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INHIBITORY EFFECT OF TADALAFIL, A PHOSPHODIESTERASE 5 INHIBITOR, ON BLADDER MECHANOSENSITIVE AFFERENT ACTIVITY IN THE RAT

Hypothesis / aims of study

Several clinical studies have demonstrated that phosphodiesterase type 5 inhibitors (PDE5-inhibitors) improve lower urinary tract symptoms (LUTS) in men (1). However, the mechanisms involved in the effect of PDE5-Iinhibitors have not been clarified. We investigated the direct effects of tadalafil, on the single unit mechanosensitive afferent activities (SAA) primarily originating from the bladder in the rat. In addition, we also studied whether this drug can affect SAA activated by intravesical acrolein to evaluate its effect on chemical cystitis.

Study design, materials and methods

Female Sprague-Dawley rats were used. Under urethane anesthesia, SAA primarily originating from the bladder were identified by electrical stimulation of the left pelvic nerve and by bladder distension. Nerves with conduction velocity (CV) > 2.5 m/sec were determined as myelinated Aδ-fibers and those with < 2.5 m/sec as unmyelinated C-fibers (2). Before drug administarion, the baselines of SAA were recorded during cystometry with saline instillation at a rate of 0.08 ml/min until intravesical pressure reached 30cmH_2O. Then, first, tadalafil was administrated intravenously at three doses, 0.01, 0.03 and 0.1 mg/kg cumulatively, and SAA during cystometry with saline-instillation were studied after each tadalafil-administration. Second, vehicle or tadalafil (0.1 mg/kg) was administrated intravenously before 0.003% of intravesical acrolein-instillation, and three cycles of investigation were performed after each administration. The SAA are expressed as a percentage of baseline activity, integrated during the whole filling phase, which is based on pressure and volume. For statistical analyses, two-way ANOVA followed by Tukey's test is applied for comparison before and after drug-administration, and unpaired Student's t-test for comparison between groups.

Results

Thirty-nine SAA were isolated in 25 rats. Twenty-one units corresponded to criteria for Aδ-fibers (CV: 9.35 ± 2.19 m/sec), and 18 for C-fibers (CV: 1.45 ± 0.11 m/sec). Bladder compliance did not change significantly after the administration of either tadalafil or vehicle (data not shown). Tadalafil decreased SAA of both Aδ- and C-fibers during saline-instillation in a dose-dependent manner (Figures 1). SAA of both Aδ- and C-fibers were significantly increased with intravesical acrolein-instillation in the vehicle-pretreated group (Figure 2A & B). However, in the tadalafil-pretreated group, the increased responses of both Aδ- and C-fibers to intravesical acrolein were not observed (Figure 2C & D), which was significantly different from the vehicle-pretreated group (Figure 3).

Interpretation of results

The results of the present study demonstrate that tadalafil can inhibit the afferent activities of mechanosensitive both Aδ- and C-fibers in the rat bladder. In addition, the used doses in this study did not affect the bladder compliance. Moreover, intravesical acrolein-instillation facilitates SAA of both Aδ- and C-fibers, which can be blocked by tadalafil.

Concluding message

The present study indicates that PDE5 inhibitors such as tadalafil, have an inhibitory action on bladder mechanosensory transduction through both Aδ- and C-fibers at least in the rat, and that PDE5 inhibitors can inhibit also facilitation of bladder sensory transduction associated with bladder inflammatory response to chemical stimulation. If these findings are valid also in the human, they may give a new insight into the possible mechanism of PDE5-inhibitors' action for improving LUTS.

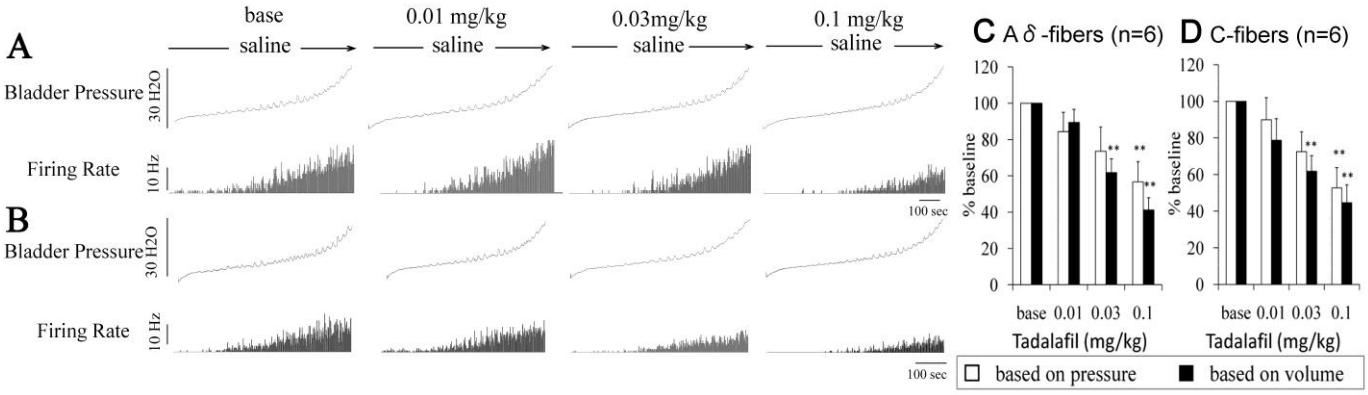

Figure 1. Representative recordings indicating a dose-dependent inhibitory effect of tadalafil on the afferent activities of Aδ-fiber (A) and C-fiber (B). Summarized results of the inhibitory effect of tadalafil on the afferent activities of A-fiber (C) and C-fiber (D).

