

TAC-302, A NOVEL NEURITE OUTGROWTH ENHANCER, THERAPEUTICALLY IMPROVES LOWER URINARY TRACT SYMPTOMS IN RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

TAC-302, cyclohexenoic-long fatty alcohol derivative, is a novel neurite outgrowth enhancer which has a beneficial effect on not only central nerve system disorder, but also peripheral neuropathy. Because it is proposed that bladder outlet obstruction (BOO) induces lower urinary tract symptoms (LUTS), such as detrusor overactivity, urgency, and increased residual urine volume, via partial denervation in urinary bladder, re-innervating by neurite outgrowth would be very useful for treating LUTS in BOO. Therefore, in this study, we investigated whether oral treatment with TAC-302 therapeutically improved LUTS in BOO rats.

Study design, materials and methods

BOO was produced by tying a ligature of 5-0 silk around the urethra in the presence of steel rod (outer diameter 1.57 mm) in 8-week-old female Sprague-Dawley rats. Sham-operated rats underwent surgery following a similar procedure without the ligation. Two weeks after the surgery, BOO rats were divided into 3 groups and were orally treated with vehicle, TAC-302 at dose of 1 and 3 mg/kg twice a day for 4 weeks, respectively. Sham-operated rats were administered vehicle for same period. Also, a part of vehicle treated-BOO rats were used for evaluating effects of α 1-blocker (tamsulosin, 3 μ g/kg, i.v.) and anti-cholinergic agents (tolterodine, 0.1 mg/kg, i.v.; solifenacin, 1 mg/kg, i.v.). At the next day of final administration, single cystometry was performed at infusion rate of 3 - 24 mL/hr under conscious conditions. For confirming neurotrophic activity of TAC-302 in the urinary bladder of BOO rats, immunohistochemical study was also performed using anti-PGP9.5 antibody (a nerve fiber marker).

Results

BOO rats showed significant increase of micturition volume, residual urine volume and bladder capacity, and significant decrease of micturition efficiency compared with Sham-operated rats. Also, BOO crushingly evoked non-voiding contraction (NVC) which was spontaneous contraction before micturition, although Sham-operated rats did not almost have the NVC. Tamsulosin significantly reduced the frequency of NVC in BOO rats, but had no effect on residual urine volume. Solifenacin and tolterodine had no effect on the frequency of NVC, but significantly increased residual urine volume in BOO rats. Oral treatment with TAC-302 significantly reduced the frequency of NVC and tended to reduce residual urine volume compared with BOO vehicle group (Figure 1). Nerve fiber density was significantly lower in the urinary bladder of BOO rats than Sham-operated rats. Then, the denervation in the urinary bladder was diminished by oral treatment with TAC-302

Interpretation of results

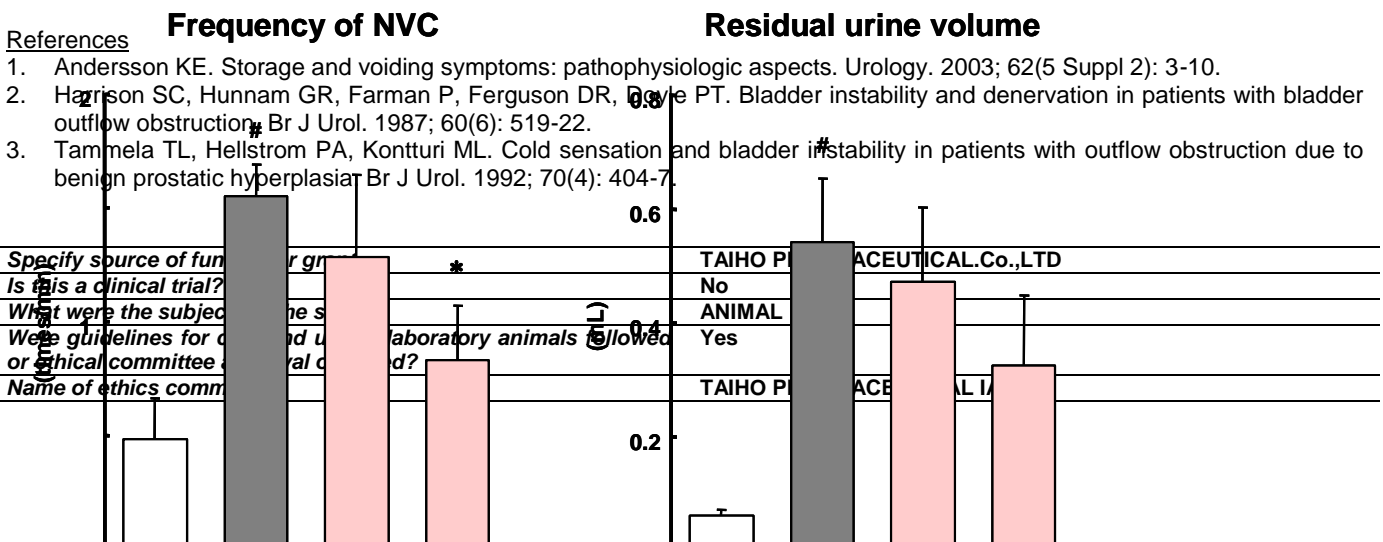
In the present study, we demonstrated that TAC-302 therapeutically improved LUTS and loss of nerve fiber density in the urinary bladder of BOO rats. Also, it is found that pharmacological property of TAC-302 is difference from those of α 1-blocker and anti-cholinergic agent. As TAC-302 has beneficial effects on nerve injury, it is possible that the improvement of bladder dysfunctions is caused by TAC-302-induced re-innervating in the urinary bladder.

Concluding message

Our data indicates that re-innervating induced by oral treatment with TAC-302, a novel neurite outgrowth enhancer, can contribute to improve LUTS in BOO. Therefore, it is expected that neurite outgrowth is a valuable target for treating LUTS caused by partial denervation, such as BPH.

References

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