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INTRAVESICAL APPLICATION OF REBAMIPIDE SUPPRESSES BLADDER INFLAMMATION AND OVERACTIVITY IN A RAT MODEL

Hypothesis / aims of study

Oral rebamipide has been used for treatment of gastritis and ulcer disease. Local application of rebamipide is effective treatment for the tissue injuries in the colon, lungs, kidneys, liver, and cornea in animal models, and it was recently approved for treating dry eye in Japan. Because the mechanism of action of rebamipide includes suppression of inflammation, inhibition of free radicals, and acceleration of wound healing, local administration of rebamipide may suppress bladder inflammation. Thus, we investigated the effects of intravesical application of rebamipide on bladder overactivity and inflammation using a chemically induced rat cystitis model.

Study design, materials and methods

Female Sprague-Dawley rats (230-260g) were injected with cyclophosphamide (CYP; 150 mg/kg) into the peritoneum under isoflurane anesthesia. Thereafter, 300 μL of 10 mM rebamipide was administered to the bladder, and the animals were kept in a supine position for 1 h under anesthesia. Control rats were injected with saline into the peritoneum and vehicle (10% DMSO in saline) was administered to the bladder. (1) The rats were placed in metabolic cages overnight for 12 h one day after rebamipide injection to evaluate changes in voiding behavior. Continuous cystometrograms in a conscious condition were also obtained 48 h after formalin treatment to measure intercontraction intervals (ICI) of the voiding reflex. (2) The bladder was harvested at 48 h, stained with hematoxylin-eosin, and inflammation was graded according to the following scale: 0, no evidence of inflammatory infiltration or interstitial edema; 1, mild (few inflammatory cell infiltrates and little or no interstitial edema); 2, moderate (moderate amount of inflammatory cell infiltrates and moderate interstitial edema); 3, severe (diffuse presence of a large amount of inflammatory cell infiltrates and severe interstitial edema). (3) Proinflammatory cytokines IL-6 and IL-1β were measured by enzyme-linked immunosorbent assay. All values are expressed as mean ± standard deviation. Two sided paired t-test was used and p values < 0.05 were considered statistically significant.

Results

(1) In the metabolic cage study, the average micturition volume decreased significantly in CYP injected rats (0.23 ± 0.04 mL) compared to vehicle-treated control rats (0.38 ± 0.03 mL). The decrease in micturition volume was not significant in the rebamipide-treated rats following CYP injection (0.31 ± 0.03 mL). In cystometry, the average ICI was significantly shorter in CYP-injected rats (9.2 ± 0.7 min) than that in the control (21.6 ± 3.1 min), but not in rebamipide-treated rats (16.3 ± 3.3 min) (Fig. 1). (2) Inflammatory changes, including submucosal edema and inflammatory cell infiltration, were observed in the bladder of CYP-injected rats, whereas inflammation of the bladder was reduced in the rebamipide-treated rats (Fig. 2). Mean inflammation scores were 0 ± 0, 2.5 ± 0.3, and 1.7 ± 0.3, respectively. (3) IL-6 in the bladder of CYP-injected rats increased by 4-fold compared to that in the control, whereas no difference was observed in rebamipide-treated rats. IL-1β also increased significantly by 18-fold in CYP-injected rats and 9-fold in CYP + rebamipide-treated rats (Fig. 3).

