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CHARACTERIZATION OF THE MECHANOSENSITIVE BLADDER AFFERENT ACTIVITIES IN RELATION WITH MICROCONTRACTIONS IN MALE RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

It has been reported that bladder microcontractions may be related to the mechanosensitive Aδ-fiber activities innervating the normal rat bladder (1). In a clinical observation in women with overactive bladder (OAB), localized bladder contractions (similar to microcontractions) were enhanced, which concomitantly occurred with urinary urgency (2). In isolated whole bladder preparations of a rat model of bladder outlet obstruction (BOO), coordination of the microcontractions is enhanced by stretch, leading to increased pressure fluctuations, suggesting that such changes may contribute to the development of detrusor overactivity (DO) (3). These previous reports suggest that the enhanced bladder microcontractions may be a trigger for development of DO/OAB. However, there has been no study directly investigating the possible relationship between the bladder microcontractions and the sensory afferent transductions in pathophysiological conditions such as BOO. Therefore, we evaluated the characteristics of mechanosensitive single-unit afferent activities (SAAs) innervating the bladder in a male rat model of BOO, and their relationship with microcontractions.

Study design, materials and methods

Twenty male Wistar rats were divided into Sham and BOO groups (N=10 in each group). 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 10 days after surgery, rats were anesthetized with urethane (1.2 g/kg, intraperitoneally). 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 (1). The intravesical pressure and SAAs were recorded and analysed during constant filling with saline until the intravesical pressure reached 30 cmH_2O. A micro-contraction was defined as the contraction of which pressure was ascending at 0.25 cmH_2O/s or more and then descending at 0.15 cmH_2O/s or more, and having more than 2 cmH_2O of amplitude. The microcontarction was divided into two phases as “contraction-1” (ascending) phase and “contraction-2” (descending) phase. The portion between the two mcrocontractions was termed as the resting phase (Figure 4 C, F).

Results

The number and amplitude of microcontractions in the BOO rats were significantly higher than those in the Sham rats (Figure 1). Totally 44 single afferent fibers were isolated (Sham: Aδ-fibers: n=10, CV: 5.99 ± 1.60 m/s, C-fibers: n=11 CV: 1.62 ± 0.10 m/s, BOO: Aδ-fibers: n=10, CV: 5.43 ± 0.79m/s, C-fibers: n=13, CV: 1.21 ± 0.12 m/s). The BOO rats showed significantly lower SAAs of Aδ-fibers than those of the Sham rats, whereas SAAs of C-fibers were not significantly different between the groups, although BOO rats tended to have lower SAAs (Figure 2). In the BOO rats, the SAAs of the Aδ-fibers at the phase of “contraction-1” were significantly higher than those at the other two phases. In contrast, there were no significant differences in the SAAs of the C-fibers in the BOO and in those of either Aδ- or C-fibers in the Sham rats among the three phases (Figures 3 and 4).

Interpretation of results

The present BOO rats showed less mechanosensitive activities of Aδ-fibers, but not significantly of C-fibers, suggesting that BOO caused denervation of bladder afferent nerves, which was more prominent in the myelinated Aδ-fibers. Moreover, the SAAs of Aδ-fibers under the BOO condition were enhanced during the ascending phases of microcontractions. This synchronized enhancement of SAAs of the Aδ-fibers with microcontrations is in line with the previous finding under the normal condition (1). Taken all together, after BOO mechanosensitive Aδ-fibers may be reduced their activities, but intermittently enhanced by propagation of microcontractions during bladder filling.

Concluding message

The present study demonstrated that in a male rat model of BOO, SAAs of mechanosensitive Aδ-fibers of the bladder were generally decreased, but periodically enhanced in association with the coordinated bladder microcontractions. The present findings may support the view that the coordination of bladder microcontractions is a trigger for facilitating mechano-afferent transductions leading to development of OAB/DO.

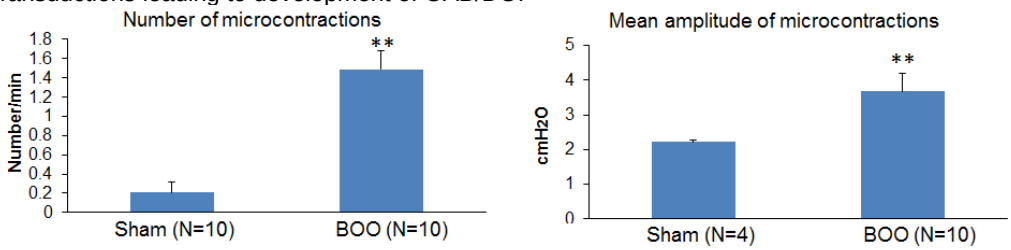

Figure 1: Influence of BOO-induction on the number and amplitude of microcontractions
Values are expressed as mean ± SEM. Six animals had no microcontraction in the Sham group. **p<0.01: significant difference from the Sham rats (unpaired t-test)

