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THE ROLE OF PERIPHERAL AND SPINAL ENDOTHELIN MECHANISMS IN THE MICTURITION REFLEX IN RATS

Aims of Study

Endothelin-1 (ET-1) is a potent, endogenous vasoactive peptide whose effects are mediated by two G-protein-coupled receptors, the endothelin-A (ETA) and the endothelin-B (ETB) receptors. In the lower urinary tract, endothelins can induce prolonged contractile responses in bladder and urethral smooth muscles from various species. However, the role of endothelin-mediated mechanisms in the neural control of the micturition reflex has not been elucidated although it has been reported that an activation of endothelin receptors in peripheral sensory nerves can induce direct nociceptive effects in somatic pathways. Thus in this study we aimed to clarify the effects of endothelin receptor activation in the bladder and the spinal cord on the micturition reflex in rats.

Methods

Adult female Spraque-Dawley rats were used. Under urethane anesthesia, cystometry was performed using a catheter inserted into the bladder through the bladder dome via a midline abdominal incision. Saline was infused at a rate of 0.04 ml/min to elicit repetitive bladder contractions. First, the effects of an activation of peripheral endothelin receptors on bladder activity were examined by intravesical infusion of ET-1 in normal rats and rats pre-treated with capsaicin (125mg/kg, s.c.) 4 days before the experiments. Secondly, the effects of an activation of endothelin receptors in the spinal cord were examined by intrathecal administration of ET-1 via implanted intrathecal catheters at the level of L6-S1 spinal cord. Effects of intravenous (i.v.) injection of ABT-627, a selective ETA receptor antagonist, on changes in bladder activity induced by either intravesical or intrathecal ET-1 administration were also investigated.

Results

Continuous instillation of ET-1 solution into the bladder at concentrations of 0.1-10 nmol/ml induced detrusor overactivity evidenced by dose-dependent decreases to 75-34% of the control value in intercontraction intervals (ICI). While ABT-627 (i.v.) had no effects on the normal micturition reflex during saline injection into the bladder, ET-1-induced detrusor overactivity was inhibited by an injection of ABT-627 (0.1 mg/kg, i.v.). ET-1-induced detrusor overactivity was also suppressed by the capsaicin pre-treatment, which induced desensitization of capsaicin-sensitive C-fiber afferents. However, in contract to the facilitatory effects by intravesical ET-1 infusion, intrathecal injection of ET-1 (0.1-10 pmol) increased the ICI dose-dependently to 90-220% of the control value, and ET-1 at a dose of 10 pmol induced urinary retention. These inhibitory effects of intrathecal ET-1 application were inhibited by intravenous injection of ABT-627 at a dose of 10 mg/kg.

Conclusions

These results indicate that the endothelin-mediated neural control of the micturition reflex has dual actions depending on the location of receptor activation. Activation of ETA receptors in capsaicin-sensitive C-fiber afferents located in the bladder can induce detrusor overactivity while ETA receptor activation in the lumbosacral spinal cord can inhibit the micturition reflex. Therefore, inhibition of peripheral endothelin receptors or stimulation of spinal endothelin receptors could be a new modality for the treatment of detrusor overactivity and/or bladder pain. In addition, rats treated with intravesical ET-1 could be a good animal model for the study of detrusor overactivity.