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Wada N[1], Shimizu T[1], Shimizu N[1], Tyagi P[1], Kanai A[2], de Groat W[3], Kakizaki H[4], Yoshimura N[1]
1. *The Department of Urology, University of Pittsburgh,* ***2.*** *The Department of Medicine, University of Pittsburgh,* ***3.*** *The Department of Pharmacology, University of Pittsburgh,* ***4.*** *The Department of Renal and Urologic Surgery, Asahikawa Medical Univeristy*

THE ROLE OF BRAIN BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) AND NERVE GROWTH FACTOR (NGF) IN BLADDER AND URETHRAL DYSFUNCTION IN MICE WITH SPINAL CORD INJURY

Hypothesis / aims of study
BDNF and NGF are reportedly involved in changes in neural pathways to induce lower urinary tract (LUT) dysfunction such as detrusor overactivity (DO) and inefficient voiding due to detrusor-sphincter dyssynergia (DSD) following spinal cord injury (SCI). However, it has not been well clarified how these two growth factors differentially affect storage and voiding functions after SCI. Furthermore, we recently reported the differences in bladder and urethral activities between rats and mice with SCI [1]. In short, the voiding efficiency of SCI mice is much worse than that of SCI rats because the urethral pumping activity, which is essential for generating efficient voiding in SCI rats, does not emerge in SCI mice. Therefore, we investigated the effects of anti-NGF or anti-BDNF antibody treatment on bladder and urethral dysfunction in SCI mice.

Study design, materials and methods
SCI was produced by complete transection of the Th8/9 spinal cord in female C57BL/6N mice. After spinal transection, their bladder was manually squeezed to eliminate the urine once daily until the evaluation. Three weeks later, an osmotic pump was placed subcutaneously to administer 10μg/kg/hr of anti-BDNF antibody (N=10) or 10μg/kg/hr of anti-NGF antibody (N=10) for 1 week. Four weeks after spinal cord transection, SCI mice were evaluated using single-filling cystometry and external urethral sphincter (EUS)-electromyogram (EMG) under an awake condition and compared with vehicle-treated SCI mice (N=10 in each). CMG-EMG traces during the voiding phase can detect intermittent voiding coinciding with reductions in intravesical pressure in the CMG recording, which occurred during periods of reduced EUS-EMG activity (Figure 1). In CMG-EMG recordings, we measured voiding contraction time, reduced EMG activity duration and the ratio of reduced EMG activity time to voiding contraction time. After the urodynamic evaluation, the bladder was removed to measure BDNF and NGF levels by the ELISA method and to compare with those of spinal intact mice. In anti-NGF antibody treated SCI mice, mRNA expression of P2X2, P2X3, TRPA1 and TRPV1 of L6/S1 dorsal root ganglia (DRG) that contain bladder and urethral afferent neurons was also evaluated.

Results
Compared to vehicle-treated SCI mice, voided volume was significantly increased and voiding efficiency was significantly better in anti-BDNF antibody-treated SCI mice (Table 1). In CMG-EMG recordings, the duration of reduced EMG activity was significantly prolonged, and the ratio of reduced EMG activity time to voiding contraction time was significantly greater in anti-BDNF antibody-treated SCI mice than those in vehicle-treated SCI mice. Bladder BDNF levels of SCI mice were significantly increased compared with spinal intact mice (124±5.5 vs 18±1.7 pg/mg protein) and bladder BDNF was decreased after anti-BDNF antibody treatment (30±1.5 pg/mg protein).
Compared to vehicle-treated SCI mice, the integral value of non-voiding contractions (NVCs) during the storage phase was significantly decreased in anti-NGF antibody-treated SCI mice (Table 2). In CMG-EMG recordings, all voiding parameters were not different between groups. Bladder mucosal NGF levels of SCI mice were significantly increased compared with spinal intact mice (2.7±0.4 vs 1.1±0.2 μg/mg protein). Bladder mucosal NGF was decreased after anti-BDNF antibody treatment (2.2±0.4 μg/mg protein), but without significant differences. The expression of mRNA of TRPA1 and TRPV1 was increased in SCI mice compared to spinal intact mice, and significantly decreased after anti-NGF treatment.

