18

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BLADDER NERVE GROWTH FACTOR (NGF)-EXPRESSION PREDICTS OUTCOME IN PATIENTS TREATED BY INTRAVESICAL CAPSAICIN FOR REFRACTORY DETRUSOR HYPERREFLEXIA

Aim of Study. We investigated the bladder expression of NGF in patients with a chronic spinal pathology and prospectively performed a correlation between the peripheral intensity of NGF and the outcome to therapy by intravesical capsaicin, used in order to treat refractory urinary incontinence.

Methods. 12 patients, 7 women and 5 men (mean age 40.8 yr., range 24 to 62), suffering from chronic spinal myelopaty, were enrolled. Three patients showed a detrusor acontractility (areflexia) and nine a detrusor hyperreflexia. They were offered to undergo intravesical infusion of high dosage of capsaicin to treat their refractory urinary incontinence. Cystoscopy and bladder biopsy, to detect bladder NGF expression by monoclonal antibody *Nerve Growth Factor-2.5S Sigma*, were performed before starting the therapy. Clinical follow-up, simple voiding patter and a filling cystometrogram were recorded after 3 and 6 months.

Results. In 5 over 9 patients with detrusor hyperreflexia, a strongly positive NGF immunohistochemical staining was recorded. It was localized in the basal layer of urothelium, in lynphocitic inflammatory cells, in nerve fibers and in the nerve bundles. Some positivity was observed in the smooth muscle cells. A low-moderate or absent NGF immunohistochemical staining was recorded in the patients with a diagnosis of detrusor areflexia. The patients with intense NFG immunohistochemical staining reported a significant clinical improvement after intravesical capsaicin (4 were dry after six months and one occasionally showed incontinence). In the five patients with an intense NGF staining (+++), a highly significant increase of bladder capacity was observed after 3 (basal vs three months: 186±016 vs 382±26 ml, $P<0.01$) or 6 (380±25, $P<0.01$ vs basal) months. In contrast, the bladder capacity of the three patients with detrusor overactivity but a lower NGF staining (+, ++) increased less markedly after capsaicin instillation at the intermediate end point (basal vs three months: 163±15 vs 247±32, $P<0.05$) and this effect was no longer significant at the 6th month (220±12, ns vs basal).

Conclusion. Our findings show high bladder NGF immunohistochemical staining in patients suffering from spinal cord lesion and that its density could be related to intravesical capsaicin outcome used in order to treat detrusor hyperreflexia. The results support the soundness of a new approach in the treatment of neurogenic incontinence and show that it is worthwhile to continue to explore the physiopathology of sensory innervation in voiding pathology.

19

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NERVE GROWTH FACTOR (NGF) GENE THERAPY USING REPLICATION DEFECTIVE HERPES SIMPLEX VIRUS (HSV) VECTORS FOR DIABETIC BLADDER DYSFUNCTION

Aims of Study

Diabetic cystopathy resulting from sensory neuropathy may potentially be treated by direct gene therapy. We investigated NGF gene transfer to the

bladder and bladder afferent pathways in a diabetic model. We employed HSV type 1 vectors which express a functionally active form of mouse β-NGF.

Methods

NGF expression during latent (10 weeks) infection was examined by ELISA and immunohistochemistry following injection of HSV-NGF expression vectors ($1x10^{6-8}$) into the bladder wall of the adult female SD (250-275 gr) rat with and without streptozotocin (STZ) [75 mg/kg]. Six wk. after STZ-induction (glucose > 350 mg/dl) the animals were injected with nonreplicating, latency promoter driven HSV-NGF and were sacrificed after an additional 4 weeks. Metabolic cages were used to monitor urination frequency and voided volume. Cystometrogram were done at the time of sacrifice and ELISA and immunohistochemistry were performed.

Results

Replication defective vectors containing HSV-1 latency promoter (LAP-2) driving β-NGF gene were able to express NGF in the bladder and DRG at 4 weeks after bladder injection. ELISA analysis confirmed an approximately 4 fold increase of NGF expression in both bladder and L6-S1 DRG.

STZ-treated rats with sham-HSV at 10 wk. had much higher voided volume per micturition (3.69 ± 0.98 ml) [n=3] than control animals (0.55 ± 0.40 ml) ($p<0.001$). However, STZ-induced rats that were injected with HSV-NGF [n=5] had voided volume per micturition of only 2.19 ± 0.55 ml at week-10. STZ-induced animals injected with sham HSV had CMG bladder capacity of 3.20 ± 0.84 while HSV-NGF injected animals had capacity of 1.40 ± 0.69 ml.

Conclusions

NGF gene could be expressed in the bladder and bladder afferent pathways using a nonreplicating latency promoter HSV vectors that is well tolerated. This is the first demonstration that NGF gene therapy can revert the STZ-induced diabetic bladder changes. This technique of gene transfer might be useful for treating patients with diabetic cystopathy.

20

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MORPHOLOGICAL CHANGES ASSOCIATED WITH IMPAIRED DETRUSOR CONTRACTILITY.

Aims of study

Elbadawi *et al* [1] first described abnormalities, using qualitative electron microscopic study of detrusor muscle biopsies in patients with impaired contractility in the stable unobstructed bladder compared with normal. These ultrastructural features were later refined [2]. Patients with impaired contractility were found to have specific morphological features termed the degeneration pattern. That is the presence of disruptive muscle cell profiles in at least 50% of randomly studied fields. Disruptive degeneration features include sarcoplasmic vacuolation, sequestration or blebbing, cell shrivelling and fragmentation as well as the presence of cell debris in intercellular spaces.