238

Honda M[1], Inoue S[1], Hinata N[1], Takenaka A[1], Chancellor M[2], Yoshimura N[3]
1. *Department of Urology, Tottori University Faculty of Medicine,* ***2.*** *Department of Urology, William Beaumont Hospital,* ***3.*** *Department of Urology, University of Pittsburgh School of Medicine*

EFFECTS OF SENSORY NEURON-SPECIFIC RECEPTOR AGONIST ON VOIDING FUNCTION IN A RAT MODEL OF CYSTITIS INDUCED BY CYCLOPHOSPHAMIDE

Hypothesis / aims of study

A novel family of G-protein-coupled receptors has been recently 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). However, it is unknown whether SNSRs have a role in various pathological conditions in the lower urinary tract, such as interstitial cystitis, bladder outlet obstruction, spinal cord injury. The aim of study is to elucidate the urodynamic effects of activation of SNSRs on cyclophosphamide (CYP)-induced overactive bladder in rats.

Study design, materials and methods

Adult female Sprague-Dawley rats weighing 235 to 258 g were used. Experimental and control rats were injected with CYP (200 mg/kg, intraperitoneally) or a corresponding volume of saline, respectively. Continuous cystometrograms were performed 48 hours after CYP or saline injection. CYP-treated and control rats were anesthetized with isoflurane followed by urethane (1.2 g/kg subcutaneously). Thereafter the abdomen was opened through a midline incision and a PE-60 polyethylene catheter connected to a pressure transducer and amplifier was implanted into the bladder through the bladder dome. This catheter was used to fill the bladder by continuous infusion of saline and record intravesical pressure during cystometry. After intravesical catheter insertion, saline was continuously infused for one hours at a rate of 0.04 ml per minute to record cystometrograms during a control period. A selective rat SNSR1 agonist, bovine adrenal medulla 8-22 (BAM 8-22) was then administered intravenously (10, 30 and 100 μg/kg, n=6 per dose) or intrathecally (0.03, 0.1 and 0.3 μg, n=6 per dose) and changes in bladder activity were monitored. Intravenous injections were made through a cannula (PE-10) inserted into the right jugular vein. Intrathecal administrations were made through a catheter (PE-10) implanted via an incision in the dura at the Th11 vertebra under isoflurane anesthesia 3 days before the experiments. The catheter was directed caudal in the spinal subarachnoid space and positioned at the level of the L6-S1 spinal cord. The volume of fluid in the catheter was kept constant at 6 μl. Single doses of drugs were then administered in a volume of 2 μl, followed by a 7 μl flush with saline. Cystometric parameters were recorded and compared before and after drug administration. All data values are expressed as the mean ± SE. Statistical significance was determined with one-way ANOVA with $p<0.05$ considered significant.

Results

CYP treatment induced a higher basal pressure and a shorter intercontraction interval compared with the control group. In control rats, intravenous or intrathecal administration of BAM 8-22 significantly increased intercontraction intervals in dose dependent fashion, but did not affect basal pressure at any doses tested. Intravenous administration of BAM 8-22 at 10, 30 and 100 μg/kg (n=6 per dose) significantly increased intercontraction intervals at doses of 30 and 100 μg/kg to 101.9 ± 2.6%, 126.6 ± 5.1% and 137.8 ± 6.3% of the control value, respectively (at 30 and 100 μg/kg, $p <0.01$) in the CYP-treated rats. Intrathecal administration of BAM 8-22 at 0.03, 0.1 and 0.3 μg (n=6 per dose) also significantly increased intercontraction intervals at doses of 0.1 and 0.3 μg to 101.8 ± 2.8%, 124.8 ± 5.3%, 142.4 ± 6.6% of the control value, respectively (at 0.1 and 0.3 μg, $p <0.01$) in the CYP-treated rats. Intravenous or intrathecal administration of BAM 8-22 did not changes basal pressure or maximum pressure at any doses tested in the CYP-treated rats.

Interpretation of results

In the present study, a selective rat SNSR1 agonist, BAM 8-22 given intraveously or intrathecally to the CYP-treated rats, increased intercontraction intervals. These findings indicate that activation of SNSRs can improve CYP-induced overactive bladder. 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 intervals without affecting maximum pressure or basal pressure. CYP has been used as a chemical agent to induce cystitis and bladder overactivity in rats. The metabolite of CYP, acrolein, is eliminated in the urine, thereafter, stimulating capsaicin-sensitive bladder afferents, and inducing neurogenic inflammation and bladder overactivity (3). A previous study reported that SNSR-positive neurons were mainly found in the non-peptidergic, isolectin-B4-postive C-fiber population of rat dorsal root ganglion neuron (1). Therefore, it is possible that the effects of BAM 8-22 are mediated by suppression of capsaicin-sensitive C-fiber activity.

Concluding message

The results in this study indicate that activation of SNSRs can ameliorate CYP-induced overactive bladder via suppression of capsaicin sensitive C-fiber afferent pathways in rats.

Thus, SNSRs could be an effective target for the treatment of bladder dysfunctions such as overactive bladder and interstitial cystitis/bladder pain syndrome, for which C-fiber afferent hyperexcitability has been proposed to be an important pathophysiological basis.

References

1. Lembo PM, Grazzini E, Groblewski T, O'Donnell D, Roy MO, Zhang J et al. Proenkephalin A gene products activate a new family of sensory neuron-specific GPCRs. Nat Neurosci 2002; 5(3):201-219.
2. Grazzini E, Puma C, Roy MO, Yu XH, O'Donnell D, Schmidt R et al. Sensory neuron-specific receptor activation elicits central and peripheral nociceptive effects in rats. Proc Natl Acad Sci USA 2004; 101(18):7175-7180.

3. Masuda H, Ichiyanagi N, Yokoyama M, Sakai Y, Kihara K, Chancellor MB, deGroat WC et al. Muscarinic receptor activation in the lumbosacral spinal cord ameliorates bladder irritation in rat cystitis models. BJU Int 2009; 104(10):1531-1537.

Disclosures

Funding: NIH DK088836 and DOD PR110326 **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Institutional Animal Care and Use Committees of University of Pittsburgh and Tottori University