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FUNCTIONAL ROLES OF ALPHA1D-ADRENERGIC RECEPTOR FOR COLD STRESS-INDUCED DETRUSOR OVERACTIVITY IN RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

In patients with bladder outlet obstruction, cold stress that is suddenly drop or continuously exposure to low environmental temperature exacerbates lower urinary tract symptoms such as urinary urgency and frequency. It was previously reported that alpha1-adrenergic receptors (a1-ARs) mediate cold stress-induced detrusor overactivity in normal healthy rats (1). In addition, muscarinic acetylcholine receptors are closely associated with lower urinary tract function. In this study, we determined if a1-AR antagonist, naftopidil, and muscarinic acetylcholine receptor antagonist, imidafenacin could inhibit the cold stress-induced detrusor overactivity in bladder outlet obstruction (BOO) rats.

Study design, materials and methods

Ten weeks female Sprague-Dawley (SD) rats were anesthetized, and then a polyplopylene tube (PE-50, Becton Dickinson and Company, MD, USA) was placed adjacent to the urethra. Both of the urethra and tube were moderately ligated with a 5-0 silk, and then, the tube was carefully removed (BOO group). Eight SD rats were treated without the ligature (sham operation group). At 4 weeks after the ligature, they were divided into three groups: naftopidil-, imidafenacin- and vehicle-treated rats. Two days prior to cystometric investigations, the rats were cannulated. Micturition patterns of the cannulated conscious rats were recorded at room temperature (RT, 27 ± 2ºC) for 20 min. The rats were intravenously administered with 0.3 mg/kg naftopidil, 0.3 mg/kg imidafenacin or vehicle. Five minutes later, they were smoothly transferred to a low temperature (LT, 4 ± 2ºC), and then the micturition patterns were again recorded for 40 min. The rats having 2 to 5 ml bladder capacity under room temperature were examined. After cystometric investigations, the urinary bladders were removed. The expression levels of a1D-AR and muscarinic acetylcholine receptor 3 (M3) mRNA within the bladders were semi-quantitatively analysed with housekeeping gene, beta-actin, by real-time reverse transcription-polymerase chain reaction (RT-PCR).

Results

In vehicle-treated control, naftopidil-treated rats and imidafenacin-treated rats under RT, micturition patterns that were basal pressure, micturition pressure, voiding interval, and bladder capacity did not show significant differences. During LT period, the basal pressure of all groups was significantly increased, while micturition pressure did not alter. After transferring to LT, voiding interval and bladder capacity of the control (18.7 to 7.3 min, $P<0.01$, 3.12 to 1.17 ml, $P<0.01$) and imidafenacin-treated rats (15.4 to 6.13 min, $P<0.01$; 2.58 to 1.02 ml, $P<0.01$) were significantly decreased (Fig. 1A and 1B). In the naftopidil-treated rats, the voiding interval and bladder capacity under LT period were also decreased (15.7 to 9.29 min, $P<0.01$; 2.60 to 1.51 ml, $P<0.01$). However, the decreases of voiding interval and bladder capacity in the naftopidil-treated rats were significantly inhibited compared to the control and imidafenacin-treated rats ($P<0.05$, Fig. 1). The expression level of a1D-AR mRNA within the bladders of BOO group was significantly higher than that of the sham operation group ($P< 0.01$, Fig. 2). In the M3 mRNA expression level, there was no significant difference between the BOO and sham group.

Interpretation of results

In this study, muscarinic acetylcholine receptor antagonist, imidafenacin did not affect on cold stress-induced detrusor overactivity, such as decreases of voiding interval and bladder capacity. However, a1-AR antagonist, naftopidil partially inhibited the decreases of voiding interval and bladder capacity induced by cold stress. In addition, while M3 mRNA expression level of BOO group did not alter, BOO group showed higher expression level of a1D-AR mRNA compared to sham operation group. Naftopidil has a high affinity of a1D-AR. Therefore, this study suggested that a1D-AR might mediate a portion of the cold stress-induced detrusor overactivity. Also, administration of a1D-AR antagonist has a potential to treat for bladder storage symptoms such as urinary frequency and nocturia that are exacerbated by cold stress.

