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THERAPEUTIC EFFECTS OF ENDOTHELIN RECEPTOR ON BLADDER OVERACTIVITY IN RATS WITH CHRONIC SPINAL CORD INJURY

Hypothesis / aims of study

It has been demonstrated that hyperexcitability of C-fiber bladder afferent pathways is involved in the emergence of overactive bladder in various pathological conditions including spinal cord injury[1]. We previously reported that activation of endothelin-A (ET_A) receptors in capsaicin-sensitive C-fiber afferents in the bladder can induce detrusor overactivity in rats[2]. Thus, we hypothesized that inhibition of bladder ET_A receptors can suppress bladder overactivity mediated by C-fiber hyperexcitability. Therefore, this study was undertaken to examine the effects of suppression of endothelin receptors on bladder function and ET-1 levels in the bladder in rats with chronic spinal cord injury (SCI).

Study design, materials and methods

Female Sprague-Dawley rats were used in this study. Awake cystometrograms were performed 4 weeks after SCI induced by spinal cord transection at the Th8-9 vertebral level. Saline was infused at a rate of 0.08 ml/min to elicit bladder contractions. SCI rats exhibited non-voiding contractions (NVCs) before micturition and insufficient voiding.
After every bladder contraction, infusion was stopped and post-void residual volume (RV) was measured. Following parameters were evaluated before and after intravenous (i.v.) injection of ABT-627, an ET_A receptor antagonist, or A-192621, an ET_B receptor antagonist; mean amplitudes of non-voiding contractions (NVCs), the number of NVCs, voided volume, voiding efficiency, and micturition pressure. Cystometry was also performed in spinal cord intact animals to examine the effects of ET antagonists on normal micturition. In addition, the protein and mRNA levels of ET-1 in the bladder from spinal cord intact rats and SCI rats were also measured using enzyme-linked immunosorbent assay (ELISA) and quantitative real–time polemerase chain reaction.

Results

In SCI rats, ABT-627 (1 mg/kg, i.v.), but not A-192621 (10 mg/kg, i.v.), significantly decreased the amplitudes of NVCs from 18.5 ± 2.0 cmH_2O to 13.3 ± 1.3 cmH_2O ($P < 0.01$, n=6) and the number of NVCs from 4.4 ± 0.7 to 2.6 ± 0.6 ($P < 0.01$, n=6). There were no significant changes in pressure threshold, maximum voiding pressure, voided volume or voiding efficiency after administration of ABT-627 or A-192621. In addition, neither ABT-627 nor A-192621 affected cystometric parameters in spinal intact rats. ELISA analysis for ET-1 showed significantly elevated protein concentrations in SCI rats compared with spinal cord intact rats (2.60 ± 0.07 vs. 2.08 ± 0.07 pg/mg protein: $p < 0.01$). Significant upregulation of the ET-1 mRNA was also noted in bladders from SCI rats compared with spinal cord intact rats ($p < 0.05$).

Interpretation of results

The protein and mRNA levels of ET-1 in the bladder are significantly increased in chronic SCI rats compared with spinal intact rats. Inhibition of ET_A receptors, but not ET_B receptors suppressed bladder overactivity as evidenced by a reduction in the number and mean amplitude of NVCs in chronic SCI rats, while ET_A receptor inhibition had no effects on the normal micturition reflex.

Concluding message

These results suggest that upregulation of ET-1 is involved in the mechanism inducing C fiber-mediated bladder overactivity in chronic SCI rats and that suppression of ET_A receptor can reduce detrusor overactitiy as shown by suppression of NVCs in SCI rats. Thus, ET_A receptor antagonists could be effective for the treatment of neurogenic detrusor overactivity in pathological conditions such as SCI.

References

1. J.Urol 168(5); 1897-1913
2. J.Urol 172(4 Pt 1); 1533-1537

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