

## **B3-ADRENERGIC RECEPTOR-INVOLVING PATHWAYS MEDIATE RAT DETRUSOR OVERACTIVITY INDUCED BY COLD STRESS**

### Hypothesis / aims of study

Cold stress produced by sudden change or continuous exposure to low environmental temperature exacerbates lower urinary tract symptoms (LUTS) such as urinary urgency, frequency, and nocturia. We previously reported that rats exposed with cold stress exhibited detrusor overactivity. The cold stress-induced detrusor overactivity was mediated resiniferatoxin-sensitive C-fiber sensory nerve pathway (1) through transient receptor potential melastatin 8 channels (2) and  $\alpha$ 1-adrenergic receptors (3). In this study, we investigated to determine if pathways related with  $\beta$ 3-adrenergic receptors (ARs) mediated cold stress-induced detrusor overactivity.

### Study design, materials and methods

In this study, we used 10-weeks female Sprague-Dawley (SD) rats, and CL 316243 (Gigma-aldrich, Inc., MO, USA) as  $\beta$ 3-ARs agonist. Two days prior to cystometric investigations, the bladder was prepared by cannulation. Cystometric measurements of the free-moving catheterized rats were taken at room temperature (RT, 27 $\pm$ 2°C) for 20 min, and then they were intravenously administrated with 1.0 mg/kg CL 316243 or vehicle (in each n=5). After 5 min of treatment, the rats were gently and quickly transferred to the cold room for low temperature (LT, 4 $\pm$ 2°C) exposure, and then the micturition patterns were monitored for 40 min. After LT exposure, the rats were returned to RT (re-RT, 27 $\pm$ 2°C). For analysis, the LT exposure was divided into Phase I and Phase II, each of which was 20 min. Throughout the experiments, the following cystometric parameters were analyzed: basal pressure, maximum micturition pressure, voiding interval, micturition volume, residual volume, and bladder capacity.

### Results

At RT, measured values of CL 316243- and vehicle control-treated rats did not have any differences. During the first 20 min after transfer from RT to LT, Phase I, the control rats exhibited detrusor overactivity patterns such as increased micturition frequency (Fig. A). In contrast, the detrusor overactivity patterns of the CL 316243-treated rats were partially inhibited during Phase I (Fig. B). In the Phase I, basal pressure of both CL 316243-treated and control rats significantly increased, while micturition pressure and residual volume did not alter. In the control rats, voiding interval (7.23 $\pm$ 1.65 to 3.12 $\pm$ 0.44 min; P<0.01), micturition volume (1.15 $\pm$ 0.24 to 0.60 $\pm$ 0.12 ml; P<0.01), and bladder capacity (1.33 $\pm$ 0.19 to 0.61 $\pm$ 0.12 ml; P<0.01) significantly decreased. These values of the CL 316243-treated rats tended to decrease; however the decreases of voiding interval (7.64 $\pm$ 0.76 to 5.02 $\pm$ 0.50 min), micturition volume (1.14 $\pm$ 0.12 to 0.74 $\pm$ 0.11 ml), and bladder capacity (1.29 $\pm$ 0.12 to 0.84 $\pm$ 0.09 ml) were significantly inhibited compared to the control rats (P<0.01, P<0.05, P<0.05, respectively). During the second 20 min of LT exposure, Phase II, the detrusor overactivity patterns of control rats slowly disappeared. In the Phase II, the micturition parameters of CL 316243-treated rats did not alter. After returning to RT, the measured values of both groups immediately recovered to the baseline RT values.

### Interpretation of results

This study showed that treatment of  $\beta$ 3-ARs agonist, CL 316243 partially inhibited cold stress-induced detrusor overactivity that caused decreased voiding interval, micturition volume, and bladder capacity. It is well known that  $\beta$ 3-ARs agonist promotes and/or improves bladder storage functions. Therefore, this study suggested that  $\beta$ 3-ARs agonists might have a potential to treat for cold stress-exacerbated LUTS.

### Concluding message

The CL 316243-treated rats did not exhibit typical cold stress-induced detrusor overactivity. Therefore, pathways involving  $\beta$ 3-ARs mediated cold stress-induced detrusor overactivity.

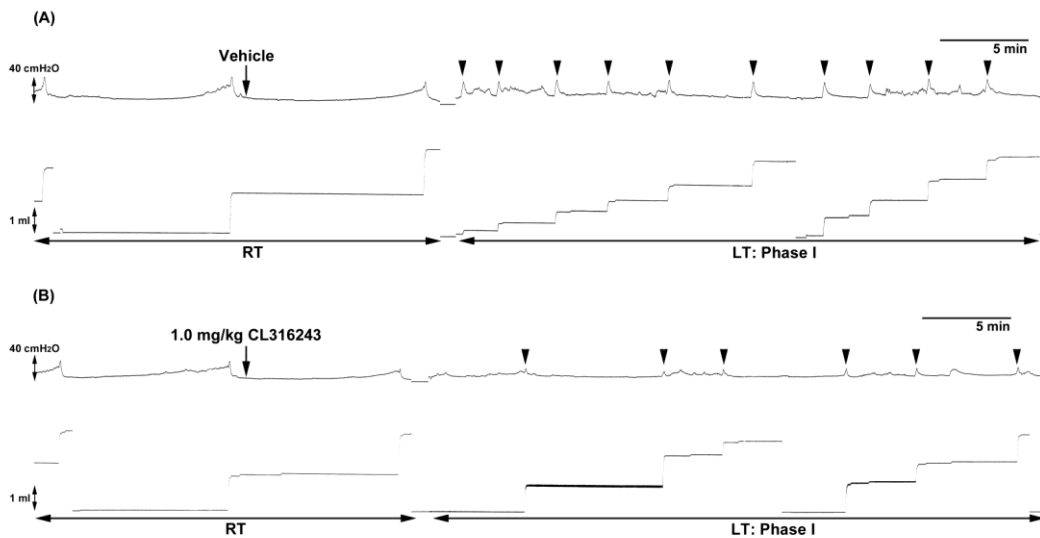


Figure. Micturition patterns affected by transferring from RT to LT. (A) Vehicle-treated control rats, (B) 1.0 mg/kg CL316243-treated rats. Arrowheads: micturition point during Phase I period under LT. □

### References

1. Imamura, et al. *Neurourol Urodyn* 27: 348-352, 2008.
2. Chen, et al. *Neurourol Urodyn* 29: 506-511, 2010
3. Chen, et al. *Neurourol Urodyn* 28: 251-256, 2009

### Disclosures

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