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Aizawa N[1], Fukuhara H[2], Fujimura T[2], Homma Y[2], Igawa Y[1]
1. *Department of Continence Medicine, The University of Tokyo Graduate School of Medicine,* ***2.*** *Department of Urology, The University of Tokyo Graduate School of Medicine*

EFFECTS OF TADALAFIL, A PDE TYPE 5 INHIBITOR, ON THE BLADDER MECHANOSENSITIVE AFFERENT ACTIVITIES RELATED TO MICROCONTRACTIONS IN MALE RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

A recent randomized control study in women with overactive bladder (OAB) demonstrated significant improvement of OAB symptoms with a low dose of tadalafil, a PDE type 5 inhibitor, as compared with placebo [1]. During the storage phase, enhanced localized microcontractile activity has been suggested to contribute to the development of urinary urgency in patients with OAB [2]. An animal study showed that tadalafil has an inhibitory effect on the increased mechanosensitive bladder afferent activities induced by intravesical instillation of acrolein in rats [3]. These findings lead the hypothesis that tadalafil ameliorates OAB symptoms by inhibiting localized bladder microcontractions and their related abnormally increased bladder mechanosensive afferent activities. In this study, we evaluated the effects of chronic administration of tadalafil on the bladder mechanosensitive single-unit afferent activities (SAAs) and their relation with microcontractions in a male rat model of BOO.

Study design, materials and methods

Twenty-six 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, daily oral administration of tadalafil (0.1 or 1 mg/kg) or its vehicle (0.5% methyl cellulose) was started, and at 10 days after surgery, the rats were anesthetized with urethane after administration. Through 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 (CVs) more than 2.5 m/second were designated as Aδ-fibers and those with CV less than 2.5 m/second as C-fibers. The intravesical pressure and SAAs were recorded and analysed during constant filling at a rate of 10 mL/hour 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/second or more and then descending at 0.15 cmH_2O/second 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 in CVs, bladder weight, bladder compliance, and amplitude and number of microcontractions between groups (Table 1). During bladder filling, SAAs of C-fibers, but not of Aδ-fibers, in the high dose (1 mg/kg) of tadalafil-treated group was significantly lower than those in vehicle- and the low dose (0.1 mg/kg) of tadalafil-treated groups (Figure 1). In the vehicle-treated group, the SAAs of both Aδ- and C-fibers during the ascending phase of microcontraction were significantly higher than those at the other two phases. In contrast, such intermittent increases in SAAs of C-fibers associated with the ascending phase of microcontractions were not observed in both doses of tadalafil-treated groups, while those of Aδ-fibers were preserved (Figure 2).

Interpretation of results

Tadalafil-administrations, even at a high dose (1 mg/kg), did not inhibit microcontractions themselves, but inhibited the intermittently enhanced SAAs of C-fiber during the ascending phase of microcontractions. Furthermore, when treated at the high dose, this inhibitory action of tadalafil became conspicuous by supressing whole SAAs of C-fibers no matter which phases. These results suggest that PDE type 5 in the BOO rat bladder are involved in the activation of the bladder mechanosensitive afferent C-fibres during bladder filling, especially in their facilitation related to microcontractions.

Concluding message

Tadalafil inhibited bladder mechanosensitive C-fiber activities especially in a way to supress their intermittent enhancement associated with bladder microcontractions in male BOO rats. Such pharmacological action of tadalafil may contribute to improve bladder abnormal sensation associated with OAB/BOO.

Table 1. Characteristics of CVs of Aδ- and C-fibers, bladder weights, bladder compliances, and the amplitude and number of microcontractions in vehicle- or tadalafil-treated male BOO rats at day 10 post-operatively

parameters		vehicle (N=10)		tadalafil 0.1 mg/kg/day (N=8)		tadalafil 1 mg/kg/day (N=8)	
		Aδ-fibers (n=15)	C-fibers (n=25)	Aδ-fibers (n=20)	C-fibers (n=18)	Aδ-fibers (n=13)	C-fibers (n=20)
CV (m/second)		3.3 ± 0.4	1.7 ± 0.1	4.7 ± 0.5	1.6 ± 0.1	4.3 ± 0.5	1.7 ± 0.1
bladder weight (mg)		216.0 ± 17.5		184.1 ± 6.7		193.8 ± 13.8	
bladder compliance (mL/ΔcmH_2O)		0.027 ± 0.002		0.029 ± 0.002		0.025 ± 0.002	
micro-contractions	amplitude (cmH_2O)	2.87 ± 0.37		2.42 ± 0.17		2.64 ± 0.19	
	numbers (times/minute)	1.45 ± 0.17		0.74 ± 0.17		1.43 ± 0.32	

