

INHIBITORY EFFECTS OF INTRAVESICAL ADMINISTRATION OF SILODOSIN, A SELECTIVE ALPHA1A-ADRENOCEPTOR ANTAGONIST, ON SINGLE-UNIT PRIMARY BLADDER AFFERENT ACTIVITIES OF THE RAT

Hypothesis / aims of study

Silodosin, a highly selective antagonist for α 1A-adrenoceptor (α 1A-AR) subtype, has been proven to improve voiding symptoms in men with LUTS/BPH, additionally this drug have also been demonstrated to improve storage symptoms (1). However, the mechanisms to improve storage symptoms have not been clarified yet, and it has been recently proposed that α 1-ARs contribute to the afferent pathways innervating the bladder. We investigated direct effects of intravesical administration of silodosin on single unit afferent nerve fiber activities (SAAs) of the primary bladder afferent nerves in rats.

Study design, materials and methods

Eleven female Sprague-Dawley rats were used. Under intraperitoneal urethane anesthesia (1.2 g/kg), through a laminectomy, bilateral L6 dorsal roots were cut, and 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 of which conduction velocity (CV) is more than 2.5 m/second were determined as A δ -fibers and those with less than 2.5 m/second as C-fibers. At the beginning of the experiments, the SAAs measurements with constant bladder filling with saline (at 0.08 ml/minute until the intravesical pressure reached 30cmH₂O) were repeated three times and the third measurement served as the control observation. Then, the SAAs measurements were repeated with constant instillation with silodosin (10 μ M) further three times (after-1, -2 and -3). In each cystometry, bladder compliance was calculated between the start and end of this bladder filling.

Results

During silodosin-instillation, bladder compliance significantly increased from the control value (control: 0.0151 ± 0.0011 , after-1: 0.0184 ± 0.0014 , after-2: 0.0175 ± 0.0014 , after-3: 0.0186 ± 0.0016 ml/cmH₂O). Thirteen single afferent fibers (A δ -fibers: n=7, CV: 3.43 ± 0.66 m/sec, C-fibers: n=6 CV: 1.44 ± 0.10 m/second) were isolated. The SAAs of A δ -fibers decreased during silodosin-instillation, whereas those of C-fibers did not change significantly (Figures 1 and 2).

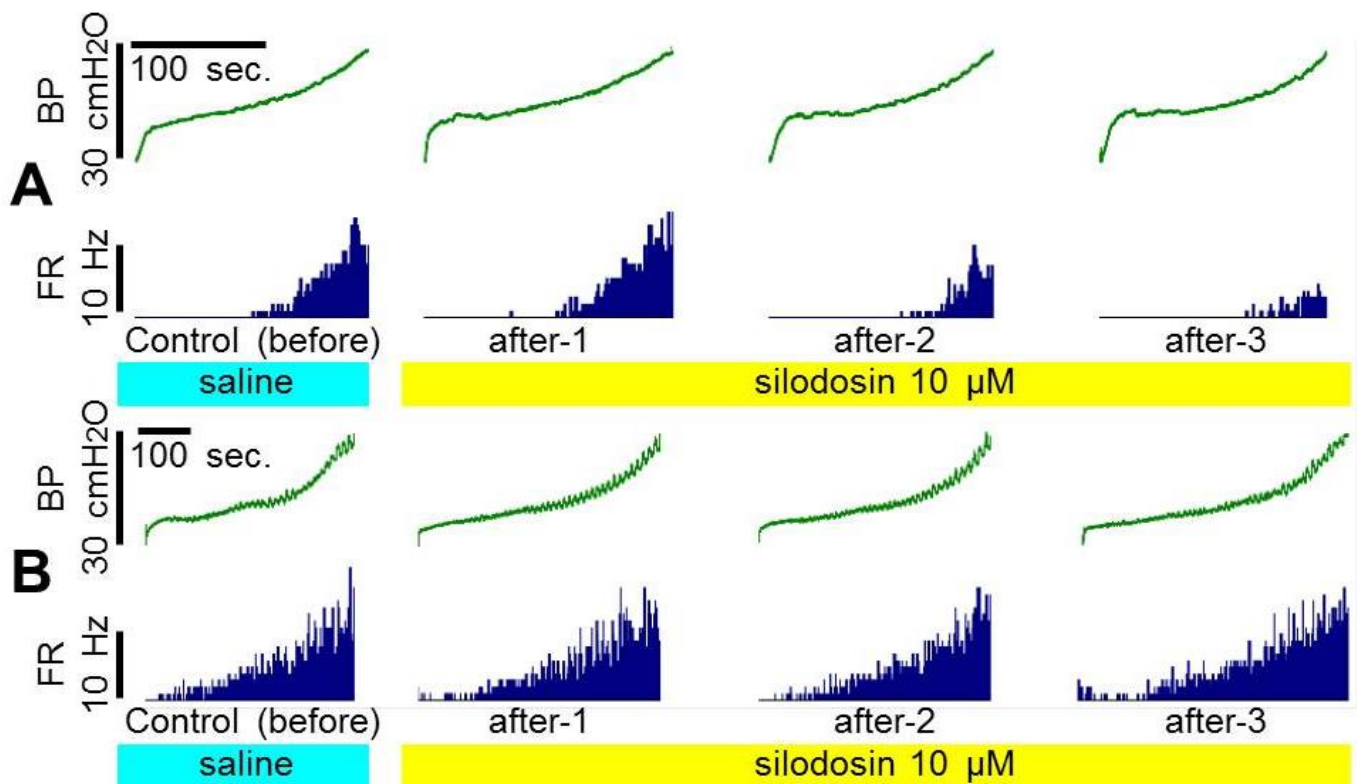


Figure 1. Representative traces of bladder pressure (BP) and firing rate (FR) of A δ -fiber (A) and C-fiber (B) during intravesical instillation with saline and silodosin.



Figure 2. Effect of intravesical silodosin-administration on SAAs of A δ -fibers (white bars, n=7) and C-fibers (black bars, n=6). The values are expressed as a percentage of control activity (mean \pm S.E.M.).
* P <0.05: significant differences from control (repeated measures ANOVA followed by Dunnett's test)

Interpretation of results

The present results indicated that the inhibition of the bladder α 1A-AR can suppress the SAAs of A δ -fibers of the primary bladder afferents in normal urethane-anesthetized rats. It has been demonstrated that α 1A-AR was expressed in the normal rat bladder urothelium (2), which actively participates on sensory functions, expressing various receptors for neurotransmitters, including receptors for norepinephrine (α - and β -adrenergic). Moreover, a recent animal study reported that the expression of α 1A-AR subtype mRNA was detected in the microvessels of the normal rat bladder, and silodosin possibly relax the bladder microvessel and can change the bladder blood flow and the oxidative reaction (3). The inhibitory effect of A δ -fiber activity induced by silodosin in the present study might result from its actions on the urothelium and bladder blood flow directly or indirectly.

Concluding message

The present results clearly demonstrate that intravesical administration of silodosin can inhibit A δ -fibers, but not C-fibers, of the primary bladder afferents in normal urethane-anesthetized rats. These findings suggest that bladder α 1A-ARs have a facilitatory action on the mechanosensitive bladder afferent activities through the A δ -fibers. The present study may support clinical observation that silodosin can improve storage symptoms in men with LUTS/BPH (1).

References

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Disclosures

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