

EFFECT OF SILODOSIN, A SELECTIVE ALPHA1A-ADRENOCEPTOR ANTAGONIST ON PRIMARY BLADDER AFFERENT ACTIVITY AND BLADDER MICROCONTRACTIONS IN RATS

Hypothesis / aims of study

Silodosin, a highly selective antagonist for α 1A-adrenoceptor (α 1A-AR) subtype, has been proven to improve both voiding and storage symptoms in men with LUTS with suggestive of benign prostatic enlargement (1). However, the mechanisms of the silodosin's action to improve the storage symptoms have not been clarified. It has been suggested that α 1-ARs contribute to the afferent pathways innervating the bladder. Moreover, bladder microcontractions may associate with these afferent activities, especially in A δ -fibers rather than C-fibers (2). We investigated effects of silodosin on single unit afferent nerve fiber activities (SAAs) of the primary bladder afferent nerves and its relationship with microcontractions in rats.

Study design, materials and methods

Thirty female Sprague-Dawley rats were used. Under anesthesia with urethane (1.2 g/kg, intraperitoneally) bilateral L6 dorsal roots were transected via a laminectomy. The fine filaments were dissected from the left L6 dorsal roots and placed across a bipolar electrode for monitoring SAAs. Nerve fibers primarily originating from the bladder were identified by electrical stimulation of the left pelvic nerve and by bladder distension. Nerves with conduction velocities (CV) more than 2.5 m/second were designated as A δ -fibers and those with CV less than 2.5 m/second as C-fibers. Two measurements were performed in separate animals; First: At the beginning of the experiments, the afferent activity measurements with constant bladder filling (at 0.08 ml/min until the intravesical pressure reached 30cmH₂O) were repeated three times and the third measurement served as the control observation. Then, silodosin was administered intravenously (i.v.) at three doses, 0.3, 3 and 30 μ g/kg cumulatively, and SAAs during cystometry with saline-instillation were studied after each silodosin-administration. Second: the bladder was emptied and saline instilled until the intravesical pressure reached 30cmH₂O. The bladder was kept under an isovolumetric condition, allowed to stabilize for 5 minutes, after which, vehicle was administered i.v. and the recording was performed further 5 minutes. A similar procedure was repeated with i.v. administration of silodosin (0.3 μ g/kg) instead of vehicle. The bladder pressure, number of microcontractions (> 1.5 cmH₂O) and SAAs were analysed for 3 minutes before and after each-administration.

Results

Totally 37 single-unit afferent fibers (A δ -fibers: n=18, CV: 4.76 \pm 0.77 m/second, C-fibers: n=19, CV: 1.62 \pm 0.10 m/second) were isolated. SAAs of A δ -fibers, not C-fibers, in response to bladder filling significantly decreased after silodosin-administration in a dose-dependent manner (Fig. 1). At the highest dose (30 μ g/kg), bladder compliance significantly increased from the baseline value. During an isovolumetric condition of the bladder, silodosin-administration significantly decreased the SAAs of A δ -fibers, but not C-fibers compared with vehicle-administration. There was no significant effect on either the mean basal bladder pressure or microcontractions (Figs. 2 and 3).

Interpretation of results

The present results demonstrate that the selective α 1A-AR antagonist, silodosin, can inhibit A δ -fibers, but not C-fibers, of the primary bladder afferents in the rat. However, silodosin did not inhibit the bladder microcontractions, suggesting other mechanisms than suppression of bladder microcontractions involved in its inhibitory action on the A δ -fiber's activity. It has been reported that bladder overdistention/emptying induced bladder blood flow decrease/partial recovery and caused bladder overactivity via a mechanism other than capsaicin sensitive C-fiber activation, and tamsulosin (α 1-AR antagonist) increased bladder blood flow and ameliorate bladder overactivity (3). Such action on bladder blood flow might be indirectly contributed to the suppression of A δ -fibers in the present results although we need further investigation.

Concluding message

The present study demonstrates that silodosin can inhibit the single unit bladder afferent activity of the A δ -fibers, but not the C-fibers, which is not associated with the suppression of the bladder microcontractions.

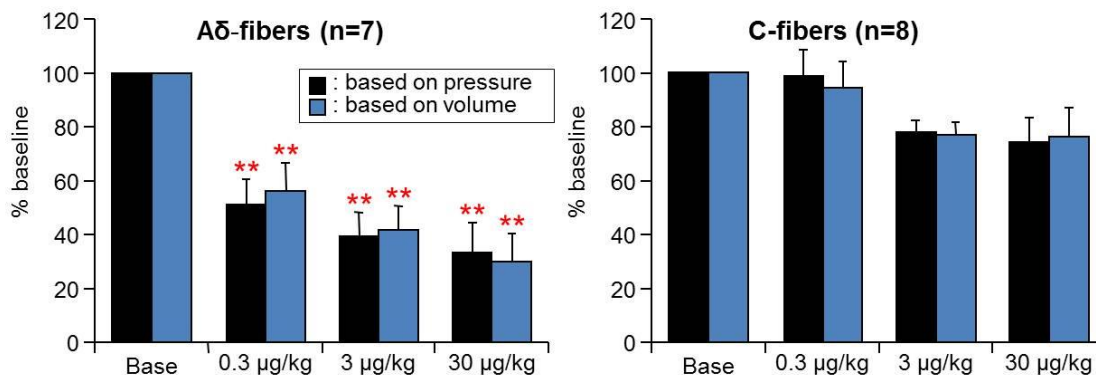


Figure 1. Responses to intravenous administration of silodosin of the A δ -fibers (left) and C-fibers (right) integrated during the whole filling phase. The values are expressed as a percentage of base-line activity (mean \pm S.E.M.).

