

ACTIVATION OF PROTEASE-ACTIVATED RECEPTOR 2 INDUCES URINARY FREQUENCY VIA C-FIBER AFFERENT PATHWAYS IN RATS

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INTRODUCTION AND OBJECTIVE: One of the major mechanisms inducing bladder inflammation including interstitial cystitis involves the deployment of immune cells, such as mast cells in the bladder. It is known that trypsin or tryptase that are released by mast cells can activate the protease-activated receptor 2 (PAR-2) expressed in afferent nerves, and that activation of PAR-2 can stimulate the release of substance P and calcitonin gene-related peptide in peripheral tissues. PAR-2 activation can also reportedly induce bladder overactivity in rats. Thus, we sought to elucidate the detailed mechanisms underlying PAR-2-induced bladder overactivity, such as the involvement of C-fiber afferent pathways and the production of prostaglandins

METHODS: Continuous cystometry (0.04 ml/min) was performed in adult female Sprague-Dawley rats under urethane anesthesia in order to examine the effect of intravesical infusion with 10^{-4} M SLIGRL-NH₂, a PAR-2 agonist. The effects of C-fiber desensitization by capsaicin pretreatment (125 mg/kg s.c., 4 days before cystometry) and indomethacin (10 mg/kg s.c. prior to intravesical application with SLIGRL-NH₂) were also examined on urinary frequency induced by SLIGRL-NH₂.

RESULTS: Intravesical infusion with 10^{-4} M SLIGRL-NH₂ alone had no effects on any cystometric parameters. However, following intravesical pretreatment with protamine sulfate (10 mg/ml) to increase urothelial permeability, 10^{-4} M SLIGRL-NH₂ significantly decreased intercontraction intervals (21.2±3.0 to 13.2±1.5 min), micturition volumes (1.03±0.1 to 0.58±0.08 ml), and threshold pressure (12.7±1.9 to 9.3±0.7 cmH₂O). These excitatory effects of PAR-2 activation were suppressed by capsaicin pretreatment or indomethacin application

CONCLUSIONS: These findings suggest that stimulation of PAR-2 can induce bladder overactivity mediated by activation of C-fiber afferents and the production of prostaglandins. Thus, PAR-2, which is activated by proteases released from inflammatory cells, may contribute to urinary frequency and bladder pain in chronic bladder inflammation including interstitial cystitis.

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