Interpretation of results

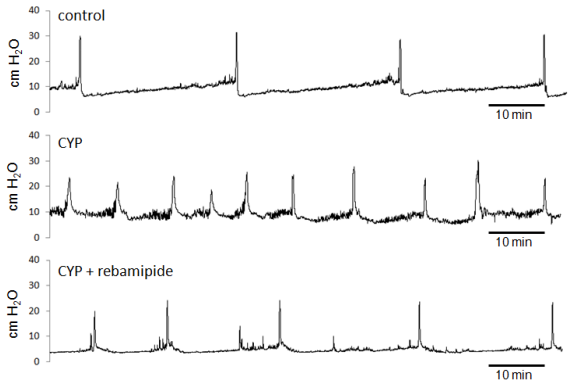
CYP administered into the peritoneum is transformed to its metabolite, acrolein, which is excreted in urine and injures the urinary tract. Inflammation, as evidenced by the increase in pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6, and multi-morphological inflammatory cell infiltration were observed in the bladder of CYP-treated rats. Physiologically, these rats showed overactive bladder. The results of this study revealed that intravesical application of rebamipide suppressed bladder overactivity with a reduction in bladder inflammatory changes in a chemically induced cystitis rat model. Since the pathophysiology of CYP-induced bladder inflammation and IC/PBS are similar, the CYP-induced cystitis model is used as an interstitial cystitis/painful bladder syndrome (IC/PBS) model. Intravesical application of rebamipide, therefore, could protect against urothelial damage in patients with IC/PBS.

Concluding message

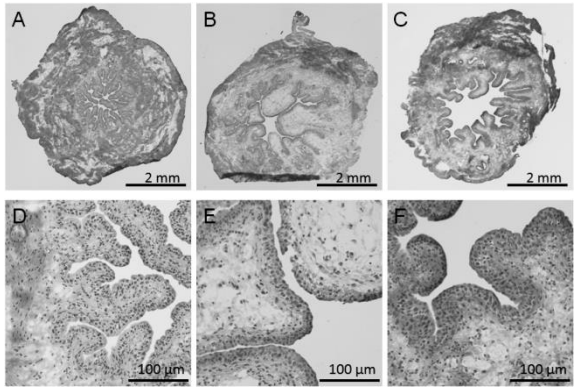
Intravesical rebamipide administration relieved bladder overactivity in a CYP-induced cystitis model by suppressing the inflammatory reaction. This may be a new strategy for treating patients with IC/PBS.

Fig. 1 Cystometry

Fig. 2 Hematoxylin/eosin staining of bladder

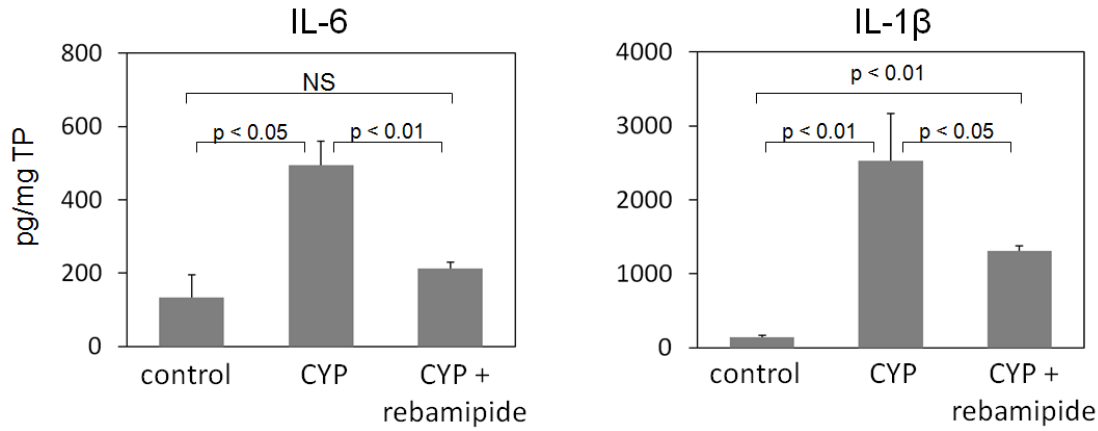


Intercontraction interval was shortened in the CYP-injected rats, which was reversed in the CYP-injected rats treated with intravesical rebamipide.



A, D; control, B,E; CYP-injected rats, C, F; CYP- injected rats treated with intravesical rebamipide. Images were taken at magnifications of x4 in A, B, and C, and at x20 in D, E, and F.

Fig. 3 IL-6, and IL-1β in bladder



Disclosures

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