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EFFECTS OF SILODOSIN AND IMIDAFENACIN ON THE BLADDER MECHANOSENSITIVE AFFERENT ACTIVITIES OF A-DELTA- AND C-FIBERS RELATED WITH MICROCONTRACTIONS IN MALE RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

A previous human study revealed that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localized bladder micromotions (microcontractions), which were more sustained with higher frequency when they felt urgency [1]. Another study demonstrated that in rats with bladder outlet obstruction (BOO), bladder mechanosensitive Aδ-fiber afferent activities were reduced, but intermittently enhanced by propagation of microcontractions during bladder filling [2]. These studies suggested that enhanced bladder microcontractions and its related afferent activities may contribute to the development of urgency associated with storage dysfunctions, but there have been no pharmacological investigations to confirm this concept. In this study, we evaluated the effects of silodosin, an α1A-adrenoceptor (α1A-AR) antagonist, and imidafenacin, an anti-cholinergic agent, on the bladder mechanosensitive single-unit afferent activities (SAAs), related with microcontractions, in a male rat model of BOO.

Study design, materials and methods

Thirty-eight male Wistar rats were used. To create partial BOO, the proximal urethra was ligated with a steel rod (1.2 mm in diameter) and then the rod was removed. At 4 days after surgery, an osmotic pump, which was filled with silodosin (0.12 mg/kg/day) or imidafenacin (3 μg/kg/day) or each drug's vehicle, was implanted subcutaneously. At 10 days after surgery, the rats were anesthetized with urethane. After the laminectomy, 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/s were designated as Aδ-fibers and those with CV less than 2.5 m/s as C-fibers. The intravesical pressure and SAAs were recorded and analysed during constant filling with saline until the intravesical pressure reached 30 cmH_2O. A microcontraction was defined as the contraction of which amplitude was more than 2 cmH_2O, and pressure was ascending at 0.25 cmH_2O/s or more and then descending at 0.15 cmH_2O/s or more. The microcontraction was divided into two phases as "ascending" and "descending" phases. The portion between the two microcontractions was termed as the "resting" phase.

Results

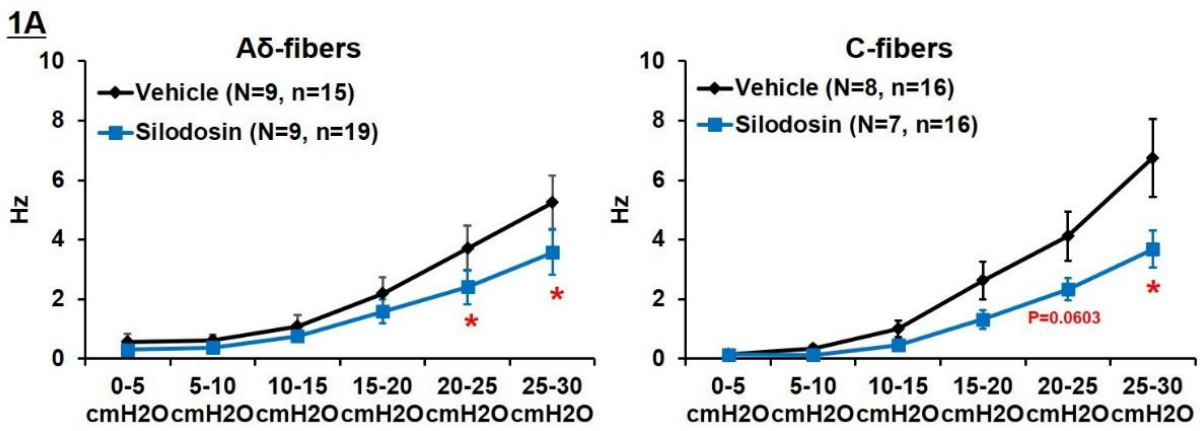
There were no significant differences of the number and amplitude of microcontractions between groups (silodosin vs. its vehicle, imidafenacin vs. its vehicle) although silodosin and imidafenacin tended to decrease the number of microcontractions. SAAs of both Aδ- and C-fibers in silodosin- or imidafenacin-treated groups were significantly lower than those in each vehicle-treated group (Figure 1). In both of the vehicle-treated groups, the SAAs of both Aδ- and C-fibers at the ascending phase of microcontractions were significantly higher than those at the other two phases. In contrast, such different responses of SAAs on microcontractions among three phases were not observed in the silodosin and imidafenacin groups (Figure 2).

Interpretation of results

Silodosin and imidafenacin inhibited SAAs of both Aδ- and C-fibers, suggesting that α1A-AR and muscarinic receptors in the BOO rat bladder are involved in the activation of the bladder mechanosensory afferent fibres during bladder filling. Since SAAs were intermittently enhanced by propagation of microcontractions in the vehicle-treated groups, but not in the silodosin- or imidafenacin-treated groups, these drugs inhibited the exaggerated SAAs responses related with microcontractions. These results may explain how α1A-AR antagonists and anti-cholinergic agents suppress urgency associated with BOO.

Concluding message

Silodosin and imidafenacin inhibited SAAs of both mechanosensitive Aδ- and C-fibers in a way by inhibiting the SAAs intermittently enhanced by propagation of bladder microcontractions in male BOO rats.