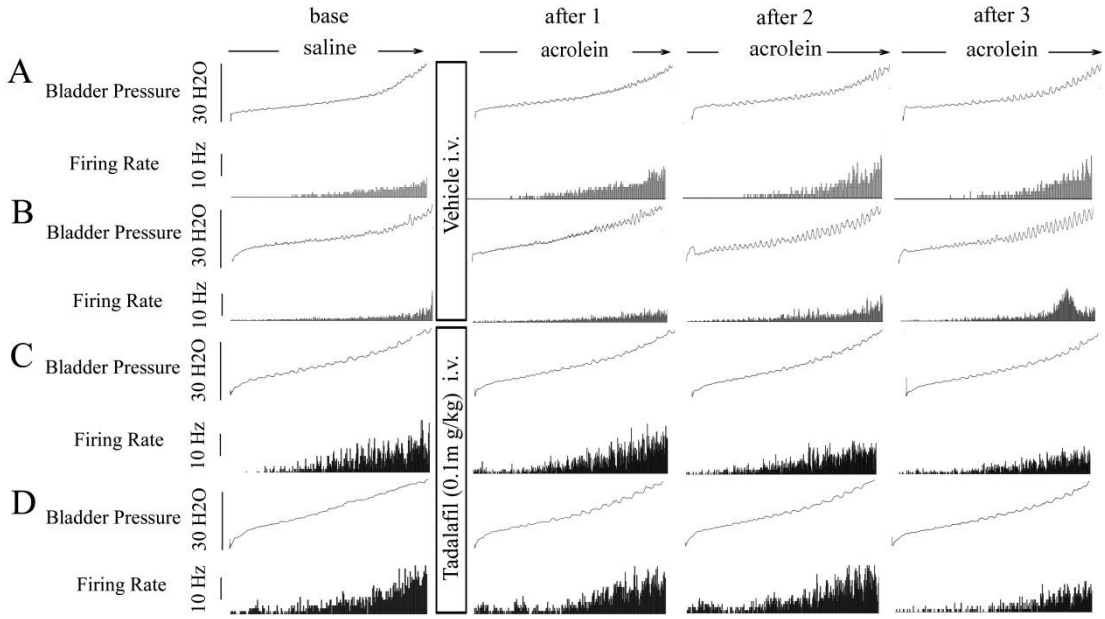

Figure 2. Representative recordings indicating the effect of intravesical instillation of acrolein on the afferent activities of Aδ- (A, C) and C-fibers (B, D) in the pretreated with vehicle(A, B) and tadalafil (C, D).

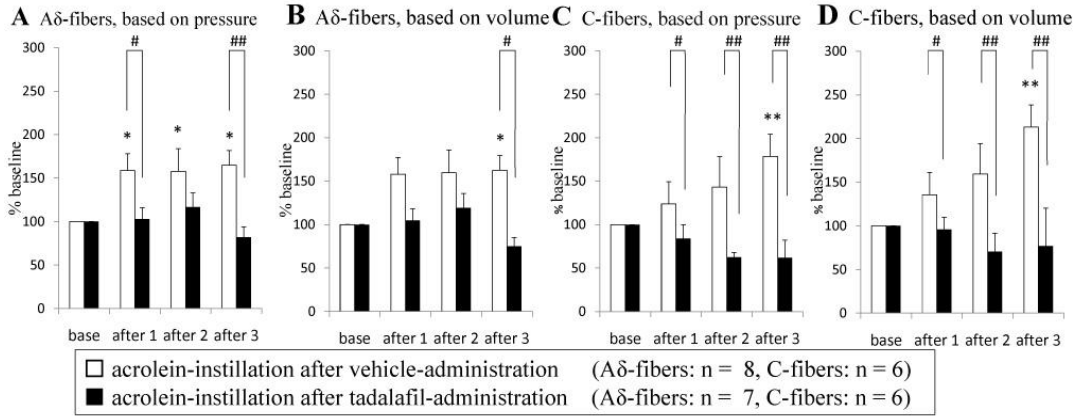

Figure 3. Responses of the Aδ-fibers (A, B) and C-fibers (C, D) integrated during the whole filling phase based on pressure (A, C) and volume (B, D) to intravesical instillation of acrolein before (base) and after vehicle-administration or tadalafil-administrations. Three cycles of investigation were performed after each administration (after 1, 2, and 3).
**P*<0.05, ***P*<0.01: significant differences from base (two-way ANOVA followed by Tukey's test). $^{\#}P$<0.05, $^{\#\#}P$<0.01: significant differences between groups (unpaired Student's *t*-test).

References
1. Neurourol Urodyn 2011;30: 292
2. J Neurophysiol 1994; 72: 2420

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**The Animal Ethics Committees of the University Antwerp Faculty of Medicine**