were mounted isometrically at a resting tension of 500 mg in a 5 ml organ bath filled with Krebs-HEPES buffer maintained at 37°C and bubbled with 95%O₂-5%CO₂. The strips were connected to force transducers for isometric tension recordings (Pleden Controls Ltd, UK). Following amplification, the tension changes were computerized via MacLab™/8 using Chart™ 5 software (AD Instruments Ltd).
  - The experiments, collection and use of any tissue or other samples are carried out in accordance with the Research Plan, all relevant laws, regulations and codes of practice, including having obtained informed consent of patients in writing.
- **In vitro contractile experiments**
  - After an equilibration period, concentration-response curves for sildenafil (from 10⁻⁷M to 3.10⁻⁵M) were generated in the presence or absence of a NO donor, SNAP (S-nitroso-N-acetylpenicillamine 10 µM) or vehicle. In another set of experiments, frequency-response curves (FRCs) to electrical field stimulation (EFS) were generated in the presence or absence of a NO donor, SNAP (S-nitroso-N-acetylpenicillamine 10 µM) or vehicle. In some experiments, strips were pre-contracted KCl (50 mM) and CRCs to sildenafil (10⁻⁷M) or vehicle were performed.

RESULTS

**Effect of sildenafil on human detrusor smooth muscle**

- **Effect of sildenafil on carbachol or KCl-induced human detrusor contraction**
  - Sildenafil induced a significant concentration-dependent relaxation of carbachol- or KCl-induced contraction of human bladder strips when compared to vehicle. In contrast, sildenafil only slightly attenuated KCl-induced detrusor contraction.

- **Effect of sildenafil on EFS-induced human detrusor contraction**
  - Sildenafil at 10⁻⁷M failed to modify EFS-induced contractions whereas at 10⁻⁵M, it significantly inhibited EFS-induced contractions.

**Involvement of the NO/cGMP and the cAMP pathways in sildenafil-induced relaxation**

- Relaxation of carbachol-precontracted human bladder by sildenafil involves a cGMP-independent mechanism pathway, indeed, a NO donor does not enhance sildenafil effect.
- Sildenafil inhibits carbachol-induced human bladder contractions via a cAMP-dependent mechanism pathway.
- Sildenafil also exerts its inhibitory effect by an other pathway, independent of cGMP or cAMP signaling pathways, since some relaxing activity remains in presence of both MDL 75,330A and ODQ.

**Involvement of K+ channels in sildenafil-induced relaxation**

- Kᵥᵥᵥᵥᵥᵥᵥᵥᵥᵥᵥᵥᵥᵥ, BKᵥᵥᵥᵥ, and SKᵥᵥᵥᵥ channels are involved in the relaxation elicited by sildenafil on human detrusor tissue.

CONCLUSIONS

- **The present study demonstrates that sildenafil exerts a direct relaxing effect on human detrusor smooth muscle.**
  - This relaxing effect involves the cAMP-dependent and K+ channels-dependent signaling pathways.
  - In contrast, the contribution of the NO-cGMP signaling pathway in sildenafil-induced relaxation appears to be minor.