

THE KAMPO MEDICINE CHOREITO ATTENUATES DETRUSOR OVERACTIVITY AND BLADDER PAIN IN RATS WITH INTERSTITIAL CYSTITIS-LIKE SYMPTOMS INDUCED BY TRANILAST

Hypothesis / aims of study

Interstitial cystitis (IC) is a chronic bladder disease characterized by lower urinary tract symptoms such as urinary frequency, urgency and bladder pain with inflammation of bladder wall, causing a deterioration in the quality of life. However, no effective modality for controlling these symptoms is available. Our previous report showed that high-dose tranilast administration induced IC-like symptoms, such as urinary frequency, low locomotor activity and increased vascular permeability of bladder wall [1]. Choreito (CRT), a kampo medicine, which is used for the treatment of urolithiasis, is known to improve urinary frequency and urgency in patients with overactive bladder in Japan. In order to clarify whether CRT improves IC symptoms, we examined the bladder and locomotor activity, and vascular permeability and cytokine of bladder wall with or without CRT in the rats with IC-like symptoms induced by tranilast.

Study design, materials and methods

Fifty adult female Sprague–Dawley rats were divided into 4 group; (1) normal, (2) control IC, (3) low dose CRT-treated IC (0.1% CRT p.o.) and (4) high dose CRT-treated IC (1% CRT p.o.) groups. In the IC groups, 0.4% tranilast with or without CRT (0.1 or 1%) were orally administered. After 4 week of treatments, rats were subjected to the evaluation of locomotor activity, continuous cystometry measurements, and vascular permeability and cytokine of the bladder wall. Locomotor activity measurement, which is a surrogate index of pain, was calculated as the sum of movements during the light or dark period. The bladder activity (maximum bladder contraction pressure, the frequency of voiding bladder contractions, and the baseline intravesical pressure) were performed by continuous cystometry under urethane anesthesia. Vascular permeability was observed the leakage of dye solution from the bladder tissue after intravenous administration of Evans blue. The cytokine levels were measured by Bio-Plex suspension array system.

Results

(1) In the control IC group, rats exhibited lower locomotor activity (dark period) compared to the normal group, and which were ameliorated by high dose treatment of CRT (Fig. A).

(2) In cystometry measurements, the frequency of voiding interval was significantly shorter in the control IC group compared to the normal group, and CRT treatments significantly suppressed the decrease of voiding interval in a dose dependent manner (Fig. B). However, there was no significant difference in the maximum contraction pressure and the baseline intravesical pressure between the control IC and CRT-treated groups.

(3) In the vascular permeability measurement, Evans blue leakage from bladder tissue was significantly higher in the control IC group, and high dose treatment of CRT inhibited the increase of dye leakage (Fig. C).

(4) In the control IC group, Bio-Plex suspension array revealed that cytokine level of IFN γ and VEGF significantly increased compared to the normal group, but IL-1 β , TNF α , IL-4, IL-6, IL-10 and IL-17 had no change, and CRT treatment suppressed the increase of IFN γ of bladder tissue (Fig. D).

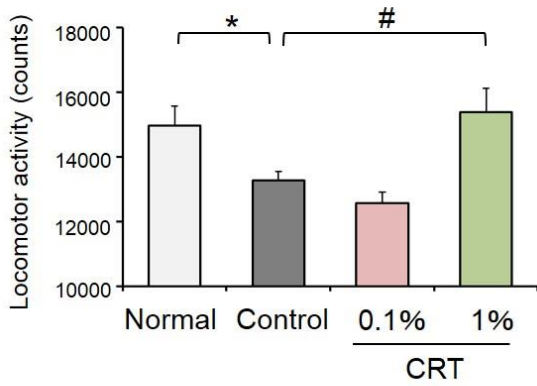
Interpretation of results

These results indicate that; (1) high-dose tranilast administration induces IC-like symptoms, such as decreased locomotor activity and voiding interval, and increased vascular permeability and IFN γ in the bladder tissue, (2) CRT treatment suppressed the decreased locomotor activity and voiding interval, and increased vascular permeability and IFN γ in the bladder tissue. Since marked increase of IFN γ , which is one of the pro-inflammatory cytokines, was suppressed by CRT treatment in the control IC group, one of the mechanisms of improvements of IC-like symptoms after CRT treatment may be anti-inflammatory effect via inhibition of IFN γ .

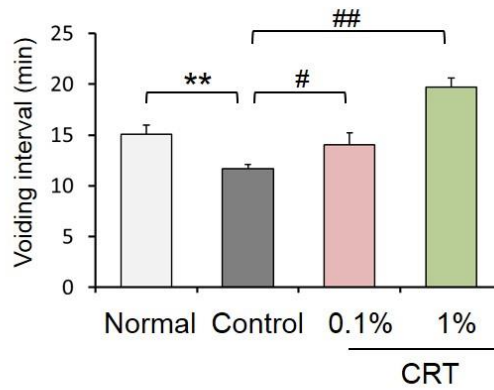
Concluding message

We propose possible clinical application of CRT as a medicine for treatment of lower urinary tract syndromes including IC. Further, the elucidation of mechanisms of the drug may open the way to the development of new pharmacotherapeutic strategies aimed at a wide variety of lower urinary symptoms.

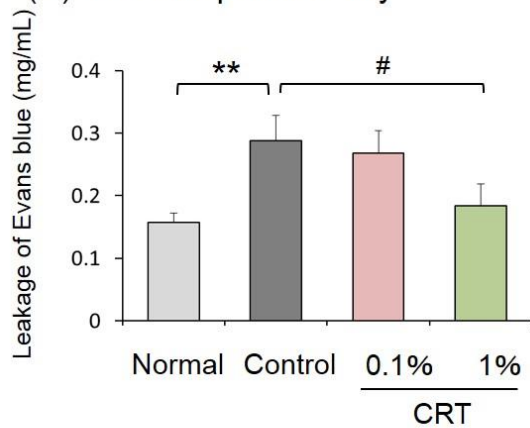
(A) Locomotor activity



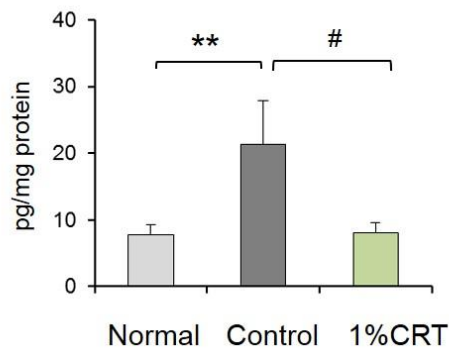
(B) Voiding interval



(C) Vascular permeability



(D) IFN γ



* $P < 0.05$, ** $P < 0.01$, v.s. normal group, # $P < 0.05$, ## $P < 0.01$, v.s. control group

References

1. Nishijima S, Sugaya K, Kadekawa K, et al. High-dose tranilast administration to rats creates interstitial cystitis-like symptoms with increased vascular permeability. *Life Sci.* 2013; 93(23):897-903.

Disclosures

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