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# DETRUSOR OVERACTIVITY INDUCED BY INCREASED LEVELS OF NERVE GROWTH FACTOR IN BLADDER AFFERENT PATHWAYS IN RATS

## Aims of Study

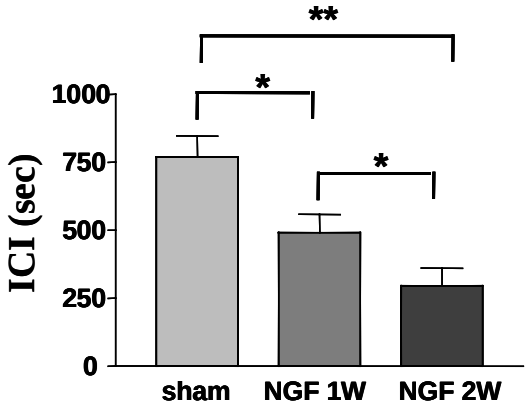
It is well known that neurotrophic factors such as nerve growth factor (NGF) is required for the differentiation and maturation of cells in the central and peripheral nervous system and that it can also affect the functional and morphological properties of peripheral sensory neurons. Previous study has demonstrated that NGF levels increased in the spinal cord and hypertrophied bladders in rats with spinal cord injury. In addition recent studies revealed that intrathecal administration of NGF-antibody can neutralize NGF in the spinal cord and reduce NGF levels in bladder afferent pathways, resulting in suppression of detrusor overactivity after spinal cord injury [1)]. Overall, these data suggest that NGF may be involved in inducing hyperexcitability of bladder afferent pathways that underlies the emergence of detrusor overactivity after spinal cord injury. Thus, to reinforce this hypothesis, we investigated the effects of chronic intrathecal application of NGF on micturition reflex in normal spinal intact rats.

## Methods

Adult female Sprague-Dawley rats (204-256 g) were used. An intrathecal catheter was implanted at the level of the L6-S1 spinal cord following a laminectomy at the Th11 vertebra under halothane anesthesia. Three to four days after intrathecal catheter implantation, the intrathecal catheter was connected to an osmotic mini pump for continuous delivery of either vehicle (artificial cerebrospinal fluid, n=7) for 2 weeks or NGF (200 µl of 1.0 mg/ml) for either one (n=5) or two (n=7) weeks. Seven and fourteen days after intrathecal injection of either vehicle or NGF, awake continuous cystometry (CMG) was performed. During CMG, voided volume (VV), intercontraction interval (ICI), maximal voiding pressure (MVP), pressure threshold for voiding (PT) and baseline intravesical pressure (BP) were measured. After CMG, the L5-6 and S1 dorsal root ganglia (DRG) were removed under anesthesia from vehicle- or NGF-treated rats. DRG tissues were also obtained from untreated spinal intact rats (n=3). In L5, L6 and S1 DRG, ELISA measurements were performed in each animal to determine tissue NGF levels. Total protein concentration for the same samples was also determined. All tissue NGF values were standardized by tissue protein levels and expressed as pg/mg of total protein.

## Results

Fig. 1 - In CMG, ICI and VV were significantly decreased in NGF treated rats in a time dependent manner compared with vehicle-treated rats. * $P < 0.05$, ** $P < 0.01$



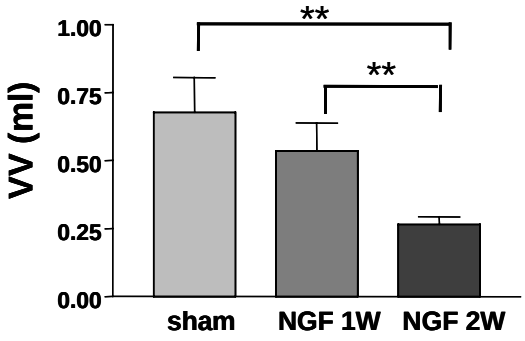




Table 1 – During CMG, MVP, BP and PT were not significantly changed by NGF treatment. In ELISA measurement, NGF levels in L6 and S1 DRG significantly increased in NGF treated rats compared with untreated and vehicle-treated rats. However, no significant difference was found in NGF levels between the groups treated with NGF for 1 and 2 weeks. NGF levels in L5 DRG were not significantly different in untreated, vehicle- and NGF treated rat.
* P< 0.05 compared with vehicle treated rats.

| | Untreated | n | Vehicle | n | NGF 1W | n | NGF 2W | n |
|---|---|---|---|---|---|---|---|---|
| MVP (cmH2O) | | | 38.0 ± 2.8 | 7 | 38.0 ± 3.0 | 5 | 37.6 ± 3.1 | 7 |
| PT (cmH2O) | | | 9.6 ± 0.58 | 7 | 11 ± 1.3 | 5 | 9.7 ± 0.68 | 7 |
| BP (cmH2O) | | | 5.9 ± 0.6 | 7 | 7.2 ± 2.2 | 5 | 6.6 ± 0.4 | 7 |
| NFG L6 (pg/µg) | 27.8 ± 2.6 | 3 | 30.8 ± 2.6 | 6 | 44.0 ± 4.1* | 6 | 49.4 ± 5.2* | 7 |
| NGF S1 (pg/µg) | 31.4 ± 7.1 | 3 | 35.2 ± 2.2 | 6 | 42.0 ± 2.3* | 6 | 45.2 ± 2.9* | 7 |
| NGF L5 (pg/µg) | 29.1 ± 7.8 | 3 | 34.3 ± 3.2 | 6 | 32.0 ± 3.1 | 5 | 37.1 ± 3.9 | 7 |

**Conclusions**

Intrathecal application of NGF at the lumbosacral spinal cord increased NGF levels in L6 and S1 DRG, which contain bladder afferent neurons, and induced detrusor overactivity. Thus it is concluded that increased NGF levels in bladder afferent pathways are at least in part responsible for emergence of detrusor overactivity, which is often seen after spinal cord injury, and that detrusor overactivity become more severe with the longer duration of exposure of afferent neurons to NGF. Therefore it is likely that rats treated with exogenous NGF could be a good animal model for the study of neurogenic detrusor overactivity and that targeting NGF levels in bladder afferent pathways could be effective for the treatment of detrusor overactivity.

**Reference**

1. J Urol 2002 Nov;168(5):2269-2274