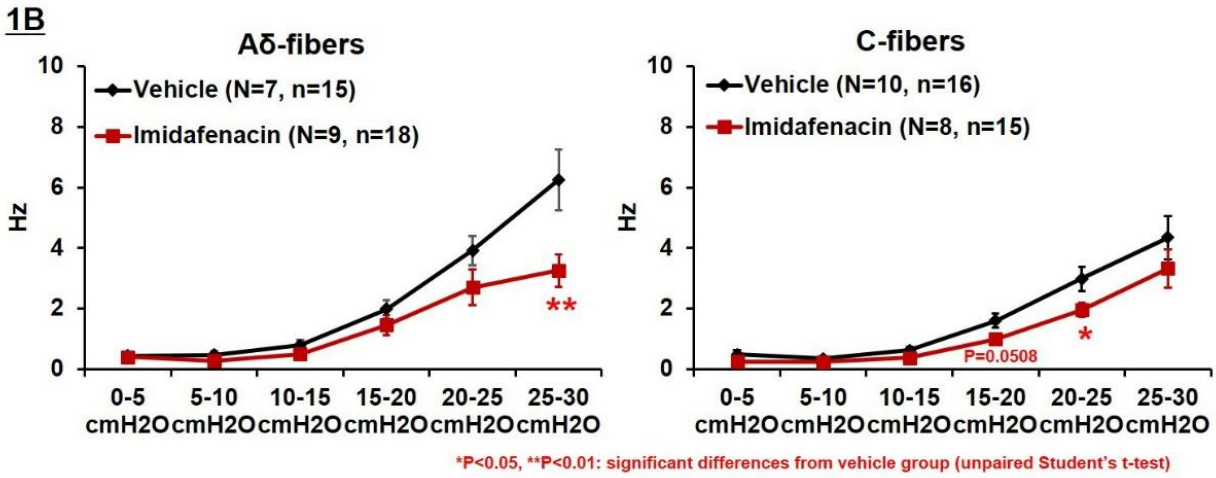


Figure 1. Effects of silodosin (A) and imidafenacin (B) on mechanosensitive SAAs of the Aδ- and C-fibers in male rats with BOO
The horizontal and vertical axes indicate the intravesical pressure and firing rate of SAAs, respectively. Values are expressed as mean ± SEM.

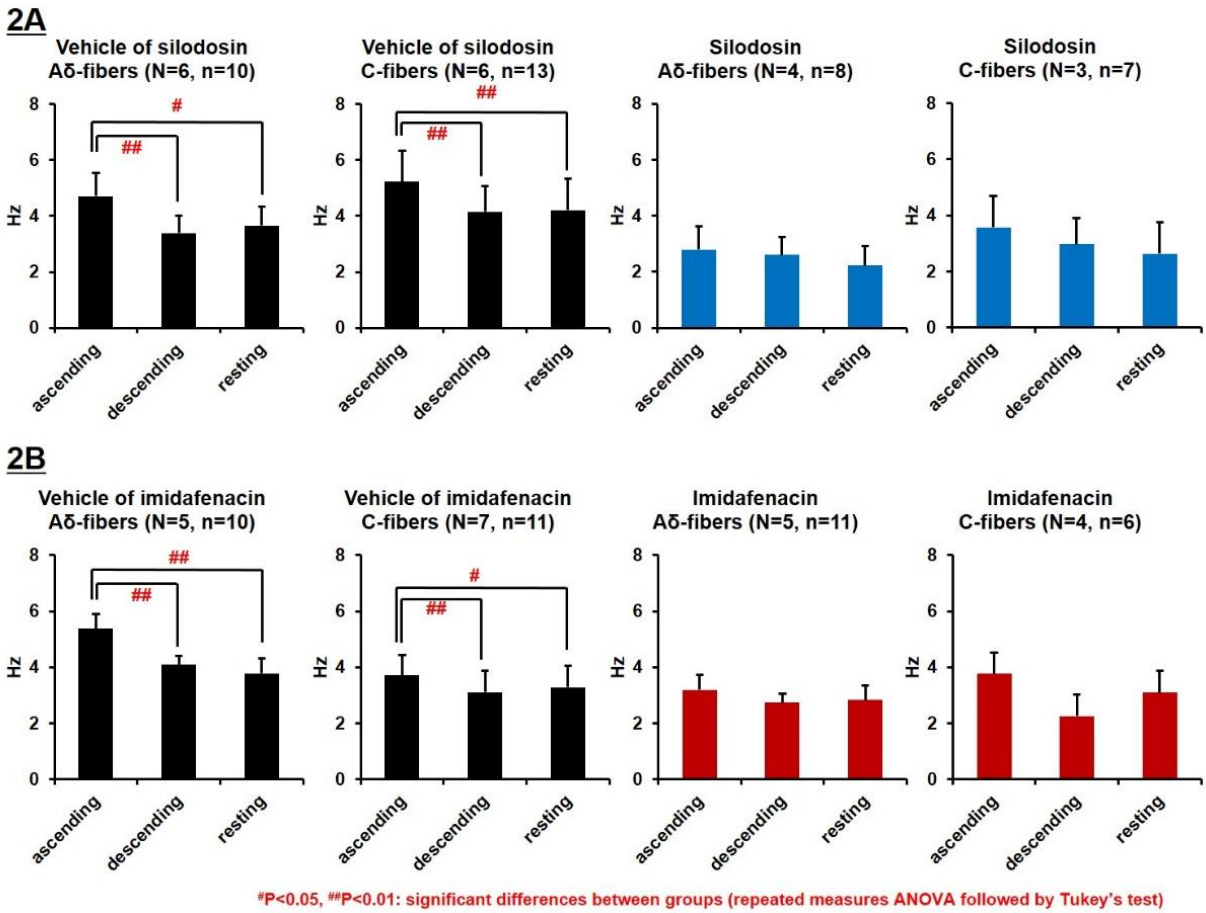


Figure 2. SAAs changes associated with microcontraction phases in male BOO rats treated with silodosin or its vehicle (A), and with imidafenacin or its vehicle (B)
The vertical axis indicates firing rate of SAAs. Values are expressed as mean ± SEM.

References
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Disclosures
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