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TRANSIENT RECEPTOR POTENTIAL CHANNEL M8 (TRPM8) EXPRESSING ON SKIN MEDIATES DETRUSOR OVERACTIVITY INDUCED BY COLD-STRESS AND MENTHOL-SPRAYING IN CONSCIOUS RATS

Hypothesis / aims of study

We showed that an exposure of low temperature [1] or a menthol-spraying [2] induced detrusor overactivity in conscious rats. A portion of the response was mediated by C-fiber sensitive neurological pathway [1], and transient receptor potential channel M8 (TRPM8) expressing on the skin [2]. In this study, we determined if TRPM8 antagonist (N-(4-t-Butylphenyl)-4-(3-chloropyridin-2yl) tetrahydropyrazine-1(2H)-carboxamide; BCTC) could inhibit the detrusor overactivity induced by cold-stress or menthol-spraying.

Study design, materials and methods

Twenty four female 10-weeks Sprague-Dawley (SD) rats were randomly separated into 4 groups; 0 (control), 2, 20 and 200 μM BCTC per 200 g-body weight administration group (n=6 in each group). Two days after cannulation, cystometric investigations of the conscious and free-moving rats were performed at room temperature (RT, 27±2°C), and then intravenously administrated with BCTC solution. Ten minutes after administration, the rats were transferred to low temperature (LT, 4±2°C) condition. In each temperature condition, the micturition patterns were recorded for 20 min. Similarly, other 6 SD rats were performed with cystometric investigations at RT. The rats were intravenously administrated with saline (control). At 10 minutes after, the rats were sprayed with 90% menthol on the legs at 5 min intervals for 20 min (first spraying). Thirty minutes after spraying, the rats were intravenously administrated with 200 μM BCTC per 200 g-body weight. At 10 min after, the rats were sprayed with 90 % menthol on the legs at 5 min intervals for 20 min (second spraying). During the menthol spraying, the micturition parameters were recorded.

Results

After transferring to LT, the voiding interval and bladder capacity of control and 2 μM BCTC-administrated rats were significantly decreased (Figure 1). However, the voiding interval and bladder capacity of the 20 and 200 μM BCTC-administrated rats did not decrease compared to the control and 2 μM BCTC-administrated rats (Figure 1). During the first menthol spraying, the voiding interval and bladder capacity of saline-administrated rats were significantly decreased (from 4.76±0.42 to 2.19±0.22 min, from 0.88±0.09 to 0.44±0.03ml, respectively, Figure 2A and B). However, during second menthol spraying, the voiding interval (5.68±0.57 min) and bladder capacity (1.01±0.10 ml) of 200 μM BCTC-administrated rats did not decreased compared to the first menthol spraying (Figure 2C).

Interpretation of results

TRPM8 antagonist, BCTC partially inhibited the cold-stress induced detrusor overactivity through whole body cooling, and the effects were depended on the doses. The high dose of BCTC inhibited the menthol-spraying induced detrusor overactivity via TRPM8 expressing on the skin. In this study, we showed that the cold-stress induced detrusor overactivity were mediated by skin TRPM8. Further study will be needed to investigate the functional roles of BCTC in central and peripheral nervous system.

Concluding message

This study showed that TRPM8 antagonist, BCTC partially inhibited the detrusor overactivity induced by cold-stress and menthol-spraying via TRPM8 expressing on the skin.

