Sildenafil relaxes human detrusor by cGMP-independent signaling pathways

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OBJECTIVES

Lower urinary tract symptoms (LUTS) comprise voiding urinary symptoms which are related to urethral obstruction (obstructive component) and storage urinary symptoms which are more particularly related to bladder dysfunction (irritative component) 1.

Controlled clinical trials have recently demonstrated that daily phosphodiesterase 5 (PDE5) inhibitors including sildenafil indicated for the on demand treatment of erectile dysfunction (ED) are effective treatment for both obstructive and irritative LUTS suggestive of benign prostate hyperplasia (BPH) in male patients with or without ED 3-4. However, the mechanism of action for these effects, more particularly on irritative symptoms, remains yet to be elucidated.

It is very tempting to speculate that PDE5 inhibitors could relieve bladder irritative symptoms through direct action on detrusor smooth muscle. A recent controlled pilot study in spinal cord injured male patients with neurogenic detrusor overactivity which has reported a significant improvement of urodynamic parameters with vardenafil administration 5, supports an effect on bladder function.

The aim of this study was to assess the ability of sildenafil to relax human bladder tissue and to investigate the signaling pathways that could be involved in this sildenafil-mediated relaxation.

RESULTS

The exact mechanism by which sildenafil relaxes human detrusor deserves further investigation.

Sildenafil induced a significant concentration-dependent relaxation of carbachol-induced contractions.

By which mechanism of action does sildenafil relax human bladder tissue ?

Sildenafil inhibits carbachol-induced human bladder contractions via a cGMP-independent mechanism pathway.

Sildenafil also exerts its inhibitory effect by another pathway, independent of cGMP or cAMP signaling pathways, since some relaxing activity remains in presence of both MDL 12,330A and ODQ.

K⁺ channel-dependent mechanism of action?

The relaxing effect exerted by sildenafil on carbachol-precontracted human bladder tissue does not rely on a cGMP-signaling pathway and is thus probably not mediated through the inhibition of PDE5 isoenzymes.

Conversely, this relaxant effect is dependent on a cAMP-signaling pathway. In addition, K⁺ ATP, BKCa and SKCa channels are also involved in this relaxing effect.

Data Analysis

Data were expressed as mean ± SEM for N experiments corresponding to N = bladder samples obtained, from N different patients. Statistical comparisons of the CRC were performed with a two-way ANOVA statistic analysis test and Bonferroni’s post-test. In case of interaction between the two factors (concentration and drug) with the two-way ANOVA statistic analysis, a modified Student’s t-test with the Bonferroni adjustment for multiple comparisons was performed. P values < 0.05 were considered statistically significant. Statistical analysis was performed with GraphPad Prism® 4.03 software.

CONCLUSIONS

The relaxing effect exerted by sildenafil on carbachol-precontracted human bladder tissue does not rely on a cGMP-signaling pathway and is thus probably not mediated through the inhibition of PDE5 isoenzymes.

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References