Interpretation of results
The anti-BDNF antibody treatment improved the voiding dysfunction as shown by increased voiding efficiency due to increased voided volume in SCI mice. The improvement of voiding efficiency was induced by a prolonged duration of reduced EMG periods, implying the increased synergistic activity of EUS during voiding. The anti-NGF treatment induced the improvement of DO as evidenced by a decrease in NVCs in association with the reduction of the expression of TRPA1 and TRPV1 in DRG, which are predominantly expressed in C-fiber afferent pathways; however, its effect on NVCs seemed to be less compared with previous SCI rat studies, which showed that the anti-NGF treatment almost completely inhibited NVCs [2]. Taken together, these results indicate that BDNF and NGF are involved in SCI-induced voiding and storage dysfunction, respectively. Also, in contrast to the previous findings of the greater contribution of bladder NGF overexpression to DO in SCI rats, NGF overexpression seems to have a lesser role in storage dysfunction to induce DO in SCI mice.

Concluding message
BDNF and NGF targeting treatments could be effective for treating voiding and storage problems such as DSD/inefficient voiding and DO, respectively, after SCI.

Figure 1: CMG-EMG in SCI mouse

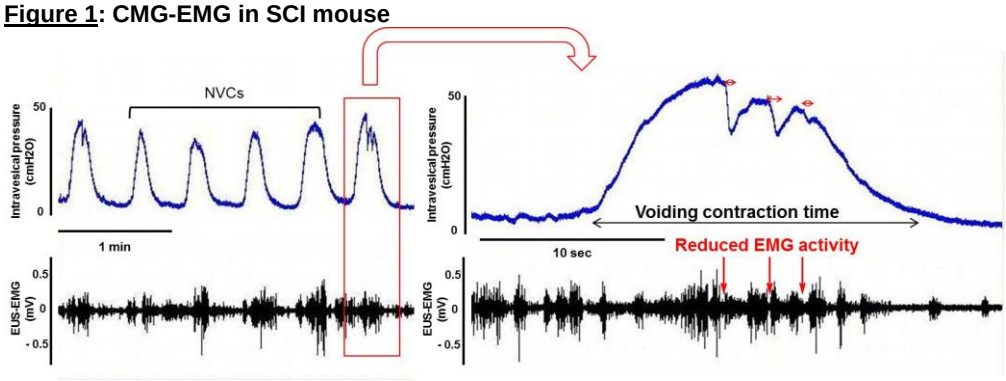

Table 1: Urodynamic parameters in vehicle-treated and anti-BDNF treated SCI mice

† p<0.05 vs vehicle treated SCI mice	Vehicle treated SCI mice	Anti-BDNF Ab treated SCI mice
Single CMG		
NVC integral in 3 minutes before voiding contraction (cmH_2O*sec)	708 ±98	887 ±53
Threshold pressure (cmH_2O)	7.9 ±0.8	6.8 ±1.3
Micturition pressure (cmH_2O)	45.2 ±2.1	51.3 ±3.7
Voided volume (*ml*)	0.031 ±0.004	0.063 ±0.009 †
Postvoid residual urine (*ml*)	0.26 ±0.03	0.27 ±0.03
Bladder capacity (*ml*)	0.298 ±0.03	0.330 ±0.04
Voiding efficiency (%)	12.3 ±1.6	20.4 ±2.9 †
CMG-EMG		
Voiding contraction time (*sec*)	21.5 ±1.0	21.3 ±1.2
Reduced EMG activity time (*sec*)	0.97 ±0.15	1.89 ±0.38 †
Ratio of reduced EMG activity to voiding contraction time (%)	4.5 ±0.6	8.7 ±1.7 †

Table 2: Urodynamic parameters in vehicle-treated and anti-NGF treated SCI mice

† p<0.05 vs vehicle treated SCI mice	Vehicle treated SCI mice	Anti-NGF Ab treated SCI mice
Single CMG		
NVC integral in 3 minutes before voiding contraction (cmH_2O*sec)	893 ±142	537 ±71 †
Threshold pressure (cmH_2O)	9.3 ±1.0	7.3 ±0.6
Micturition pressure (cmH_2O)	51.2 ±3.7	44.5 ±4.1
Voided volume (*ml*)	0.046 ±0.009	0.027 ±0.007
Postvoid residual urine (*ml*)	0.28 ±0.04	0.21 ±0.02
Bladder capacity (*ml*)	0.321 ±0.04	0.237 ±0.02
Voiding efficiency (%)	15.2 ±2.4	12.4 ±3.0
CMG-EMG		
Voiding contraction time (*sec*)	26.8 ±2.0	24.1 ±1.9
Reduced EMG activity time (*sec*)	1.25 ±0.20	1.52 ±0.36
Ratio of reduced EMG activity to voiding contraction time (%)	4.6 ±0.6	4.8 ±1.0

References

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Disclosures

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