

PDE5 gene expression and relaxant effects of vardenafil in male and female human and rat detrusor muscle

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OBJECTIVES

Recent clinical data suggested that PDE5 inhibitors could be used for the treatment of Lower Urinary Tract Symptoms (LUTS) in male patients¹⁻³. Female patients with overactive bladder (OAB) also experience LUTS of the same nature: urgency with or without urge incontinence, frequency and nocturia. LUTS are usually associated with the urodynamic observation of detrusor overactivity (DO). Accordingly we investigated the gender-specific functional effects of vardenafil and the relative distribution of PDE5 mRNA on rat and human detrusor smooth muscle in males and females.

References

1. J Urol. 2007 Apr;177(4):1401-7. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. McVary KT, Roehrborn CG, Kaminetsky JC, Auerbach SM, Wachs B, Young JM, Esler A, Sides GD, Denes BS.
2. J Urol. 2007 Mar;177(3):1071-7. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. McVary KT, Monnig W, Camps JL Jr, Young JM, Tseng LJ, van den Ende G.
3. J Urol 2008 (soon to be published). A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Stief CG; Porst H; Neuser D; Beneke M; Ulbrich E.

The aim of this study was to assess the relative distribution of PDE5 mRNA and the ability of vardenafil to relax rat and human bladder tissue from males and females.

MATERIALS & METHODS

Human and rat detrusor strip preparation

Human bladders samples were obtained from male (n=6-10) and female (n=4-6) informed and consenting donors undergoing cystectomy for bladder cancer with no known bladder dysfunction according to their medical chart. Serosal and mucosal layers were removed from the bladder sample, and detrusor strips were mounted in 5 ml organ baths filled with Krebs-HEPES buffer maintained at 37°C and continuously bubbled with 95%O₂-5%CO₂. Rat bladder strips were dissected from male and female Sprague Dawley rats (n=10 for each gender). The strips were connected to force transducers for isometric tension recordings (Pioden Controls Ltd, UK). Following amplification, the tension changes were computerized via MacLab™/8 using **in vitro contractile experiments**.

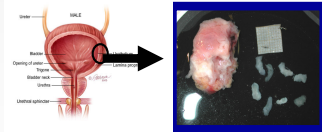
After an equilibration period, concentration-response curves to vardenafil (from 0.001µM to 30µM) were generated on carbachol (10⁻⁸M)-induced precontraction.

PDE5 gene expression

PDE5 gene expression profiling was done by TaqMan RT-PCR using specific primer for rat and human PDE5 and normalizing these results to beta-actin mRNA as house keeping gene.

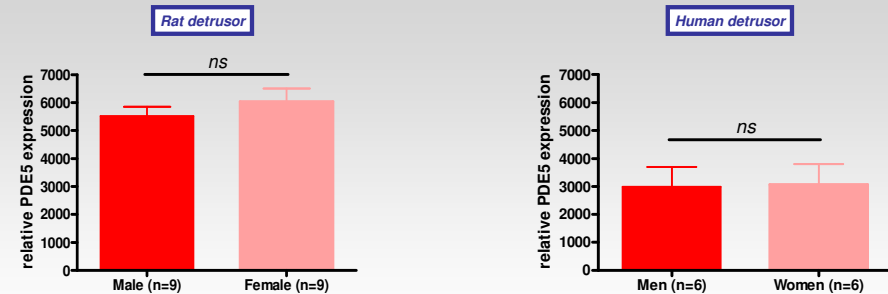
Data Analysis

Data were expressed as mean ± SEM for N experiments corresponding to N = bladder samples obtained, from N different rats or 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.



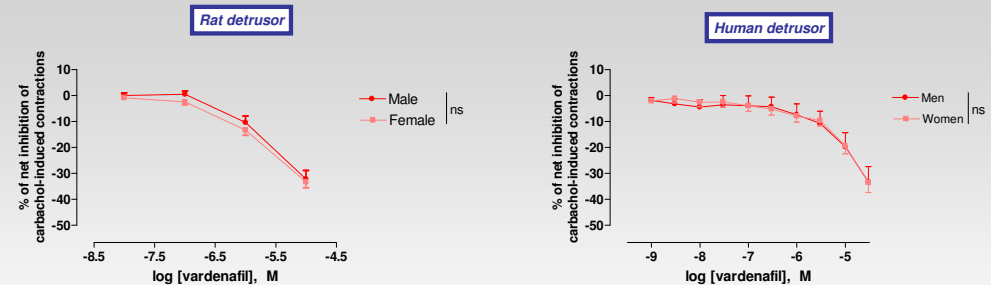
RESULTS

PDE5 gene expression



- A substantial PDE5 gene expression in rat and human detrusor tissue was detected.
- No gender-specific differences in PDE5 mRNA levels were found in the detrusor smooth muscle neither in rats nor in human tissues.
- Expression levels were 2-fold higher in rats compared with human tissues (p<0.01).

Functional assays



E _{max}	Rat Detrusor	Human Detrusor
Male	34 ± 3 %	20 ± 5 %
Female	33 ± 2 %	19 ± 3 %

- Vardenafil is able to relax human and rat detrusor significantly
- The relaxing effect of vardenafil is greater in rat compared to human tissues
- There is no significant differences in the relaxing effect of vardenafil between male and female, either in rat or in human tissues

CONCLUSIONS

- PDE5 mRNA is equally expressed in male and female rat and human detrusor tissues.
- Vardenafil exerts similar relaxing effects on both male and female detrusor strips from rats and humans.
- Since the effects of vardenafil on LUTS could be at least partly mediated via the direct relaxation of the bladder detrusor smooth muscle, thereby reducing bladder tone, these results might further imply a potential for treatment of female OAB in addition to the treatment of male LUTS.