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Therapeutic effects of p38 MAP kinase inhibitor in storage and voiding dysfunction in mice with spinal cord injury (SCI)

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Introduction & Objectives: The second messenger signalling pathways stimulated by nerve growth factor (NGF), which is up-regulated in SCI bladders, involve activation of p38 MAP kinase (MAPK), which is a serine-threonine kinase that is activated by phosphorylation and mediates cellular responses to a variety of chemical and physical insults. However, it remains to be elucidated whether the p38 MAPK pathway is also involved in lower urinary tract (LUT) dysfunction induced by SCI. Hence, we investigated the effects of p38 MAPK inhibitor (p38 MAPK i) treatment on SCI-induced LUT dysfunction.

Materials & Methods: C57BL/6N mice were used, and SCI was induced by complete transection of the Th8/9 spinal cord. SCI mice were divided into 2 groups; (1) SCI mice treated with a p38 MAPK i (SB203580) and (2) SCI mice with artificial cerebrospinal fluid (CSF) for 2 weeks through an intrathecal catheter connected to an osmotic pump that was implanted into the intrathecal space of L6-S1 spinal cord two weeks after SCI,. SCI mice were evaluated using cystometry (CMG) under an awake condition. L6 dorsal root ganglia (DRG) were then removed from CSF and p38 MAPK i treated SCI mice as well as CSF treated normal (spinal intact) mice to evaluate the levels of TRPV1, TNFα and iNOS transcripts by real-time PCR. We also evaluated the effects of p38 MAPK i on electrophysiological properties of capsaicin sensitive bladder afferent neurons of SCI mice.

Results:

Figure 1; Single CMG recordings in SCI mice

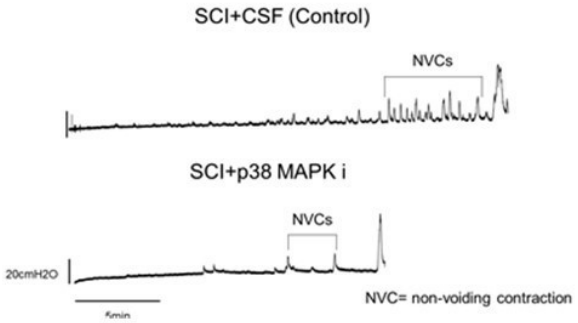

Figure 2; Urodynamic parameters

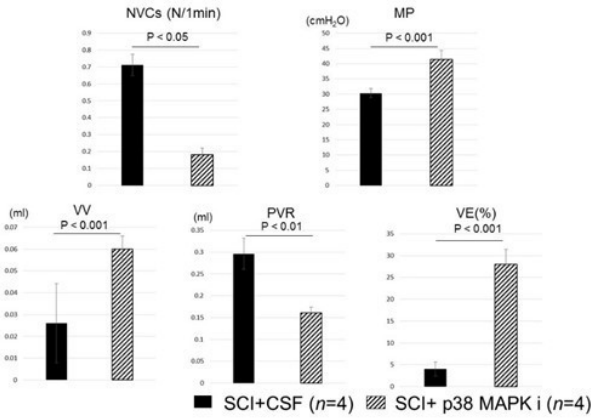

Figure 3; Real-time PCR results

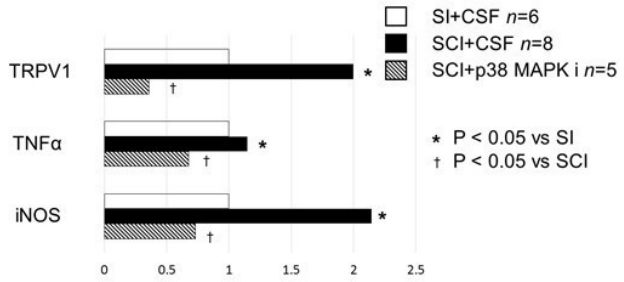

Table. Electrophysiological properties of capsaicin sensitive bladder afferent neurons

	SI	SCI	SCI + p38 MAPK inhibitor
Spikes:			
Number of cells/mice	19/13	24/11	20/8
Diameter (μm)	25.4 ± 4.8	29.3 ± 3.8*	28.5 ± 3.8*
Input capacitance (pF)	26.9 ± 11.6	36.6 ± 10.4*	36.1 ± 10.6*
Resting membrane potentials (mV)	–50.0 ± 0.29	–50.0 ± 0.68	–50.0 ± 0.31
Spike threshold (mV)	–21.5 ± 8.7	–31.2 ± 5.2*	–19.3 ± 8.4#
Peak membrane potential (mV)	39.7 ± 21.1	37.0 ± 15.6	48.5 ± 15.0#
Spike duration (ms)	2.3 ± 1.0	3.7 ± 1.4*	2.5 ± 1.8#
Number of spikes (800 ms depolarization)	1.1 ± 0.3	5.3 ± 4.1*	1.1 ± 0.3#
K^+ current density:			
Number of cells/mice	24/9	24/9	18/7
Slow decaying K_A current density (pA/pF)	48.4 ± 35.8	22.6 ± 14.6*	49.4 ± 26.3#
Sustained K_{DR} current density (pA/pF)	120.7 ± 80.1	54.9 ± 35.4*	63.2 ± 29.9*

Values are means ± SD. *$P < 0.05$ and #$P < 0.05$, when compared with the Bonferroni method to the SI and SCI group, respectively. K_A, A-type K^+; K_{DR}, delayed rectifier-type K^+; SCI, mice with spinal cord injury; SI, spinal cord intact mice; SCI + p38 MAPK inhibitor, SCI mice treated with p38 Mitogen-Activated Protein Kinase inhibitor (0.51 μg per hour, i.t.) for 2

Compared to CSF treated SCI mice, non-voiding contractions during bladder filling were significantly reduced, and intercontraction intervals and micturition pressure were significantly improved, along with the reduction of post-void residual volume, in p38 MAPK i treated SCI mice (fig1,2). The expression of TRPV1, TNFα and iNOS mRNA was increased in SCI mice compared to spinal intact mice, and significantly decreased after p38 MAPK i treatment in SCI mice. p38 MAPK i treatment also reduced p38 phosphorylation in L6 DRG of SCI mice (Fig3). In capsaicin-sensitive bladder afferent neurons, the threshold for eliciting action potentials was significantly reduced in control SCI compared to SI mice, and SCI induced hyperexcitability was reversed by p38 MAPK inhibitor (Table).

Conclusions: These results suggest that p38 MAPK is involved as an important NGF-downstream molecule in LUT problems such as detrusor overactivity and inefficient voiding after SCI.