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PHYSIOLOGICAL ROLE OF THE BLADDER ALPHA1D-ADRENOCEPTOR IN THE ACTIVATION OF SINGLE-UNIT PRIMARY BLADDER AFFERENT ACTIVITY IN RATS

Hypothesis / aims of study

Clinical observation have revealed that a relatively selective α1D-adrenoceptor (α1D-AR) antagonist, naftopidil, improve not only voiding symptoms but also storage symptoms in men with LUTS/BPH (1). As harmonized with such observation, an animal study demonstrated that systemically administrated naftopodil elongated voiding interval in cystometry and inhibited the mechanosensitive multiple bladder afferent activities (2). However, direct effects of bladder α1D-AR-inhibition on the individual mechanosensitive afferent activity innervating the bladder have not been evaluated yet. In the present study, we investigated the effect of intravenous and intravesical administrations of BMY7378, a highly selective α1D-AR antagonist, on mechanosensitive single-unit afferent activities (SAAs) of the primary bladder afferent nerves in rats.

Study design, materials and methods

Female Sprague-Dawley rats were used. Under urethane aesthesia (1.2 g/kg, intraperitoneally), bilateral L6 dorsal roots were transected via a 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/second were designated as Aδ-fibers and those with CV less than 2.5 m/second as C-fibers. At the beginning of the experiments, the afferent activity measurements with constant bladder filling (at 0.08 ml/minutes until the intravesical pressure reached 30cmH_2O) were repeated three times and the third measurement served as the base-line observation. Then two experiments were performed in separate animals; first, BMY7378 was administrated intravenously (i.v.) at three doses, 0.3, 3 and 30 μg/kg cumulatively, second, BMY7378 was administrated intravesically 3 times with a dose of 10 μM. After each drug administration or during drug instillation, further SAAs measurements were carried out (Figure 1). In the intravesical instillations of the drug, protamine sulphate (10 mg/ml, 0.3 ml, for 1 hour) was instilled into the bladder before the experiment to facilitate the drug-penetration through the glycosaminoglycan layer on the urothelium.

Results

Twenty-nine single afferent fibers (Aδ-fibers: n=15, CV: 5.46 ± 0.68 m/second, C-fibers: n=14 CV: 1.77 ± 0.11 m/second) were isolated from 22 rats. Intravenous administration of BMY7378 decreased SAAs of Aδ-fibers in a dose-dependent manner, and the effect was significant only at the highest dose. Intravesical administration of BMY7378 significantly decreased SAAs of Aδ-fibers at the 2nd- and 3rd-filling (Figures 2 and 3). On the contrary, SAAs of C-fibers did not change by BMY7378 at either way of administrations (Figure 3).

Interpretation of results

Since the results of the SAAs with intravenously and intravesically administrated BMY7378 were similar, the present results suggest that the inhibition of the bladder α1D-AR can suppress the SAAs of Aδ-fibers of the primary bladder afferents in the rat. A clinical study revealed that there was a relationship between the expression of α1D-AR mRNA in the bladder mucosa and storage phase urodynamics in LUTS/BPH patients, and suggested that α1D-ARs play a role in bladder sensation (3). The present study may support such previous clinical observation, and may give us further information that the α1D-ARs located near the bladder lumen have a facilitatory effect on the mechanosensitive Aδ-fiber activities even under normal conditions.

Concluding message

The present results clearly demonstrate that the intravenously and intravesically administrated selective α1D-AR antagonist, BMY7378, can inhibit Aδ-fibers, but not C-fibers, of the primary bladder afferent nerves in the rat. These findings may give us a new insight into possible mechanisms of action when we use α1-AR antagonists in the treatment of LUTS/BPH.

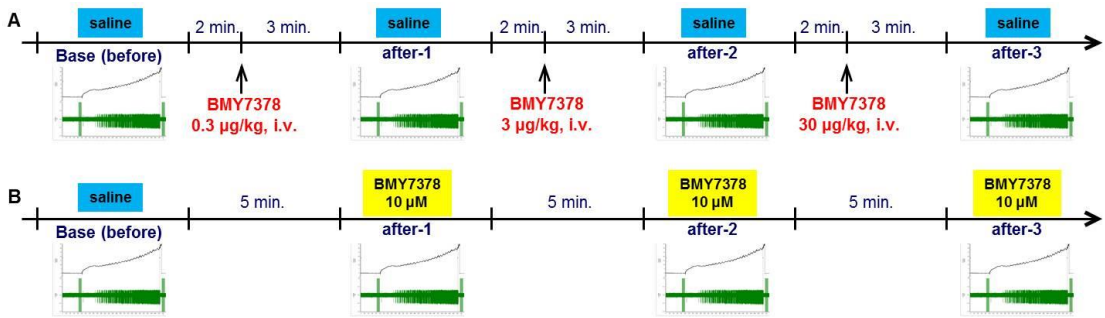

Figure 1. Experimental protocols before and after intravenous drug administrations (A) and during drug instillations (B)

