Is relaxation of human detrusor by sildenafil relying on PDE5 inhibition?

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PDE5 inhibitors: first-line therapy in erectile dysfunction (ED).

ED is often associated with lower urinary tract symptoms (LUTS), independently of age and cardiovascular comorbidities.
PDE5 inhibitors for LUTS/BPH: Clinical trials

Patients with LUTS associated with BPH

+++ irritative symptoms

- Sildenafil
- Tadalafil
- Vardenafil

+++ obstructive symptoms

Randomized placebo-controlled trials


Roehrborn et al., J Urol 2008; Oct;180(4):1228-34 *


*double-blinded
Mechanism of action?

+++ irritative symptoms

? 

PDE5 inhibitors

+++ obstructive symptoms

NO-cGMP pathway
Objectives

+++ irritative symptoms

? 

- Assess the ability of sildenafil to relax human detrusor smooth muscle

- Investigate the signaling pathways that could be involved in sildenafil-mediated relaxation

PDE5 inhibitors
Experimental design

- **Human bladder samples**
  - Bladder samples were obtained from 20 patients (65±2.1 years) undergoing cystoprostatectomy for infiltrating bladder cancer with no history of bladder dysfunction according to their medical chart.

- **Evaluation of the smooth muscle contractile reactivity with isolated organ baths**
  - Strips are excised from the tissue samples and connected to force transducers for isometric tension recording.
  - Organ baths are filled with Krebs buffer maintained at 37°C and bubbled with 95%O2 and 5%CO2, pH 7.4.
Effect of sildenafil on carbachol-precontracted human detrusor strips

By which mechanism of action does sildenafil relax human bladder tissue?
NO/cGMP-dependent mechanism of action?

Effect of guanylate cyclase inhibition

Effect of a NO donor

- 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.

Effect of adenylate cyclase inhibition

Pre-treatment

- vehicle
- MDL-12,330A 10 µM

$p<0.001$, two-way Anova

Sildenafil inhibits carbachol-induced human bladder contractions via a cAMP-dependent mechanism pathway.
Other mechanisms of action?

Effect of guanylate and adenylate cyclases inhibition

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 123,330A and ODQ.
**Effect of BK_{Ca} channels blocking**

- Iberiotoxin 30 nM
- Pre-treatment
- log [sildenafil], % of inhibition of carbachol-induced contractions
- p<0.01, two-way ANOVA

**Effect of SK_{Ca} channels blocking**

- Apamin 100 nM
- Pre-treatment
- log [sildenafil], % of inhibition of carbachol-induced contractions
- p<0.001, two-way ANOVA

**Effect of K_{ATP} channels blocking**

- Glibenclamide 10 µM
- Pre-treatment
- log [sildenafil], % of inhibition of carbachol-induced contractions
- p<0.001, two-way ANOVA

- K_{ATP}, BK_{Ca}, and SK_{Ca} channels are involved in the relaxation elicited by sildenafil on human detrusor tissue
Conclusions

- The relaxant effect of sildenafil on carbachol-induced human detrusor contraction involves cAMP-dependent signaling pathway and K+ channels dependent mechanism of action.

- The contribution of the NO-cGMP signaling pathway in sildenafil-induced relaxation appears to be minor.

- Sildenafil in part improves urinary symptoms in men with LUTS associated with BPH via direct relaxation of the detrusor.