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INCREASED SKIN TRPM8 BY ESTROGEN DEFICIENCY MAY INDUCE DETRUSOR OVERACTIVITY MEDIATED ALPHA1D-ADRENERGIC RECEPTORS TRIGGERED BY SUDDEN COLD STRESS

Hypothesis / aims of study

A sudden drop of temperature or serious cold sensation is empirically known to induce lower urinary tract symptoms (LUTS), including urgency, and urinary frequency. It was reported that cold stress significantly decreased voiding interval, micturition volume, and bladder capacity in conscious rats [1].The transient receptor potential channel melastatin member 8 (TRPM8) expressing on the skin partially mediated the micturition responses [2]. It was also reported that alpha 1-adrenergic receptor blockers prevented the decreases of voiding interval and bladder capacity [3]. In postmenopausal women, prevalence of LUTS are often developed by the cold stress. However, the mechanisms are not well known. In this study, we determined if alpha1D-adrenergic receptor blockers inhibited the cold stress-induced detrusor overactivity of ovariectomized rats, and expression levels of TRPM8 receptors on the skin were increased with the ovariectomy.

Study design, materials and methods

Five weeks prior to cystometric investigation, 12 female Sprague-Dawley (SD) rats at 30 old weeks were received bilateral ovariectomy (OVX), and divided into saline-administration and naftopidil-administration groups (n=6 in each). Six SD rats were received sham operation. Cystometric investigation was performed on conscious and free-moving rats at room temperature (RT, 28±2ºC) and low temperature (LT, 4±2ºC). Before transferring to LT, the ovariectomy-received rats were intravenously administrated with 1mg/kg naftopidil or saline, and sham-operated rats were administrated with saline. During the cystometric investigations, their micturition parameters were recorded. After the cystometric investigation, expression level of TRPM8 on the lump skin was estimated with real-time RT-PCR and immunohistochemistry. Statistical differences were determined by non-repeated measures ANOVA followed by the Scheffe's test. Differences with $p<0.05$ were considered significant.

Results

Body weights of the OVX rats significantly increased than that of the sham rats. Uteruses of OVX rats were significantly smaller than that of the sham rats. Estoradiol level in serum of the OVX rats was not detected. In room temperature condition, voiding interval (VI) and bladder capacity (BC) of the OVX rats were significantly lower than these of the sham rats (Table 1). After transferring to LT, the VI and BC of the sham and saline-administrated OVX rats significantly decreased. However, the VI and BC of naftopidil-administrated OVX rats did not decrease compared to the sham and saline-administrated OVX rats (Table 1). The TRPM8 mRNA expression level of the OVX rats (2.36±0.61) was significantly higher than that of the sham operated rats (0.83±0.12, $P<0.01$). While distribusion of TRPM8, and nerve fiver-marker S-100 in the OVX rats were similar to the sham rats, the TRPM8-positive areas of the OVX rats (0.0063±0.0011) was significantly higher than that of the sham rats (0.0031±0.0005, $P<0.01$, Figure 1).

Interpretation of results

Cold stress stimulates the skin TRPM8, and the skin TRPM8 is related to alpha 1D (naftopidil) mediated urinary frequency [3]. In this study, we showed that the expression level of TRPM8 in the OVX rats was significantly higher than that of the sham rats. The increased TRPM8 in the OVX may result in the alpha 1D mediated detrusor overactivity induced by cold stress. Further study will be needed to clarify the relationship between decrease of estrogen and increase of skin TRPM8.

Concluding message

The decrease of estrogen (menopose) may increase the skin TRPM8. This fact may result in the alpha 1D mediated detrusor overactivity triggered by sudden cold stress via increased skin TRPM8.

Table 1. Voiding interval and bladder capacity in each temperature condition

	Room temperature	Low temperature
Voiding Interval (min)		
Sham rats	4.85±0.54	2.97±0.56§
Saline-administrated OVX rats	3.11±0.43**	1.98±0.37§§
Naftopidil-administrated OVX rats	4.33±0.75**	4.70±0.91¶##
Bladder Capacity (ml)		
Sham rats	1.10±0.09	0.73±0.11§
Saline-administrated OVX rats	0.54±0.06**	0.39±0.07§§
Naftopidil-administrated OVX rats	0.78±0.15*	0.83±0.15¶#

*P<0.05, **P<0.01; compared to sham rats at RT condition.

§P<0.05, §§P<0.01; compared to RT condition in each group.

¶P<0.01; comapred to sham rats transferred from RT to LT condition.

#P<0.05, ##P<0.01; comapred to saline-administrated OVX rats transferred from RT to LT condition.

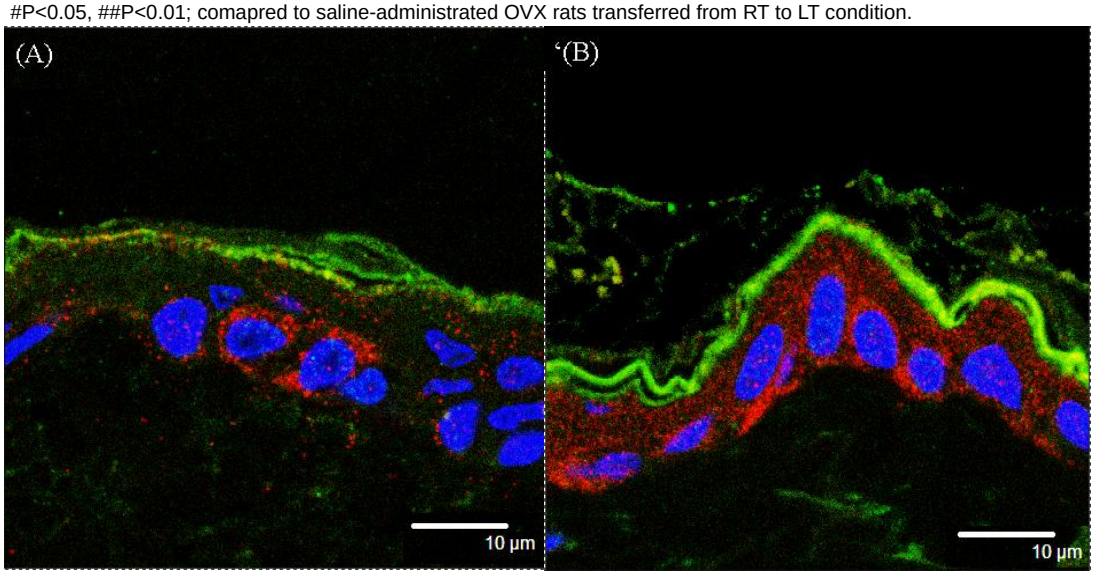

Figure 1. Expression of TRPM8 on the skin. (A) Sham rats, (B) OVX rats. Red: TRPM8 receptors; Green: S100-positive nerve fibers; Blue: nuclei.

References

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Disclosures

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