267

Kitta T[1], Tanaka H[1], Sano H[1], Furuno T[1], Mitsui T[1], Moriya K[1], Nonomura K[1]
1. Hokkaido University

TYPE 4 PHOSPHODIESTERASE INHIBITOR SHOWS ANTI-INFLAMMATORY EFFECTS AND REDUCES URINARY FREQUENCY IN THE HYDROCHLORIDE INDUCED INTERSTITIAL CYSTITIS RAT MODEL

Hypothesis / aims of study
Interstitial cystitis (IC) is a chronic painful bladder disease of unknown aetiology. Though there are some reports of the usefulness of drugs, effective therapy has still not been established yet. Type 4 phosphodiesterase (PDE4) is a high-affinity cAMP-selective isozyme. Elevation of cAMP levels by inhibition of PDE4 reportedly relaxes smooth muscles. And PDE4 inhibitors possess anti-inflammatory effects in animal models of inflammatory disease. Hydrochloric acid (HCl)-induced chemical cystitis has been proposed as a useful animal model to investigate IC. We hypothesized that PDE4 inhibitor is effective to suppress bladder overactivity and bladder pain responses in bladder hypersensitive disorders such as interstitial cystitis. The aim of this study was to evaluate the effects of orally administered YM976, a specific inhibitor of PDE4, on bladder activity in a rat model of HCl-induced cystitis.
Study design, materials and methods
In this study female Wistar rats (170-200g) with cystitis induced by intravesical instillation of 0.4 N HCl were used. The treatment group were administered orally at a volume of 10mg/kg/day of YM976 that was suspended in 0.5% methylcellulose (MC) solution during experimental period. The control groups were treated only with vehicle (0.5% MC). Micturition behavior during 24 hours was measured 3, 7 and 14 days after HCl instillation, and then cystometry in conscious freely moving was performed to compare parameters between YM976 group and vehicle group. The bladders were removed and the severity of bladder inflammation was quantified using the bladder inflammatory index (BII). [1.] The spinal cord was also removed and the L6 segment was sectioned and processed for c-fos expression.
Results
Micturition behavior and cystometric data are summarized in the following tables. Although the daily urine volumes were not different between groups, the number of micturition in YM976 group was significantly lower than that in vehicle group on day 3 and 14. The micturition volume per void of YM976 group was significantly higher than that of vehicle group on day 3. Cystometric parameters revealed that YM976 group showed significant increase in bladder capacity, voided volume and voiding efficiency and decrease the amplitude of voiding pressure on day 3. When compared with the bladder harvested from rats with intravesical saline instillation, obvious inflammatory changes were observed in the bladders of YM976 group. However, the BII scores were significantly lowered by YM976 (figure 1). The number of c-fos positive cells in the L6 segment was 66.2% lower in the YM976 group than in the vehicle group.

Table 1: Micturition profile of rats 3 days, 7 days and 14 days after HCl-induced chemical cystitis model in the two groups of rats

		Number of micturition±SE /24hours	Volume/ Micturition±SE (ml.)	Volume of micturition±SE (ml.)
Pretreatment		12.3±1.9	0.86±0.17	10.0±0.8
Day 3	Vehicle	45.5±4.5	0.11±0.05	4.9±0.6
	YM976	18.4±5.0 **	0.35±0.06 *	5.9±0.7
Day 7	Vehicle	25.0±2.0	0.34±0.08	8.7±2.7
	YM976	22.2±2.6	0.57±0.15	11.3±1.9
Day 14	Vehicle	24.7±3.1	0.49±0.04	11.9±1.4
	YM976	14.8±0.8 *	0.68±0.10	10.0±1.7

* Vehicle versus YM976 treated in each day: $p<0.05$
** Vehicle versus YM976 treated in each day: $p<0.01$

Table 2: Cystometric parameters in HCl-induced chemical cystitis model rats with vehicle or YM976 treatment on day 3 (* Vehicle versus YM976 treated: $p<0.05$)

