71

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SUPPRESSION OF DETRUSOR OVERACTIVITY BY HERPES SIMPLEX VIRUS (HSV) VECTOR-MEDIATED DELIVERY OF GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR (GDNF) IN SPINAL CORD INJURED RATS

Hypothesis / aims of study
Hyperexcitability of bladder afferent pathways has been proposed as an important pathophysiological basis of neurogenic detrusor overactivity (DO) associate with spinal cord injury (SCI). GDNF is a member of TGF-β family and well known as a potent survival factor for motor neurons. It has been also suggested that GDNF exerts anti-nociceptive effects at spinal cord and sensory afferent neuron levels in somatic pain models (1, 2). However, it is not known whether GDNF has any therapeutic effects on neurogenic DO, which is one of the major causes of overactive bladder. In this study, we therefore examined the effect of gene therapy using replication-deficient HSV vectors expressing GDNF on DO in rats with chronic spinal cord injury.

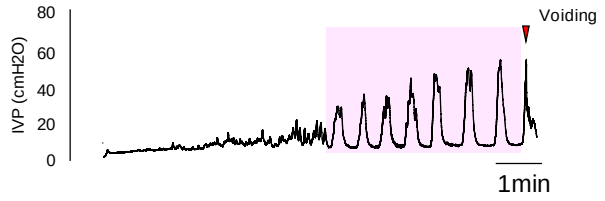
Study design, materials and methods
Adult female Sprague-Dawley rats were used. The Th8-9 spinal cord was completely transected under isoflurane anaesthesia. One week after spinalization, HSV vectors expressing GDNF were injected into the bladder wall via an abdominal incision under isoflurane anesthesia. SCI rats without HSV injection (sham) and those injected with HSV vectors encoding LacZ and green fluorescent protein (GFP) (HSV-LacZ) were used as controls. Four weeks after spinalization, cystometry during saline infusion (0.08ml per min) was performed under an awake condition and cystometric parameters (the number of non-voiding contractions: the number of NVCs, amplitudes of NVC, micturition interval: MI, micturition pressure: MP and residual urine volume: RUV and voiding efficiency; VE) were compared among groups. Also, the existence of HSV in the L6 dorsal root ganglia (DRG) was investigated by GFP immunostainiing and GDNF mRNA measurements by RT-PCR.

Results
There was no any significance in MI, MP and the number of NVCs among sham, HSV-LacZ-treated and HSV-GDNF groups of SCI rats. However, in the HSV-GDNF group, amplitudes of NVCs and RUV were significantly decreased (43.9% and 55.2% reductions from the HSV-LacZ group, respectively) along with an increase in VE, compared with HSV-untreated (sham) and HSV-LacZ groups. Retrograde transportation of HSV to the L6 DRG was observed in by positive GFP immunostaining of DRG neurons. HSV-GDNF groups showed a significant increase in GDNF mRNA in the L6 DRG compared to the HSV-LacZ group ($p<0.05$).

Interpretation of results
These results indicate that locally injected HSV-GDNF can be retrogradely transported to the afferent nerves, resulting in GDNF expression in the L6 DRG, which contains bladder afferent neurons, and can suppress DO, as evidenced by reduced amplitudes of NVCs, following SCI.

Concluding message
These new findings suggest that the HSV vector-mediated GDNF gene therapy could be a new therapeutic modality for the treatment of overactive bladder induced by neurogenic DO.

(A) Control SCI rat



(B) HSV-GDNF treated SCI rat

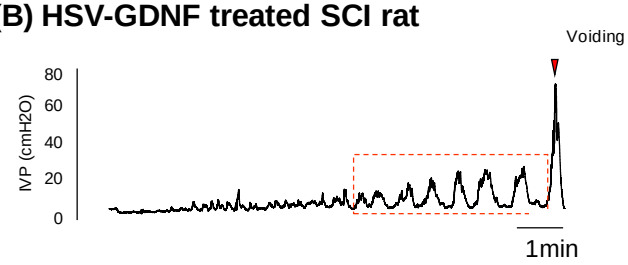


Fig. 1. Typical cystometrograms showing the effects of HSV-GDNF treatment on cystometric parameters in SCI rats.
A: The rat injected with HSV-LacZ control vectors. B: The rat injected with HSV-GDNF vectors.

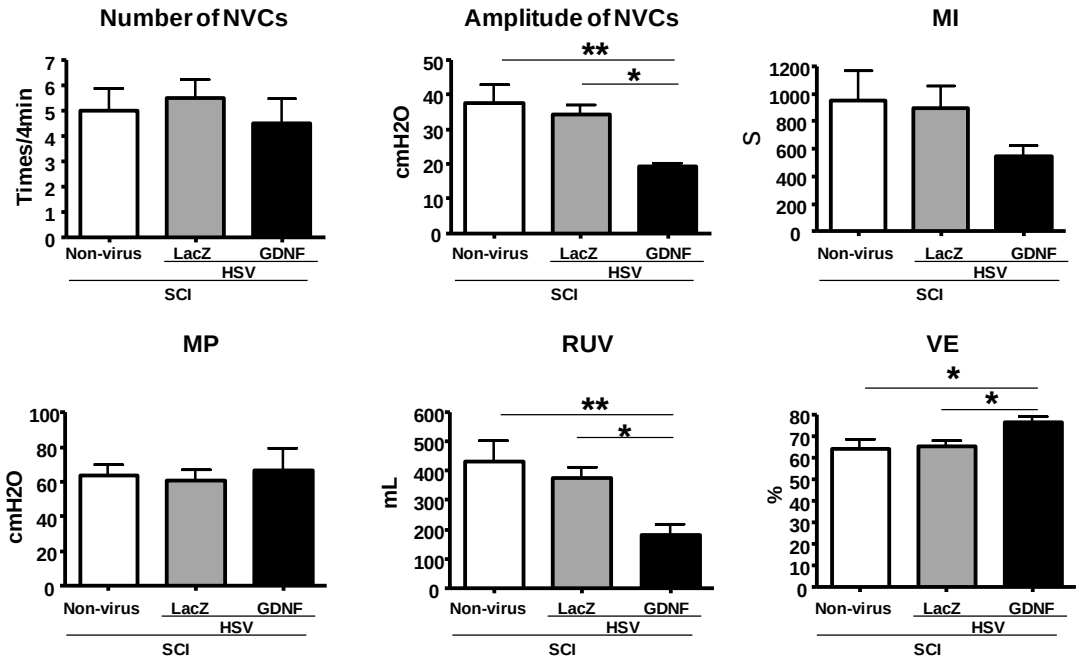


Fig. 2. Effects of bladder wall injection of HSV-GDNF vectors on cystometric parameters in SCI rats.

*p<0.05, **p<0.01（Bonferroni's Multiple Comparison Test）. NCV: non-voiding contraction. MI: micturition interval. MP: micturition pressure. RUV: residual urine volume. VE: voiding efficiency. N=5-6.

References
1. Science (2000) 290; 124-7.
2. Curr Opin Pharmacol (2003) 3; 41-5.

Disclosures
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