B3-ADRENERGIC RECEPTOR AGONIST MEDIATES COLD STRESS-INDUCED DETRUSOR OVERACTIVITY IN SPONTANEOUSLY HYPERTENSIVE RATS

Hypothesis / aims of study
Sudden change or continuous exposure to low environmental temperature, cold stress exacerbates lower urinary tract symptoms (LUTS) such as urinary urgency or frequency. We previously reported that the detrusor overactivity induced by cold stress was mediated with resiniferatoxin-sensitive C-fiber sensory nerve pathway (1) and the sympathetic hyperactivity (2) through transient receptor potential melastatin 8 channels (3). Also, the cold responses were inhibited with α1-adrenergic receptor (AR) antagonists. (2) In this study, we investigated to determine if β3-AR agonist, mirabegron could inhibit the cold stress-induced detrusor overactivity in spontaneously hypertensive rats (SHRs).

Study design, materials and methods
Fourteen female 10-weeks SHRs were maintained with a diet including 8%NaCl for 4 weeks. This study used mirabegron (Astellas Pharma Inc., Japan) as a β3-AR agonist. At 4 weeks after 8%NaCl-loading, cystometric investigations of the free-moving catheterized rats were performed at room temperature (RT, 27±2ºC). Following, the rats were intravenously injected with 1.0mg/kg mirabegron or vehicle (n=7, in each). After 5 min of treatment, the rats were gently and quickly transferred to the cold room for low temperature (LT, 4±2ºC) exposure, and then the micturition patterns were monitored for 40 min. After LT exposure, the rats were returned to RT (re-RT, 27±2ºC). Throughout the experiments, the following cystometric parameters were analyzed: basal pressure, maximum micturition pressure, voiding interval, micturition volume, residual volume, and bladder capacity. For analysis, the LT exposure was divided into Phase I and Phase II, each of which was 20 min.

Results
At RT, micturition patterns of mirabegron- and vehicle-treated control 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 (Figure A). In contrast, the cold stress-induced detrusor overactivity of the mirabegron-treated rats were partially inhibited during Phase I (Figure B). In the Phase I, the decreases of voiding interval (12.56±1.11 to 9.04±1.21 min) and micturition volume (2.16±0.30 to 1.50±0.22 ml) in the mirabegron-treated rats were significantly inhibited compared to the control rats (11.70±1.74 to 5.43±1.11 min; P<0.05, 1.90±0.36 to 0.85±0.23 ml; P<0.05, respectively). During the second 20 min of LT exposure, Phase II, the micturition parameters of both mirabegron- and vehicle-treated rats did not alter. After returning to RT, the detrusor overactivity patterns disappeared in the both groups; however, bladder capacity of the mirabegron-treated rats (2.68±0.35 ml) was significantly higher than that of the vehicle-treated rats (1.92±0.26 ml).

Interpretation of results
This study showed that treatment of β3-AR agonist, mirabegron partially inhibited cold stress-induced detrusor overactivity that caused decreases of voiding interval and micturition volume in the hypertensive rats. The treatment of mirabegron improved bladder capacity after return to RT.

Concluding message
The cold stress-induced detrusor overactivity in the mirabegron-treated SHRs was partially inhibited compared to the vehicle-treated control rats. Therefore, this study suggested that β3-AR agonists might have a potential to treat for cold stress-exacerbated LUTS.
Figure 1. Changes of micturition patterns of vehicle- (A) and mirabegron- (B) treated SHRs. After transfer to LT, the cold stress-induced detrusor overactivity of mirabegron-treated SHRs were partially inhibited compared to the control SHRs.

References

Disclosures
Funding: none Clinical Trial: No Subjects: ANIMAL Species: Rat Ethics Committee: The Animal Ethics Committee of Shinshu University (No. 230061)