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EFFECTS OF SUPLATAST TOSILATE, AN ANTIALLERGY AGENT , ON BLADDER PAIN RESPONSE OF CONSCIOUS RAT MODEL OF HCL-INDUCED CHRONIC CYSTITIS.

Hypothesis / aims of study
The inactivation of C-fibers innervating an inflamed bladder may constitute a useful strategy for treating patients with chronic inflammatory bladder conditions, including interstitial cystitis (IC) [1]. Suplatast tosilate (IPD-1151T) has been reported to improve symptoms including bladder dysfunction in patients with IC [2]. A rat model of HCl-induced cystitis displays a histologic appearance that mimics that seen in humans with IC [3]. The present study was carried out on rats with HCl-induced chronic cystitis to elucidate the effects of orally administered IPD-1151T on their bladder pain response measured by determining the bladder sensory nerve threshold via nerve-specific electric stimulation with a neurometer.

Study design, materials and methods
Chronic cystitis was induced by the intravesical application of 0.4 N HCl to the bladder of female Sprague-Dawley rats under pentobarbital anesthesia (50 mg/kg, i.p.). One day later, IPD-1151T was administered orally to the rats once daily for 7 consecutive days. One day after the last administration, the animals (alert) were examined for bladder sensory nervous system with a neurometer. Desensitization of C-fiber afferent pathways was done in some animals by pretreating them with capsaicin (total 125 mg/kg, subcutaneously, given in divided doses over 2 consecutive days) starting 4 days before the current stimulus threshold (CPT) measurement.
Neurometer measurement of the current-stimulus threshold of the bladder sensory nervous systems in rats : A 4Fr balloon catheter equipped with a small electrode line was inserted via the urethra into the bladder under diethylether inhalation anesthesia. The balloon in the bladder was made to expand with physiologic saline (0.2 mL infusion), allowing the small electrode to make contact with the bladder wall. Each rat was kept in a special arresting cage for observation of sharp pain, which was measured after the animal had awakened from the anesthesia. Stimulation of the bladder sensory nervous system with each of 3 sine-wave pulses (at 2000, 250, and 5 Hz) was applied to the bladder wall and urethra of the conscious rats by using the CPT/C neurometer in the animal response test mode (manual mode testing). The minimum intensity (mA) at which each rat vocalized or was hardly startled was taken as the current stimulus threshold, at which point the stimulus was immediately stopped. A total of 6 measurements was performed at intervals of 10 minutes. The current stimulus threshold data were reported as the means of the values obtained from 4 consecutive measurements (third, fourth, fifth and sixth) after the second measurement.

Results
HCl-induced chronic cystitis significantly decreased the threshold for pain (in mA) at 5 Hz (median value, 46.3 mA; range, 25.0-117.5) compared with that for the sham rats (median value, 108.8 mA; range, 47.5-232.8), but did not change that at 2000 or 250 Hz. IPD-1151T at a dose of 100 mg/kg (median value, 81.4 mA; range, 50.0-170.0) significantly suppressed the decrease in the threshold at 5 Hz in the chronic cystitis rats, but did not affect the threshold at 2000 or 250 Hz. Treatment with capsaicin significantly increased the threshold at 5 Hz (median value, 172.5 mA; range, 100.0-242.8) compared with that for the chronic cystitis rats.

Interpretation of results
IPD-1151T suppressed bladder sensory nerve dysfunction in this HCl-induced chronic cystitis model.

Concluding message
Orally administered IPD-1151T improved HCl-induced bladder pain responses, possibly due to lowering the sensitivity of C-fibers. These results support the clinical application of IPD-1151T for the treatment of interstitial cystitis and bladder pain syndrome.

References
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