

NEURON PROTECTION AGENT TAC-302 PREVENTS BLADDER DENERVATION AND DYSFUNCTION FOLLOWING PARTIAL BLADDER OUTLET OBSTRUCTION IN RAT

Hypothesis / aims of study

Detrusor dysfunction associated with partial bladder outlet obstruction (BOO) has been long recognized. There is much evidence indicating that outlet obstruction causes denervation in bladder smooth muscle. The pharmacological evidence of denervation is also drawn from the findings that detrusor muscle from the obstructed bladder exhibits supersensitivity to acetylcholine (main excitatory neurotransmitter) and reduction in nerve-mediated contraction. If denervation of the detrusor muscle can be prevented, it would be a novel treatment modality for detrusor dysfunction secondary to obstruction.

Recently, a new compound (TAC-302), cyclohexenone long-chain alcohol derivative, has been shown to possess some neurotrophic activity in pathologic conditions such as brain infarction. Therefore, using TAC302, we investigated whether denervation and the decreased contractility would be improved by protecting neurons against BOO.

Study design, materials and methods

At 9 weeks of age 15 male Sprague-Dawley rats received partial BOO (n=10) or SHAM surgery (SHAM group; n=5) were used. After surgery, 5 BOO rats received daily administration of 8 mg/kg TAC-302 intraperitoneally for 4 weeks, while the other 10 rats had no treatment. Four weeks following surgery, all rats were sacrificed and bladder was taken for morphological and pharmacological studies as follows;

1. Full thickness bladder serial frozen sections were made for PGP9.5 (a pan neuronal marker) immunohistochemical study.
2. Muscle strips from bladder dome were suspended in a 25 ml organ bath containing Krebs' solution. A dose response curve to carbachol (Cch) was produced by adding increasing concentrations of the drug.
3. Transmural nerve electrical stimulation (500 μ sec duration and at a frequency of 5, 10, 20, 30, 40 and 50 Hz) was performed to evaluate contractility of the detrusor muscle.
4. Using micro-dialysis method, measurement of acetylcholine (ACh) release from the nerve-ending of detrusor muscle with transmural nerve electrical stimulation (500 μ sec duration and 30 Hz frequency) was performed.

Results

Compared to SHAM group, bladder weight increased significantly following obstruction. Neurotrophic compound (TAC-302) had no effect on increased bladder weight induced by BOO. Immunohistochemical study showed that PGP9.5 positive nerve fibers were decreased in obstructed bladders. In contrast, TAC-302 well preserved these PGP9.5 positive nerves (Fig.1). The Cch dose response curves demonstrated a significant leftward shift for bladder muscle from BOO rats, suggesting detrusor muscle were supersensitive to exogenous Cch (Fig. 2). In addition, muscle strips from BOO rats showed a significant reduction in nerve-mediated contractile response (Fig. 3). TAC-302 significantly reduced supersensitivity and preserved decreased nerve-mediated detrusor contraction (Fig. 2 and 3). The amount of ACh release from the nerve-ending of BOO detrusor was significantly lower compared to that of SHAM group. With TAC-302 treatment, there was no significant change of ACh release compared to SHAM group (Fig. 4).

Interpretation of results

BOO causes denervation of bladder smooth muscle that results in supersensitivity to Cch, reduction in nerve-mediated contraction and decrease of nerve derived ACh release from detrusor. TAC-302 may improve these changes associated with BOO by preventing the development of denervation.

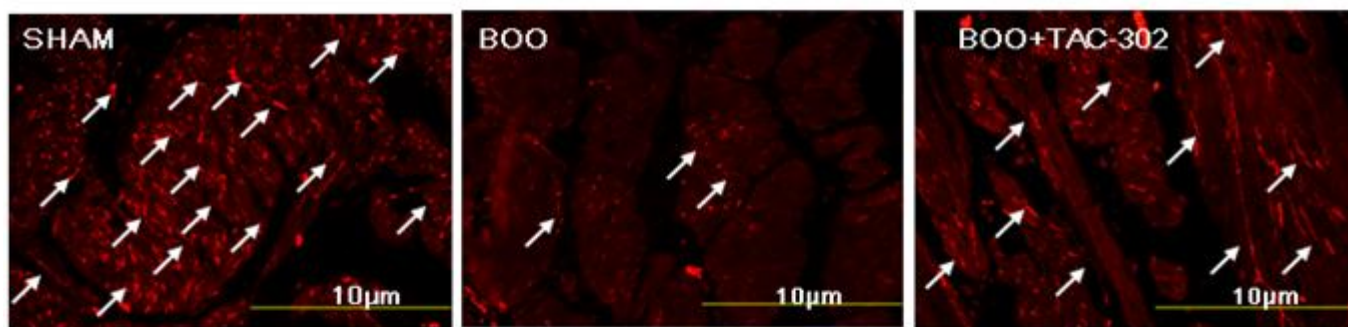
Concluding message

Clinical implication from this study is that using a neurotrophic agent such as TAC-302, neurons will be protected against denervation, which may have beneficial effects in the treatment of detrusor dysfunction secondary to obstruction.

Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** rat **Ethics Committee:** Fukushima Medical University Ethics Committee.

Fig. 1



A representative immunostaining for PGP9.5 positive nerve fibers from bladder muscle of SHAM, BOO and BOO + TAC-302 (Bars 10µm)

Fig. 2

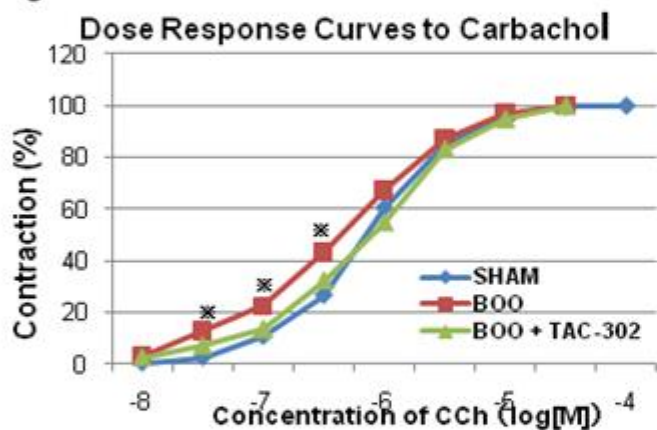
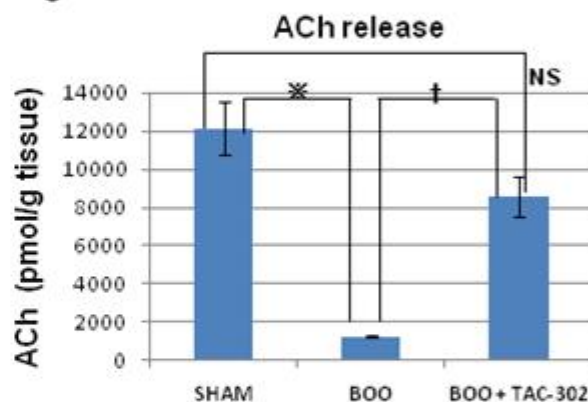


Fig. 4



NS, not significant

* p<0.05, significant difference from SHAM

† p<0.05, significant difference from BOO

Fig. 3

