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Nishijima S[1], Sugaya K[1], Kadekawa K[1], Ashitomi K[1], Yamamoto H[2]
1. *Southern Knights' Laboratory LLP,* ***2.*** *Department of Biochemistry, University of the Ryukyus*

HIGH-DOSE TRANILAST CREATES INTERSTITIAL CYSTITIS WITH INCREASED VESICAL VASCULAR PERMEABILITY IN RATS

Hypothesis / aims of study

Interstitial cystitis (IC) is a condition that results in recurring discomfort or pain in the bladder and the surrounding pelvic region. Some basic studies have been performed in animal models of IC created by intravesical infusion of hydrochloric acid or intraperitoneal injection of cyclophosphamide (1,2). However, these models develop urinary frequency and do not reflect the clinical symptoms and findings of IC. It has been reported that tranilast, an anti-allergy agent, rarely induces IC as a side effect in clinical use (3). Tranilast is also employed for the treatment of keloids and hypertrophic scars because it inhibits collagen synthesis in fibroblasts by blocking the release of transforming growth factor (TGF)-β1. Therefore, we hypothesized that administration of tranilast might induce IC by inhibiting the activity of bladder fibroblasts along with an increase of vascular permeability. In this study, we examined whether high-dose administration of tranilast could create an animal model of IC and then used the model to assess the relationship between IC and changes of vascular permeability in the bladder.

Study design, materials and methods

Fifty female Sprague-Dawley rats were divided into 4 groups and were given free access to tap water (control group, n=18), a tranilast suspension in water (2 mg/ml) (tranilast group, n=18), carbazochrome sodium sulfonate hydrate (carbazochrome) in water to inhibit vascular permeability (0.25 mg/ml) (carbazochrome group, n=7), or tranilast + carbazochrome in water (combination group, n=7). After 4-5 weeks, 7 rats from each group underwent continuous cystometry under urethane anesthesia. Then the presence of glomerulation of the bladder wall was investigated by infusion of water for distension (3 ml, 5 min) and the vascular permeability of the bladder wall was assessed by harvesting the bladder at 3 min after intravenous injection of Evans blue dye (50 mg/kg). In the control group and the tranilast group, we also measured the plasma TGF-β1 level (n=11 each), and determined the thickness of the collagen fiber layer in the bladder wall by Masson trichrome staining (n=5 each).

Results

In the tranilast group, the interval between bladder contractions during continuous cystometry was significantly ($p<0.001$) shorter (51% decrease) and leakage of Evans blue dye into the bladder wall was significantly ($p<0.001$) greater (62% increase) compared with the control group (Figure 1). Glomerulation of the bladder wall were also seen after bladder distension and thinning of the collagen fiber layer in the bladder wall was observed in the tranilast group. The plasma TGF-β1 level was lower (39% decrease) in the tranilast group than the control group, but a significant difference was not observed ($p=0.057$). There were no significant differences of any of these parameters between the carbazochrome group and the control group. In the combination group, cystometric parameters did not differ from those in the control group, but leakage of Evans blue dye into the bladder wall was significantly ($p=0.013$) greater (28% increase) compared with that in the control group. However, the leakage of Evans blue was significantly ($p=0.010$) less marked (27% decrease) in the combination group than the tranilast group.

Interpretation of results

In the tranilast group, a shorter interval between bladder contractions (urinary frequency) and glomerulation of the bladder wall on bladder distension were observed, suggesting that high-dose tranilast can create an animal model of IC. The significant increase of Evans blue leakage into the bladder wall and thinning of the collagen fiber layer, as well as the decrease of plasma TGF-β1 in the tranilast group, indicated that tranilast administration had inhibited collagen synthesis in the bladder wall and vessels by blocking TGF-β1 release from fibroblasts and had also increased vascular permeability in the bladder. Adding carbazochrome to tranilast in the combination group inhibited urinary frequency and the increase of vascular permeability in the bladder wall, supporting the above hypothesis.

Concluding message

High-dose administration of tranilast can create an IC model in rats. An increase of vascular permeability in the bladder may be one of the causes of IC. Carbazochrome inhibits vascular permeability and may be a potential treatment for IC.

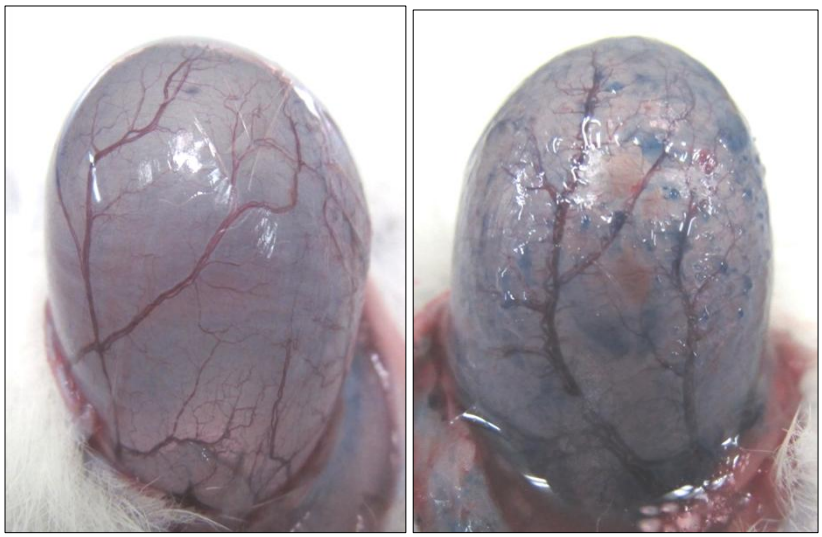

Figure 1. Distension of the bladder after intravenous injection of Evans blue in the control group (left) and the tranilast group (right).

References

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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