EFFECTS OF INTRAVESICAL ADMINISTRATION OF SENSORY NEURON-SPECIFIC RECEPTOR AGONIST ON VOIDING FUNCTION IN RATS WITH CYCLOPHOSPHAMIDE INDUCED-CYSTITIS

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). However, it is unknown whether SNSRs have a role in various pathological conditions in the lower urinary tract, such as painful bladder syndrome/interstitial cystitis, bladder outlet obstruction and, spinal cord injury. Therefore, this study was performed to elucidate the urodynamic effects of intravesical administration of a SNSR1 agonist on cyclophosphamide (CYP)-induced bladder overactivity in rats.

Study design, materials and methods

Adult female Sprague-Dawley rats weighing 230 to 246 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 isoflurane (2%) and received intraperitoneal injections of CYP to produce urinary bladder inflammation. 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 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) (300, 1000 and 3000 nM, n=6 per dose), a selective rat SNSR1 agonist, was instilled intravesically and changes in bladder activity were monitored. Cystometric parameters were recorded and compared before and after drug administration. All data values are expressed as the mean ± standard deviation. Student’s paired t-test was used to compare cystometric variables before and after the treatment, with p <0.05 considered to indicate statistical significance.

Results

CYP treatment induced a higher basal pressure and a shorter intercontraction interval compared with the control group. Intravesical administration of BAM 8-22 inhibited the micturition reflex as evidenced by increases in intercontraction intervals. Intravesical administration of BAM 8-22 at 300, 1000 and 3000 nM (n=6 per dose) significantly increased intercontraction intervals at doses of 1000 and 3000 nM to 98.6 ± 5.8%, 115.6 ± 7.2% and 120.5 ± 7.6% of the control value, respectively (at 1000 and 3000 nM, p <0.05) in CYP-treated rats. However, intravesical administration of BAM 8-22 did not changes basal pressure or maximum pressure at any doses tested in the CYP-treated rats. Intravesical administration of vehicle (saline) had no effects on the intercontraction interval, threshold pressure, basal pressure or maximum pressure.

Interpretation of results

In the present study, a selective rat SNSR1 agonist, BAM 8-22 given intravesically to the CYP-treated rats, increased intercontraction intervals. These findings indicate that activation of SNSRs can improve CYP-induced bladder overactivity. 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 urine, thereby 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-positive C-fiber population of rat dorsal root ganglion neurons (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 of our study indicate that activation of SNSRs can ameliorate CYP-induced bladder overactivity 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 painful bladder syndrome/interstitial cystitis, for which C-fiber afferent hyperexcitability has been proposed to be an important pathophysiological basis.

References

2. Chen T, Cai Q, Hong Y. Intrathecal sensory neuron-specific receptor agonists bovine adrenal medulla 8-22 and (Tyr6)-gamma2-MSH-6-12 inhibit formalin-evoked nociception and neuronal Fos-like immunoreactivity in the spinal cord of the rat. Neuroscience 2006; 141:965-975.

Disclosures

Funding: None Clinical Trial: No Subjects: ANIMAL Species: Rat Ethics Committee: Institutional Animal Care and Use Committees of University of Pittsburgh and Tottori University