Group	Bladder Capacity±SE (mL)	Voiding pressure±SE (cm H_20)	Voided Volume±SE (mL)	Voiding Efficiency±SE (%)
Vehicle	0.18 ± 0.02	27.3 ± 2.5	0.16 ± 0.02	91.0 ± 0.0
YM976	0.37 ± 0.05*	19.6 ± 2.5*	0.35 ± 0.06*	95.0 ± 0.0*

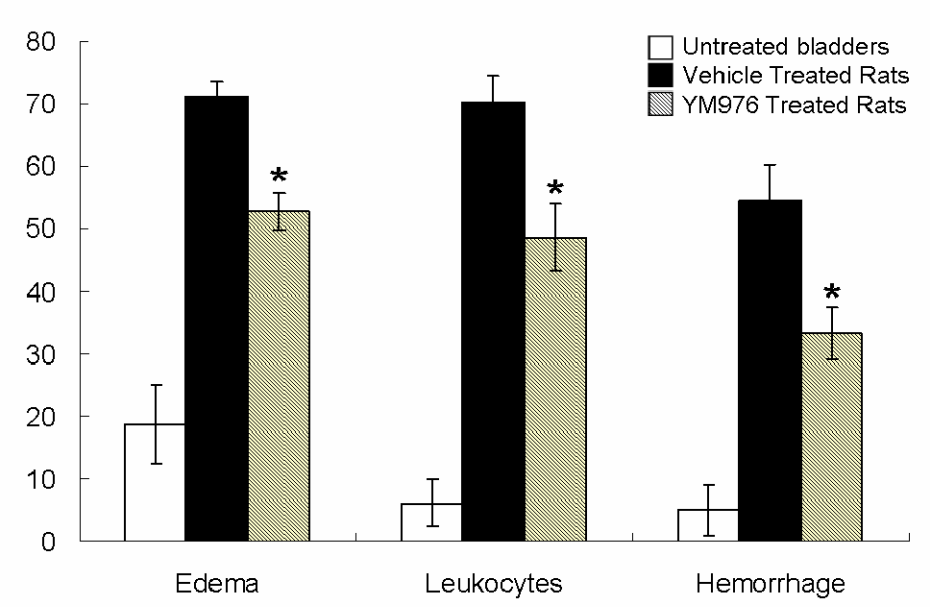

Figure 1: The bladder inflammatory index (BII) scores of the bladders with intravesical instillation of saline or HCl. Average BII scores in the bladders with saline infusion (edema/leukocyte infiltration/hemorrhage) was 18.7±6.3/6.2±2.1/5.0±2.9. Average BII scores were 71.3±3.7/70.3±4.0/54.4±5.3 in Vehicle group and 52.7±4.1/48.6±5.9/33.3±4.2 in the YM976 group, respectively. (* Vehicle versus YM976 treated: $p<0.05$)

Interpretation of results

In rats intravesical instillation of HCl induced long-lasting hyperactive voiding, and histological examination of the bladder revealed typical bladder inflammatory changes. These functional and histological changes in rats mimic those seen in the humane with IC. In the present study, daily oral administration of YM976 significantly reduced the number of micturition 3 and 14 days after HCl instillation. Compared with vehicle group, the micturition volume per void was also significantly increased by YM976 on day 3. In this study we used BII which include the major histopathological findings of cystitis, i.e., edema, leukocyte infiltration, and hemorrhage. Quantifying each parameter was comparable the severity of inflammation. Compared with vehicle group, YM976 treated rats exhibited less inflammatory changes in the bladders with a significant reduction in the BII scores, indicating that orally administrated PDE4 inhibitor has anti-inflammatory effects on HCl-induced cystitis.

Significant reduction of c-fos expression in the spinal cord was found in YM976 treated rats. An anti-inflammatory effect of the drug was though to be mainly responsible for the reduction of the spinal c-fos expression, but decreasing tonus in the bladder smooth muscle might also relate to this preferable effect. These results indicated PDE4 inhibitor might be effective in relieving urinary frequency and pain in patients with IC.

Concluding message

Oral treatment with PDE4 inhibitor, YM976, exerts protective functional and histological effects on the urinary bladder in the HCl-induced cystitis model. Thus, selective PDE4 inhibitors might be clinically useful for the treatment of interstitial cystitis.

References

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