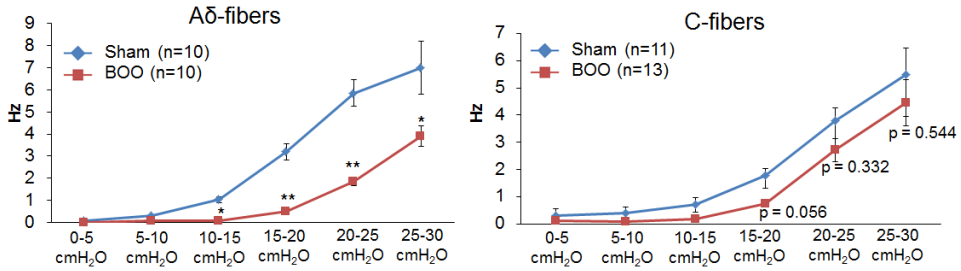

Figure 2: Influence of BOO-induction on mechanosensitive SAAs of the Aδ- and C-fibers
The horizontal and vertical axes indicate the intravesical pressure and firing rate of SAAs, respectively. Values are expressed as mean ± SEM. *p<0.05, **p<0.01: significant differences from the Sham rats (unpaired t-test)

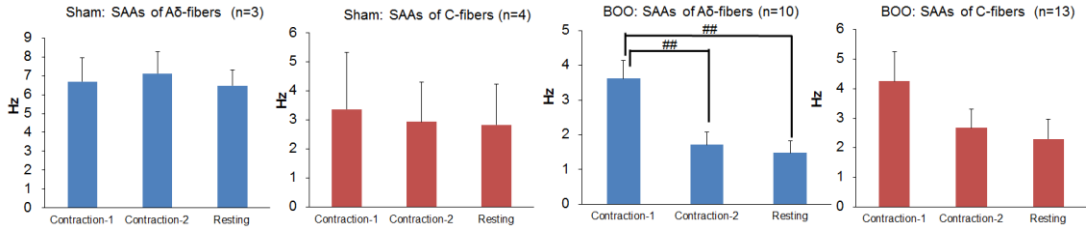

Figure 3: SAAs responses in the Sham and BOO rats during three phases of the filling cystometry
The vertical axis indicates firing rate of SAAs. Values are expressed as mean ± SEM. Data were obtained from 4 animals which had microcontructions in the Sham group. ##p<0.01: significant difference between each phase (Tukey's multiple comparison test)

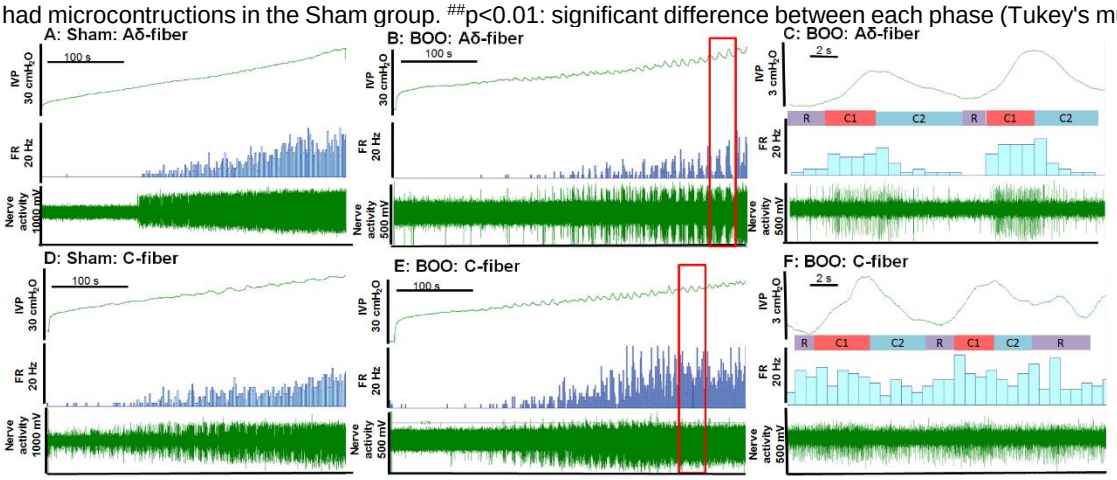

Figure 4: Representative traces of the intravesical pressure (IVP) and the firing rate (FR) of the Aδ- and C-fiber in Sham (A, D) and BOO rats (B, C, E, F)
Each red square in panel B and E is corresponding to the panel C and F, respectively.
C1: contraction-1 (ascending) phase, C2: contraction-2 (descending) phase, R: resting phase

References

1. Aizawa N, Homma Y, Igawa Y. Effects of Mirabegron, a Novel beta3-Adrenoceptor Agonist, on Primary Bladder Afferent Activity and Bladder Microcontractions in Rats Compared With the Effects of Oxybutynin. Eur Urol. 2012 Sep 5;62(6):1165-73.
2. Drake MJ, Harvey IJ, Gillespie JI, Van Duyl WA. Localized contractions in the normal human bladder and in urinary urgency. BJU Int. 2005 May;95(7):1002-5.
3. Drake MJ, Hedlund P, Harvey IJ, Pandita RK, Andersson KE, Gillespie JI. Partial outlet obstruction enhances modular autonomous activity in the isolated rat bladder. J Urol. 2003 Jul;170(1):276-9.

Disclosures

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