

LOCAL APPLICATION WITH SUPLATAST TOSILATE IMPROVES BLADDER DYSFUNCTION AND SUPPRESSES AFFERENT NERVE ACTIVITY IN CHEMICAL-INDUCED CYSTITIS RATS

Hypothesis / aims of study

Interstitial cystitis (IC) is characterized by urinary frequency, urgency, and pain. Although the etiology has not been fully elucidated and the efficient therapy has not been found yet, suplatast tosilate (IPD-1151T) has been shown to improve the symptoms of patients with IC. This was supported by our previous observation in that IPD-1151T given orally for 7 days improved bladder dysfunction in a rat model of cystitis induced by intravesical application of hydrochloric acid (HCl). Since IPD-1151T is secreted in urine after oral treatment, it is important to know the local effect of this compound on bladder. We here investigated IPD-1151T given intravesically on bladder dysfunction and afferent nerve activity in HCl-induced cystitis rats.

Study design, materials and methods

(1) Induction of cystitis

Female Sprague-Dawley rats were intravesically applied with 0.4 N HCl into the bladder under pentobarbital anesthesia (50 mg/kg i.p.). Eight days later, continuous cystometry and recording of afferent nerve activity were performed under urethane anesthesia (1.0 g/kg i.p.).

(2) Continuous cystometry

Continuous cystometry was performed at the infusion rate of 5.0 mL/hr under urethane anesthesia. Following intravesical infusion with saline, the infused solution was switched to the test solution (saline or IPD-1151T $1\text{-}25\times 10^{-5}$ M). Intercontraction intervals, micturition volume, and intravesical pressures were evaluated in each group.

(3) Recording of afferent nerve activity

A platinum bipolar electrode was attached to the left pelvic nerve. The central side of the pelvic nerve was cut to eliminate interference by efferent action potential. The afferent nerve activity was recorded during the filling phase of the bladder induced by intravesical infusion of saline or the IPD-1151T $1\text{-}25\times 10^{-5}$ M. The number of action potential spikes per the filling phase was evaluated in each group.

Results

(1) Bladder functions

HCl-induced cystitis rats showed urinary frequency that was characterized by the shortened intercontraction intervals and the decreased micturition volume. Intravesical treatment with IPD-1151T prolonged the intercontraction intervals and increased the micturition volume in a dose-dependent manner, while showed no influence on any cystometric parameters in sham rats.

(2) Afferent nerve activity

The number of action potential spikes was significantly higher in cystitis rats (21639 ± 5934 spikes) than that in sham rats (668 ± 240 spikes). Intravesical treatment with IPD-1151T dose-dependently decreased the number of action potential spikes in cystitis rats.

Interpretation of results

These findings indicate that IPD-1151T can locally effect on voiding function and afferent nerves in the bladder of cystitis rats. Since afferent nerve activity importantly contributes to micturition reflex, the suppressed afferent nerve activity might lead to an attenuated hypervoicing in IPD-1151T-treated cystitis rats.

Concluding message

IPD-1151T excreted in urine might, at least partly, contribute to the efficacy in the treatment of patients with IC, because IPD-1151T concentration used in this study is comparable to that observed in the urine after oral treatment.

FUNDING: NONE

DISCLOSURES: NONE

ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by the Guidelines on Experimental Animals at Taiho Pharmaceutical Co., Ltd.