

PROTECTION OF NEURONS FROM DENERVATION PREVENTS DETRUSOR CONTRACTILE DYSFUNCTION FOLLOWING RAT BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Detrusor dysfunction associated with bladder outlet obstruction has long been recognized. There is much evidence indicating that outlet obstruction causes denervation in bladder smooth muscle¹. 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 contraction². These changes are thought to be the basis of the abnormal behaviour of obstructed bladder, i.e., detrusor overactivity coexisting with the decreased contractility. Thus, denervation may underlie the development of detrusor dysfunction. 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 (MM-101), cyclohexenone long-chain alcohol derivative, has been shown to possess some neurotrophic activity in pathologic conditions such as brain infarction. Therefore, in the present study, we investigated whether this neurotrophic compound also prevents the development of denervation in the obstructed bladder. In addition, pharmacological studies were performed to determine whether denervation supersensitivity and the decreased contractility are improved by protecting neurons against denervation.

Study design, materials and methods

Partial bladder outlet obstruction (BOO) was obtained by the placement of a silk ligature at the bladder neck (16 rats), and control animals underwent a sham procedure (8 rats). After surgery, 8 BOO rats received daily administration of 8 mg/kg MM-101 intraperitoneally for 2 weeks, while the other 8 BOO rats had no treatment. Two weeks postoperatively, all rats were sacrificed and bladder was taken for morphological and pharmacological studies. Full thickness bladder serial frozen sections were made for Acetylcholinesterase (AChE) histochemical study and PGP9.5 (a pan neuronal marker) immunohistochemical study. In addition, muscle strips from bladder dome were suspended in a 25ml organ bath containing Krebs' solution. A dose response curve to Acetylcholine (ACh) was produced by adding increasing concentrations of the drug. Transmural nerve electrical stimulation was performed to evaluate contractility of the detrusor muscle.

Results

Compared to control group, bladder weight increased significantly following obstruction. In the BOO rats, histochemical study revealed a marked reduction in AChE staining nerves in bladder smooth muscle layer. Immunohistochemical study also showed that PGP9.5 positive nerve fibers were significantly decreased in obstructed bladders. The ACh dose response curves demonstrated a significant leftward shift for bladder muscle from BOO rats (Fig.1), suggesting that detrusor muscle were supersensitive to exogenous ACh. In addition, the BOO rats muscle strips showed a significant reduction in nerve-mediated contractile responses (Fig.2). Neurotrophic compound (MM-101) had no effect on increased bladder weight induced by obstruction. In the BOO rats treated with MM-101, both AChE and PGP9.5 staining nerves were preserved well, as compared to those in BOO rats without MM-101 treatment. Furthermore, this neurotrophic compound significantly reduced supersensitivity (Fig.1) and increased contractility (Fig.2).

Interpretation of results

Bladder outlet obstruction causes denervation of bladder smooth muscle that results in supersensitivity to ACh and reduction in nerve-mediated contraction. MM-101 can decrease supersensitivity and improve contractility by preventing the development of denervation of the bladder smooth muscle.

Concluding message

Clinical implication from this study is that using a neurotrophic agent such as MM-101, neurons will be protected against denervation, which may have beneficial effects in the treatment of detrusor dysfunction secondary to obstruction.

References

1. Effect of bladder outflow obstruction on the innervation of the rabbit urinary bladder. Br J Urol 1990; 66: 372-379.
2. Bladder outflow obstruction - A cause of denervation supersensitivity. J Urol 1987; 138: 1461-1466.

Fig.1 Dose Response curves for Acetylcholine

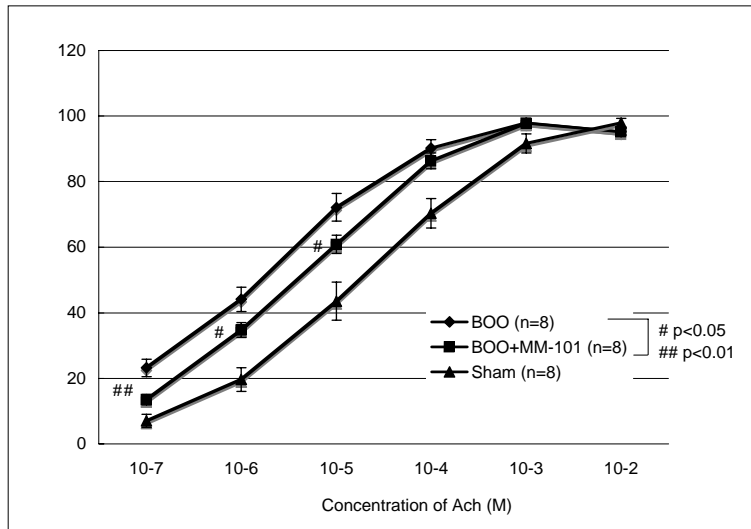


Fig.2 Nerve-Mediated Field Stimulation

