Improving voiding efficiency in the SCI rat by a 5-HT$_7$ serotonin receptor agonist

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Introduction

With spinal cord injury (SCI) rostral to the lumbosacral level, the most common constellation of lower urinary tract symptoms is loss of voluntary control of micturition, bladder hyperactivity mediated by spinal reflex pathways, and hyperreflexia of the external urethral sphincter (EUS), with loss of bladder and EUS coordination (bladder-sphincter dyssynergia).

Spinal cord neuronal 5-HT$_7$ receptors, and likewise many 5-HT-containing terminals, are found both in the dorsal horn and in the lumbar dorsolateral nucleus (Onuf’s nucleus) driving the external urethral sphincter (EUS) and external anal sphincter. In our previous study, we found that 5-HT$_7$ receptors have a positive role in micturition in SCI rats. There are no reports on the role of intravenous 5-HT$_7$ receptor agonist or antagonist in the reflex control of micturition in SCI rats. Thus, the present experiments were carried out to investigate the role of 5-HT$_7$ receptors in micturition using the selective 5-HT$_7$ receptor antagonist SB269970 and the selective 5-HT$_7$ receptor agonist LP44, on the ‘micturition reflex’ evoked by distension caused by infusing saline into the bladder in anaesthetized female SCI rats.

Materials and methods

A total of 16 adult female Sprague-Dawley rats initially weighing 250 to 275 g were used. SCI was produced in 8 rats by transection at the T$_6$ level. The cystometric study occurred 8-12 weeks post-transection.

A polyethylene catheter (PE-50) was placed in the left jugular vein for i.v. drug administration. The urinary bladder was exposed via a midline abdominal incision, a polyethylene catheter (PE-90) with a flared end was inserted through the bladder dome. The cystometric variables analyzed were micturition volume (voided volume), residual volume (volume remaining in the bladder after voiding), bladder capacity (micturition volume plus residual volume), peak intravesical pressure, and the number of high-frequency oscillations (HFOs) of the cystometry during the voiding.

Vehicle or 5-HT$_7$ receptor agonist LP44 was administered (0.003-0.3 mg/kg i.v.) Successive doses were administered cumulatively at short intervals (20 minutes maximum). The 5-HT$_7$ receptor antagonist SB-269970 was administered at 0.1 mg/kg i.v. after a dose-response study for the 5-HT$_7$ receptor agonist LP44.

Results

Fig. 1: Dose-response curves for the effects of LP44 on cystometric variables in chronic SCI rats. V = vehicle.

Fig. 2: Dose-response curves for the effects of LP44 on cystometric variables in spinally intact rats. V = vehicle.

Fig. 3: Effect of increasing doses of LP44 and finally of 0.1 mg/kg SB269970 on HFOs activity in SCI rats. A clear dose-related response of intravenous administration LP44 by increasing of the number of small oscillation per micturition and reversed by SB269970 are evident.

Conclusions

The present results have identified a major physiological function for the 5-HT$_7$ receptors, that of the control of reflex-induced bladder contraction, at least in the SCI rat. 5-HT$_7$ receptor agonist improves the bladder voiding contraction, and promotes periodic EUS activity, thereby improving voiding efficiency. In addition, this study adds to the growing evidence of the importance of the 5-HT$_7$ in the control of micturition reflex. Whether or not these results may have implications for the future treatment of voiding dysfunction in SCI patients remains to be studied.

Literature cited


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