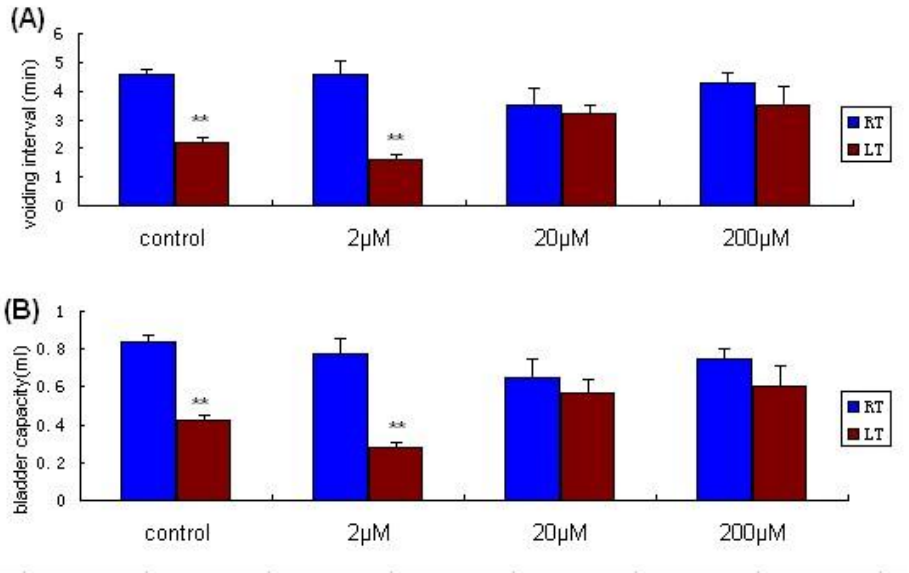

Figure 1. The effects of BCTC on the voiding interval (A) and bladder capacity (B) at RT and LT condition. **P<0.01.

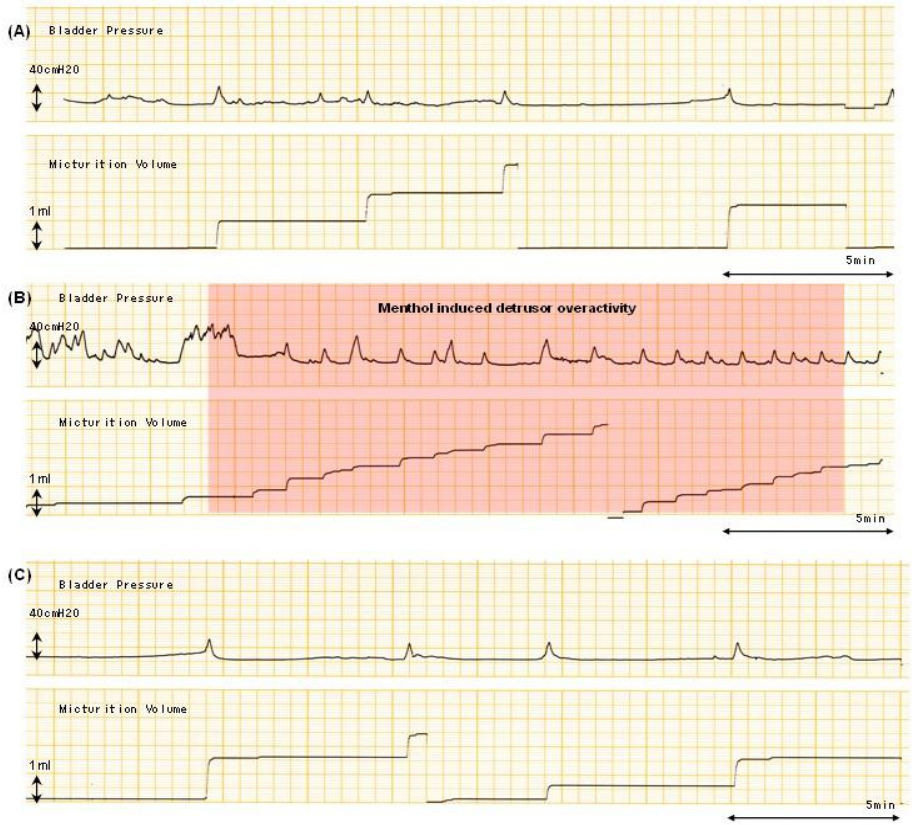

Figure 2. The effects of BCTC on micturition patterns after menthol spraying. (A) Bladder pressure (top) and micturition volume (bottom) before menthol spraying. (B) Bladder pressure (top) and micturition volume (bottom) of saline-administrated rats were changed by mentol-spraying. (C) Bladder pressure (top) and micturition volume (bottom) of 200 μM BCTC-administrated rats were not changed by menthol-spraying.

References

1. Imamura, et al. Neurourol Urodyn 2008;27:348-52
2. Chen, et al. Neurourol Urodyn 2010;29:506-11

Disclosures

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