Concluding message

This study showed that muscarinic acetylcholine receptor antagonist, imidafenacin could not inhibit the cold stress-induced detrusor overactivity in BOO rats; however, a1-AR antagonist, naftopidil, partially inhibited the cold stress-induced responses. The a1D-AR mRNA expression level within the bladders of BOO rats was significantly higher than that of sham ones. Therefore, a1D-AR partially mediated the pathway of the detrusor overactivity induced by cold stress.

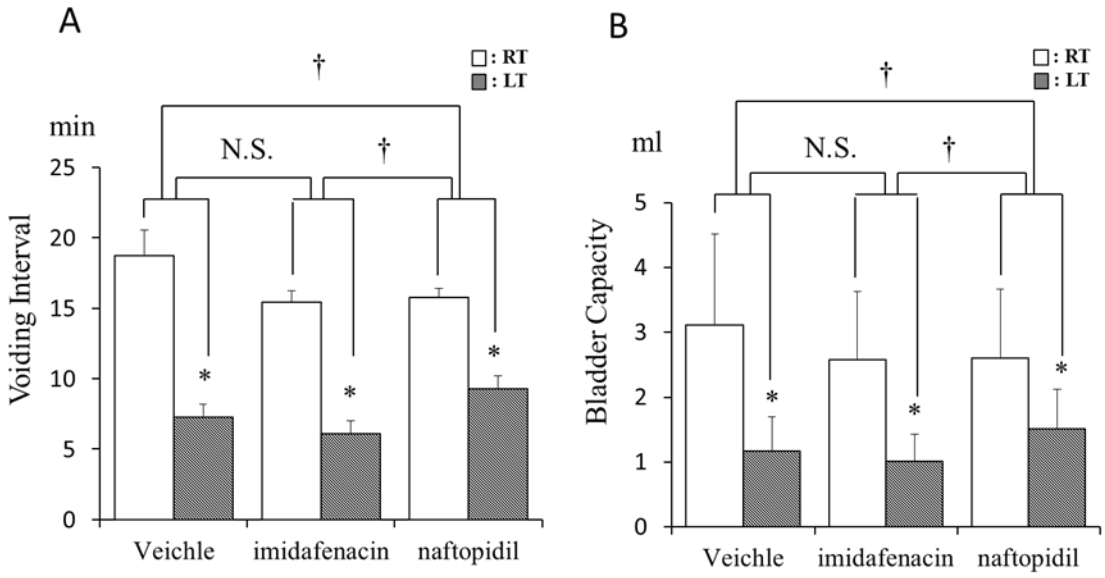

Figure 1 Changing voiding interval (A) and bladder capacity (B) with environmental temperature. The naftopidil inhibited decreases of voiding interval and bladder capacity under LT.
*P<0.01; compared to RT.
†P<0.05; compared to decreases of vehicle-treated and imidafenacin-treated rats.
N.S.; Not Significant

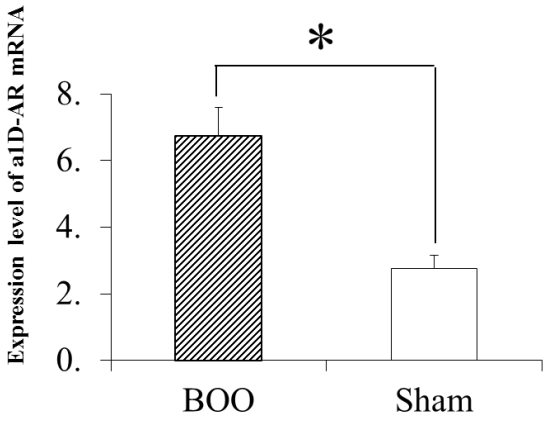

Figure 2 The expression level of a1D-AR mRNA within the bladders of BOO group was significantly higher than that of the sham operation group. (P< 0.01)

References
1. Chen Zhang et al., Neurourol.Urodyn 28: 251-256, 2009

Disclosures
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