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 patients. 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.

RESULTS

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. Sensal 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 (Ploidon Controls Ltd, UK). Following preincubation, the tension changes were computerized via MacLab®/8 using MTAS software. After an equilibration period, concentration response curves to vardenafil (from 10⁻⁸ to 30µM) were generated on carbachol (10⁻⁶M) induced precontraction.

PODE5 gene expression

PODE5 gene expression profiling was done by TaqMan RT-PCR using specific primer for rat and human PODE5 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 test and Bonferroni’s post-test. In cases 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

- 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 PDE5 inhibitors for the treatment of female OAB in addition to the treatment of male LUTS.

References