

ROLE OF TRPV1 IN MICE WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS

Hypothesis / aims of study

Transient receptor potential vanilloid 1 (TRPV1) is a nonselective cation channel which is activated by capsaicin, heat or acid. Some investigators reported that TRPV1 played an important role during urinary bladder inflammation, namely in hyperalgesia (1) and hyperactivity (2). Furthermore intravesical administration of capsaicin improved in both symptom and pain score in patients with interstitial cystitis (3). However, the mechanisms of activation during chronic urinary bladder inflammation are poorly understood. Cyclophosphamide (CYP) is an antineoplastic agent which produces chronic cystitis. Therefore, we evaluated the urinary bladder function in mice lacking TRPV1 (TRPV1 KO mice) with CYP induced cystitis.

Study design, materials and methods

1. Cystometry in conscious restrained mice. Male TRPV1 KO mice (n=12) and matching wild type control (WT mice; n=10), 10-11 weeks of age, were administered CYP (150 mg/kg) or vehicle (sterile water) intraperitoneally. Forty-five hours after administration of CYP, the mice were anesthetized with sevoflurane for surgical insertion of an intravesical catheter (PE-50). After the surgery, cystometry was performed in conscious restrained mice by infusing saline into the urinary bladder at a constant rate (0.5 ml/hr). Forty-eight hours after administration of CYP, cystometrical parameters (Intercontraction interval and maximal voiding pressure) were evaluated.

2. Histopathological examination. Male TRPV1 KO mice (n=9) and WT mice (n=11), 16-19 weeks of age, were administered CYP (150 mg/kg) or vehicle intraperitoneally. Forty-eight hours after administration of CYP, the mice were anesthetized with sevoflurane. Urinary bladder was taken intact and fixed for 24 hours in 10% buffered formalin. Tissue (3 micrometer thickness) was stained with hematoxylin-eosin. Histological damage, including hemorrhage and inflammation were evaluated.

The Animal Care and Use Committee of our University approved the experimental protocols involving the use of animals. Data are expressed as mean \pm S.E.M. The Mann-Whitney test was used when appropriate for statistical data analysis with $P < 0.05$ considered statistically significant.

Results

1. Cystometry in conscious restrained mice. In vehicle administrated mice, there was no significant difference in intercontraction interval between WT mice (337.6 ± 27.5 s) and TRPV1 KO mice (288.7 ± 35.9 s). In WT mice, Intercontraction interval of CYP administrated group (116.8 ± 8.2 s) was significantly shorter than that of vehicle administrated group ($p < 0.01$). In TRPV1 KO mice, there was no significant difference in intercontraction interval between vehicle administrated group and CYP administrated group (251.5 ± 16.5 s). There was no significant difference in maximal voiding pressure between each group.

2. Histopathological examination. Vehicle administrated mice had histologically normal urinary bladders. CYP administration caused hemorrhage and inflammation of urinary bladders in both TRPV1 KO mice and WT mice. Under microscopic examination, the area and size of hemorrhage and inflammation in the urinary bladder were similar in TRPV1 KO mice and WT mice.

Interpretation of results

Although administration of CYP caused urinary bladder inflammation in TRPV1 KO mice, obvious urinary bladder hyperactivity sign did not appear.

Concluding message

These findings indicated that TRPV1 might be responsible for mechanisms of urinary bladder hyperactivity in mice with CYP-induced cystitis. In addition to desensitization by administration of TRPV1 agonist, administration of TRPV1 antagonist may improve symptoms of patients with the chronic inflammatory bladder syndrome interstitial cystitis.

References

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