

論文審査の結果の要旨

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(論文審査の結果の要旨)

Previous studies showed that both cold stress (Imamura, NeuroUrol Urodyn, 2008) and menthol stimulation (Chen Z, NeuroUrol Urodyn, 2010) elicited detrusor overactivity in conscious rats. It is reported that transient receptor potential melastatin 8 (TRPM8) channels in skin and/or sensory neurons are activated by menthol and low temperature (<math><25\sim 28^{\circ}\text{C}</math>) stimulation (Mckemy DD, Nature, 2002; Reid G, Nature, 2001).

In this study, to investigate functional roles of transient receptor potential melastatin 8 (TRPM8) in the cold stress- and menthol spray-induced detrusor overactivity, we determined if TRPM8 channel antagonist could inhibit the both stimuli-induced responses.

Two days prior to cystometric investigation, the bladder of 10-week-old Spague-Dawley rats were cannulated. After 20 min of baseline cystometry period at room temperature (RT: $27\pm 2^{\circ}\text{C}$), the TRPM8 channel antagonist, N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)pi-perazine-1-carboxamide (BCTC), or vehicle, was administered through a jugular vein catheter.

1). A 90% menthol solution was sprayed onto rump to leg skin once every 5 min for 20 min, and then cystometric measurements were repeated. After a 30-min recovery period, the rats were intravenously administered $0.1\ \mu\text{mol}/\text{kg}$ BCTC. Five minutes later, they were again sprayed and cystometry recorded.

2). The cannulated rats were intravenously administered 0.001, 0.01, or $0.1\ \mu\text{mol}/\text{kg}$ BCTC. Five minutes later, they were exposed to low temperature (LT: $4\pm 2^{\circ}\text{C}$) for 20 min of cystometric measurements.

Results from these study:

1). The rats sprayed with menthol exhibited the decrease of the voiding interval, micturition volume, and bladder capacity. After treatment of BCTC, the rats did not show these decreases.

2). Both the BCTC-free and $0.001\ \mu\text{mol}/\text{kg}$ BCTC-treated rats exhibited cold stress-induced detrusor overactivity that characterized with decreases of voiding interval, micturition volume, and bladder capacity during LT exposure. However, the high dose, 0.01 and $0.1\ \mu\text{mol}/\text{kg}$ BCTC-treated rats partially inhibited the cold stress-induced detrusor overactivity.

3). TRPM8 channel antagonist, BCTC inhibited the detrusor overactivity induced by menthol-spray on the skin. BCTC also inhibited the cold stress-induced detrusor overactivity.

This study concluded that TRPM8 channels expressing within the skin mediate detrusor overactivity elicited by menthol spray and exposure to low temperature.

主査、副査は一致して本論文を学位論文として価値があるものと認めた。