Values are expressed as mean ± SEM.
No significant differences were found on either parameter between groups (one-way ANOVA followed by Tukey's test).

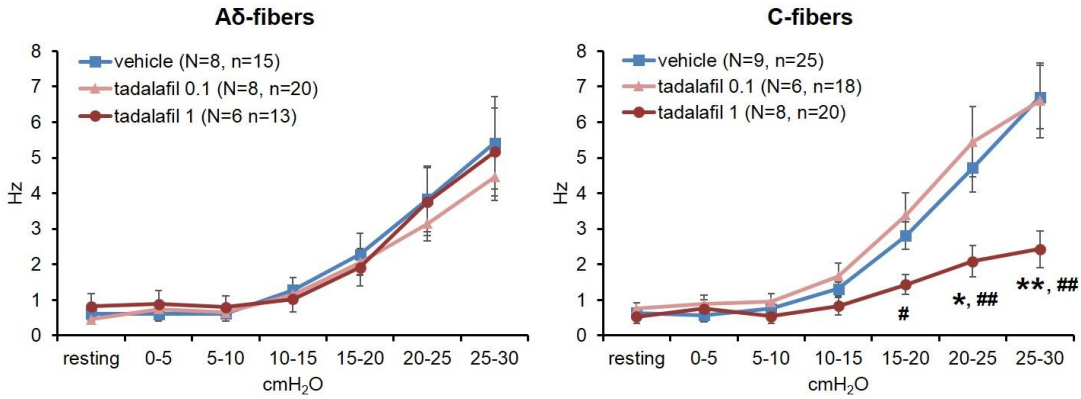

Figure 1. Effects of tadalafil (0.1 or 1 mg/kg/day) on mechanosensitive SAAs of the Aδ- and C-fibers in male rats with BOO
The horizontal and vertical axes indicate the intravesical pressure and firing rate of SAAs, respectively. Values are expressed as mean ± SEM.
*P<0.05, **P<0.01: from vehicle group, and #P<0.05, ##P<0.01: from tadalafil 0.1 group, respectively (one-way ANOVA followed by Tukey's test)

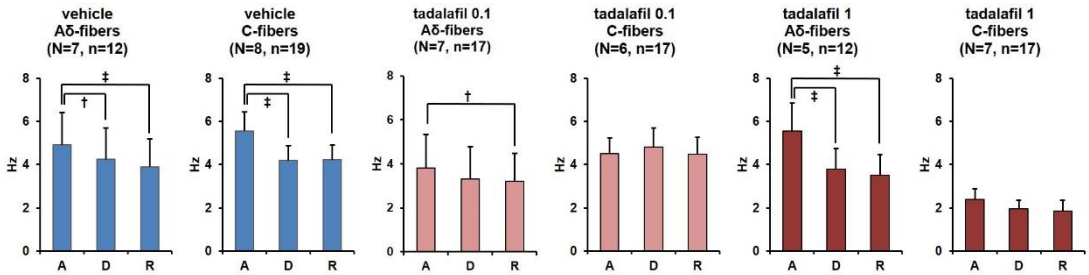

Figure 2. SAAs changes associated with microcontraction phases in male BOO rats treated with vehicle or tadalafil (0.1 or 1 mg/kg/day)
Values are expressed as mean ± SEM. The vertical axis indicates firing rate of SAAs.
†P<0.05, ‡P<0.01: between groups (repeated measures ANOVA followed by Tukey's test)
A: ascending phase of microcontraction, D: descending phase of microcontraction, R: resting phase

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Disclosures

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