

EFFECT OF TAC-302, A NOVEL NEURITE OUTGROWTH ENHANCER, ON VOIDING DYSFUNCTION IN RATS WITH STZ-INDUCED DIABETES

Hypothesis / aims of study

Metabolic syndrome and diabetes are known to be risk factors for lower urinary tract symptoms (LUTS). Then, diabetic cystopathy is one of LUTS in diabetic patients. Approximately 40-85% of patients with diabetes have some degree of diabetes cystopathy with the loss of bladder sensation and decreased contractility and compliance of detrusor. Voiding dysfunctions in diabetic cystopathy, which are characterized by an increased residual urine volume and a decreased micturition efficiency, cause various problems, such as urinary-tract infection and renal disorder. Therefore, it is very importance to cure voiding dysfunctions in diabetic cystopathy. 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. It is also reported that TAC-302 improved nerve velocity conductance in rats with diabetic mellitus (DM) induced by streptozotocin (STZ). Thus, in this study, we investigated whether oral treatment with TAC-302 improved LUTS in STZ-induced diabetic rats.

Study design, materials and methods

DM was induced by an intraperitoneal injection of STZ (65 mg/kg) in female Wistar rats. To evaluate voiding functions, single cystometry was performed at infusion rate of 12 mL/hr under urethane (0.8 mg/kg, s.c.) anesthesia condition at 8 weeks after the induction of DM. DM rats were orally treated with vehicle, TAC-302 (1-30 mg/kg), distigmine (acetylcholine esterase inhibitor: 1 mg/kg), or bethanechol (muscarinic receptor agonist: 1 mg/kg). The treatments were started from 4 weeks after the induction of DM and continued for 4 weeks (b.i.d.).

Results

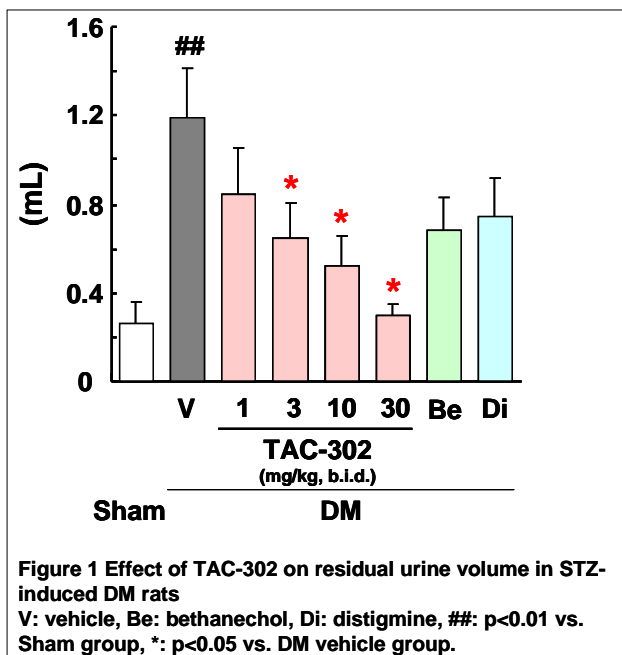
DM rats showed significant increase of micturition volume, residual urine volume and bladder capacity, and significant decrease of micturition efficiency compared with sham-operated rats, indicating STZ-induced diabetic rats show the feature of diabetic cystopathy. TAC-302 dose-dependently reduced the increase of residual urine volume and increased the decrease of micturition efficiency compared with DM vehicle group. On the other hand, chronic treatments with distigmine and bethanechol had no effect on these parameters in DM rats.

Interpretation of results

In the present study, we demonstrated that TAC-302 therapeutically ameliorated voiding dysfunctions in STZ-induced diabetic rats. Also, it is found that pharmacological property of TAC-302 is difference from those of acetylcholine esterase inhibitor and muscarinic receptor agonist.

Concluding message

Our data indicates that TAC-302, a novel neurite outgrowth enhancer, can contribute to improve LUTS in DM. Therefore, it is possible that the TAC-302 is therapeutic medicine to treat voiding dysfunction such as diabetic cystopathy.



Disclosures

Funding: Taiho Pharmaceutical Co., Ltd. **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Animal ethics committee of Taiho Pharmaceutical Co., Ltd.