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SOMATOSTATIN RECEPTOR SUBTYPE 4-MEDIATED REGULATION OF MICTURITION REFLEX IN URETHANE-ANESTHETIZED RATS

Hypothesis / aims of study

Somatostatin is synthesized and stored as 14 and 28 amino acid peptides in capsaicin-sensitive, transient receptor potential vanilloid 1 receptor (TRPV1)-expressing afferents (1). Somatostatin binds to G-protein-coupled membrane receptors (sst_1-sst_5) (1). Recent studies have demonstrated that somatostatin has an important role in neuromodulations such as pain control, presumably via somatostatin receptor subtype 4 (sst_4) (1, 2). However, it is not known whether sst_4 has a role in the control of the micturition reflex. The therapeutic value of native somatostatin is limited by its broad range of effects, mediated by five different receptor subtypes and its short plasma half life. However, potent and stable somatostatin receptor agonists acting selectively on sst_4 receptors have been synthesized and investigated. The aim of this study is to elucidate the effects of activation of sst_4 on the micturition reflex in rats.

Study design, materials and methods

Adult female Sprague-Dawley rats weighing 242 to 265 g were used. 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 2 hours at a rate of 0.04 ml per minute to record cystometrograms during a control period. An sst_4 selective agonist, NNC 26-9100 (10, 30, 100 and 300 μg/kg, n=6 per dose) was then administered intravenously and changes in bladder activity were monitored. Intravenous injections were made through a cannula (PE-10) inserted into the right jugular vein. In another group of animals, NNC 26-9100 (300 μg/kg, n=6) was administered intravenously after pretreatment with subcutaneous capsaicin (125 mg/kg) 4 days before the experiments to determine whether the effect of NNC 26-9100 was mediated by capsaicin sensitive C-fiber afferent pathways. 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

Intravenous administration of NNC 26-9100 at 10, 30, 100 and 300 μg/kg increased intercontraction intervals at doses of 30 μg/kg or higher in dose dependent fashion to 100.8 ± 1.1%, 116.4 ± 9.1%, 137.4 ± 7.5% and 165.1 ± 17.9% of the control value, respectively (at 30, 100 and 300 μg/kg, $p<0.01$). These inhibitory effects were seen immediately after administration and returned to the pre-control level within 70 minutes. Intravenous administration of NNC 26-9100 at 10, 30, 100 and 300 μg/kg also increased threshold pressure at doses of 30 μg/kg or higher in dose dependent fashion to 7.16 ± 1.23 cmH_2O, 10.49 ± 1.41 cmH_2O, 12.61 ± 1.17 cmH_2O and 17.34 ± 1.95 cmH_2O, respectively (at 30, 100 and 300 μg/kg, $p<0.01$). There were no significant changes in basal pressure, maximum pressure or post void residual at any doses tested. However, NNC 26-9100-induced increases in intercontraction intervals and threshold pressure were not seen in rats with C-fiber desensitization induced by capsaicin pretreatment.

Interpretation of results

In the present study, an sst_4 selective agonist, NNC 26-9100, given intravenously to urethane-anesthetized rats, increased intercontraction intervals and threshold pressure. These findings indicate that NNC 26-9100 has an inhibitory action on the micturition reflex in urethane-anesthetized rats. The main function of NNC 26-9100 seems to be mediated by modulation of afferent activity because NNC 26-9100 induced increases in intercontraction intervals and threshold pressure without affecting maximum pressure or basal pressure. In addition, because, in rats with capsaicin pretreatment, the inhibitory effects of NNC 26-9100 were not induced, indicating that the effects of NNC 26-9100 were mediated by capsaicin sensitive C-fiber afferent pathways. Overall, it is likely that afferent impulse transmission is attenuated following activation of sst_4 receptors expressed in bladder C-fiber afferent pathways, resulting in increases in threshold pressure for activation of the micturition reflex and intercontraction intervals.

Concluding message

The results in this study indicate that activation of sst_4 receptors can inhibit the micturition reflex via suppression of capsaicin sensitive C-fiber afferent pathways in rats. Thus, the somatostatin sst_4 receptor could be a potential target for the treatment of bladder dysfunction such as overactive bladder.

References

1. Eur J Pharmacol (2006) 539; 71-75.
2. Br J Pharmacol (2006) 149; 405-415.

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