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Honda M[1], Yoshimura N[2], Kawamoto B[1], Inoue S[1], Kobayashi N[1], Hikita K[1], Muraoka K[1], Saito M[3], Chancellor M[4], Sejima T[1], Takenaka A[1]

1. *Department of Urology, Tottori University Faculty of Medicine,* ***2.*** *Department of Urology, University of Pittsburgh School of Medicine,* ***3.*** *Department of Molecular Pharmacology, Tottori University Faculty of Medicine,* ***4.*** *Department of Urology, William Beaumont Hospital*

INHIBITORY EFFECTS OF INTRAVESICAL ADMINISTRATION OF SENSORY NEURON-SPECIFIC RECEPTOR AGONIST ON THE MICTURITION REFLEX IN RATS

Hypothesis / aims of study

A novel family of G-protein-coupled receptors has been identified in rat dorsal root ganglia and named as sensory neuron-specific receptors (SNSRs) (1). These receptors are expressed exclusively in a subset of small-diameter primary afferent neurons involved in transmission of nociceptive information (2). Recent study has demonstrated that intrathecal or intravenous administration of a SNSR1 agonist can inhibit the micturition reflex (3). However, it is unknown whether SNSR1 receptor activation in the bladder can locally affect the micturition reflex. Therefore, this study was performed to elucidate the urodynamic effects of intravesical administration of a SNSR1 agonist on the micturition reflex in urethane-anesthetized rats.

Study design, materials and methods

Twelve-week-old female Sprague-Dawley rats weighing 238 to 250 g were used. Rats were maintained under standard laboratory conditions with a 12-h light/12-h dark cycle and free access to food pellets and tap water. Rats were anesthetized with 2% isoflurane followed by urethane (1.2 g/kg subcutaneously). A midline abdominal incision was made, and a transvesical catheter (PE-60 polyethylene catheter) with a fire-flared tip was inserted into the dome of the bladder and secured with silk thread for bladder filling and pressure recording. A 3-way stopcock was connected to the transvesical catheter to monitor the bladder pressure. After transvesical catheter insertion, saline at a room temperature was continuously infused into the bladder for 2 hours at a rate of 0.04 ml per minute to record cystometrograms during a control period. After baseline cystometry, vehicle (saline) or bovine adrenal medulla 8-22 (BAM 8-22) (100, 300 and 1000 nM, n=8 per dose), a selective rat SNSR1 agonist, was instilled intravesically and changes in bladder activity were monitored. The experiments using BAM 8-22 (1000 nM) were also performed in rats pretreated with systemic capsaicin (n=8) to determine whether the effect of BAM 8-22 was mediated by capsaicin sensitive C-fiber afferent pathways. Capsaicin was administered to rats in a solution (20 mg/mL) given subcutaneously in divided doses on 2 consecutive days: 25 and 50 mg/kg on the first day and 50 mg/kg on the second day. Four days after the first administration of capsaicin, cystometry was performed. To evaluate the effectiveness of capsaicin pretreatment, an eye wipe test was performed. Cystometric parameters were recorded and compared before and after drug administration. All data values are expressed as the mean ± standard deviation. A one-way ANOVA followed by Dunnett's multiple comparison test was used for the statistical analysis between the vehicle and drug-treated rats. Student's paired *t*-test was used to compare cystometric variables before and after treatment, with $p < 0.05$ considered to indicate statistical significance.

Results

Intravesical administration of BAM 8-22 inhibited the micturition reflex as evidenced by increases in intercontraction interval, cystometric capacity, and threshold pressure. Intravesical administration of BAM 8-22 at 100, 300 and 1000 nM, (n=8 per dose) significantly increased intercontraction interval at doses of 300 nM or higher (101.2 ± 4.8%, 115.5 ± 8.7% and 119.4 ± 10.5% of the control value, respectively). Intravesical administration of BAM 8-22 at 100, 300 and 1000 nM also increased threshold pressure at doses of 300 nM or higher (5.83 ± 1.35 cmH_2O, 8.85 ± 2.16 cmH_2O and 8.96 ± 2.74 cmH_2O, respectively, from the control value of 5.28 ± 1.61 cmH_2O). However, there were no significant changes in basal pressure or maximum pressure at any doses tested. Intravesical administration of vehicle (saline) had no effect on the intercontraction interval, threshold pressure, basal pressure or maximum pressure. The inhibitory effect of intravesical administered BAM 8-22 (1000 nM, n=8) still occurred after capsaicin pretreatment (125 mg/kg, subcutaneously). Intravesical administration of BAM 8-22 in capsaicin pretreated rats increased intercontraction interval with a similar efficacy as in normal rats, and increased threshold pressure significantly. There was no significant change in basal pressure or maximum pressure. No responses were observed in the eye wiping test with capsaicin in these animals.

Interpretation of results

In urethane-anesthetized rats, local activation of SNSRs by intravesically administered BAM 8-22 has an inhibitory effect on the micturition reflex, as shown by the significant increases in intercontraction interval and threshold pressure. The main function of BAM 8-22 seems to be mediated by modulation of afferent activity, rather than efferent or smooth muscle activity, because BAM 8-22 induced increases in intercontraction interval and threshold pressure without affecting maximum pressure or basal pressure. In addition, because the intercontraction interval and threshold pressure in capsaicin-pretreated rats were significantly increased compared with normal rats, indicating that the effects of BAM 8-22 were mediated by capsaicin-resistant sensory nerves.

Concluding message

The results of our study indicate that SNSRs play an important role in the local modulation of bladder afferent activity in normal rats. Furthermore, these findings suggest that in urethane-anesthetized rats, activation of SNSRs can inhibit the micturition reflex via suppression of afferent pathways independent of capsaicin-sensitive C-fibers. These findings raise the possibility that SNSRs could be an effective target for treating bladder dysfunction such as overactive bladder via modulation of bladder afferent pathways.

References
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Disclosures
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