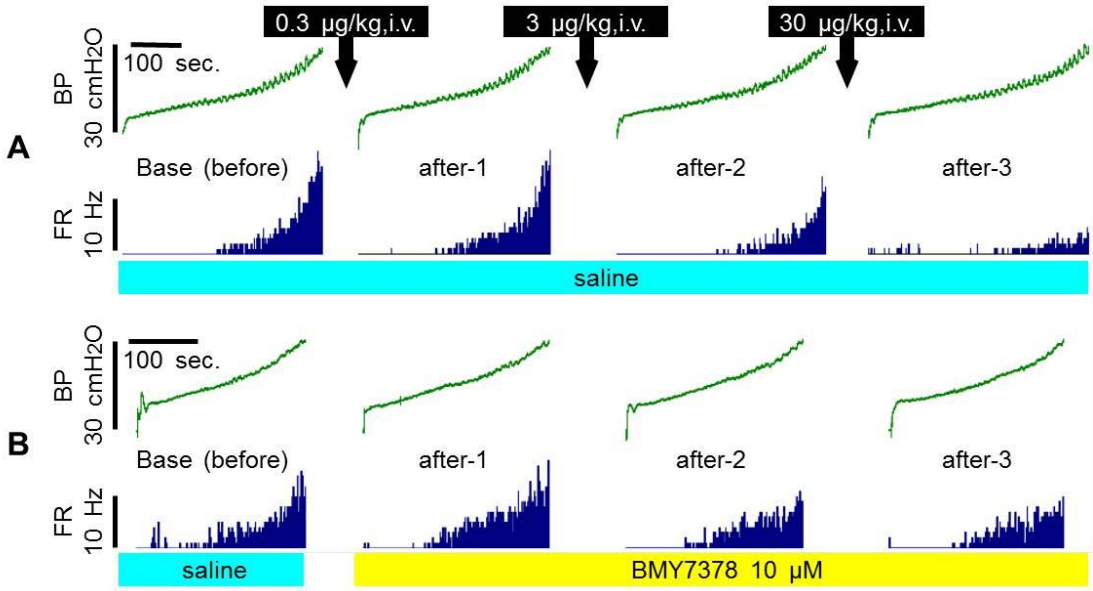

Figure 2. Representative recordings of bladder pressure (BP) and firing rate (FR) of Aδ-fibers before and after intravenous drug administrations (A) and during drug instillations (B).

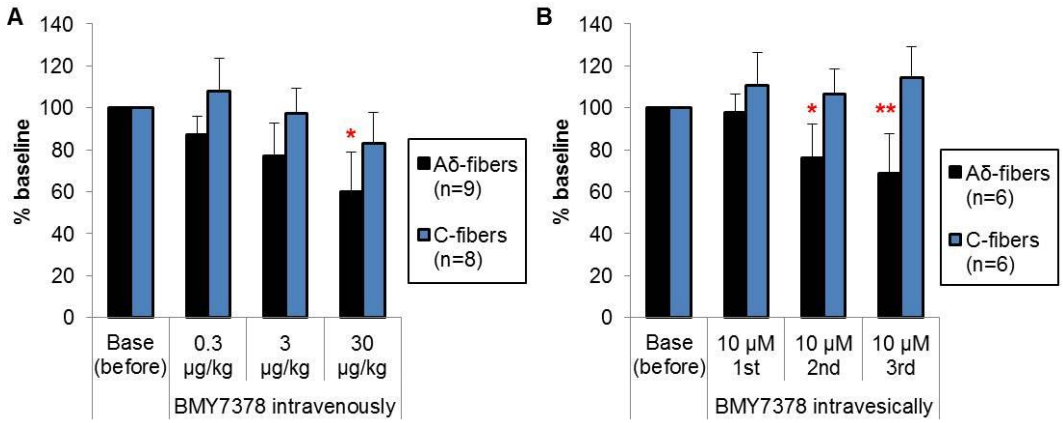

Figure 3. Effect of intravenous (A) and intravesical BMY7378-administrations (B) on SAAs of Aδ- and C-fibers
The values are expressed as a percentage of base-line activity (mean ± S.E.M.).
**P*<0.05, ***P*<0.01: significant differences from base (one-way ANOVA followed by Dunnett's test).

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Disclosures

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