** $P < 0.01$: significant difference from Base (two-way ANOVA followed by Tukey's test).

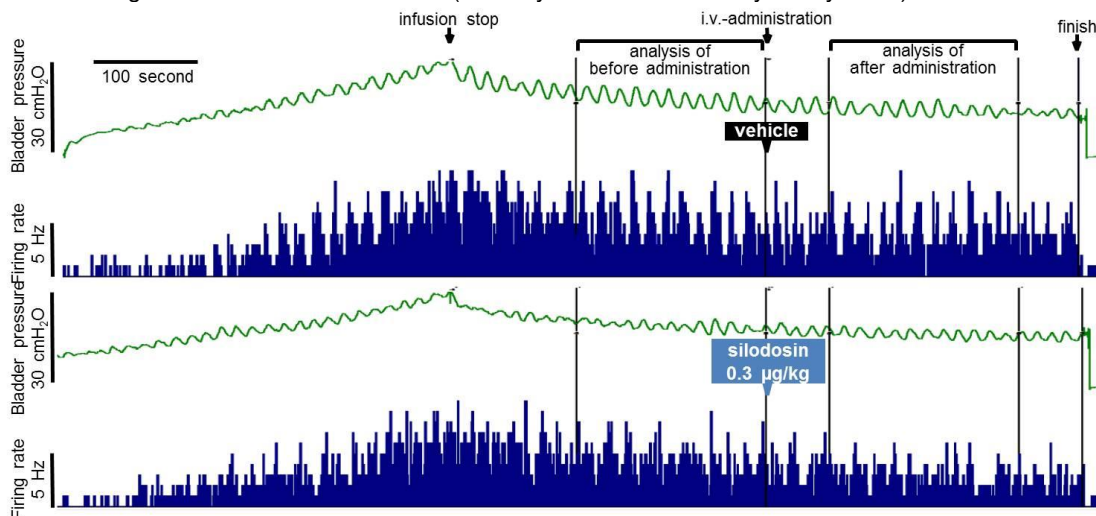
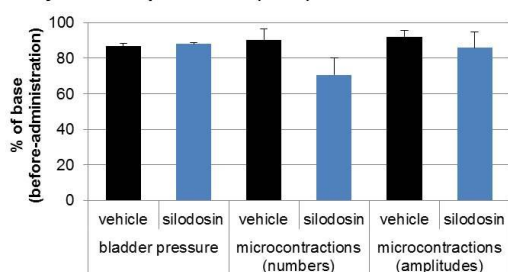


Figure 2. Representative recordings of bladder pressure and firing rate of A δ -fiber afferent activity during an isovolumetric condition before and after vehicle-(upper trace) or silodosin (0.3 μ g/kg, lower trace)-administrations.

A: cystometric parameters (n=16)



B: afferent activities

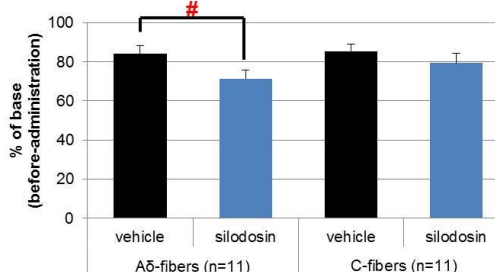


Figure 3. Comparative results of mean bladder pressure, number and amplitude of microcontractions (A), and afferent activities of both A δ - and C-fibers (B) between vehicle and silodosin-administrations. The values were represented as % of base values and compared between vehicle- and drug-administrations.

[#] $P < 0.05$: significant differences between after vehicle- and drug-administration (unpaired Student's t-test).

References

1. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Chapple CR, Montorsi F, Tammela TL, Wirth M, Koldewijn E, Fernández Fernández E; European Silodosin Study Group. *Eur Urol.* 2011 Mar;59(3):342-52.
2. Effects of mirabegron, a novel β_3 -adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. Aizawa N, Homma Y, Igawa Y. *Eur Urol.* 2012 Dec;62(6):1165-73.
3. Effect of tamsulosin on bladder blood flow and bladder function in a rat model of bladder over distention/emptying induced bladder overactivity. Okutsu H, Matsumoto S, Ohtake A, Suzuki M, Sato S, Sasamata M, Uemura H. *J Urol.* 2011 Dec;186(6):2470-7.

Disclosures

Funding: Research Grant from Kissei Pharmaceutical Co., Ltd. **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Animal Ethics Committee, The University of Tokyo Graduate School of Medicine **Ethics Committee:** Animal Ethics Committee, The University of Tokyo Graduate School of Medicine