81

Therapeutic effects of PDE9 inhibitor on lower urinary tract dysfunction (LUTD) in mice with spinal cord injury (SCI)

Eur Urol Suppl 2019; 18(1);e109

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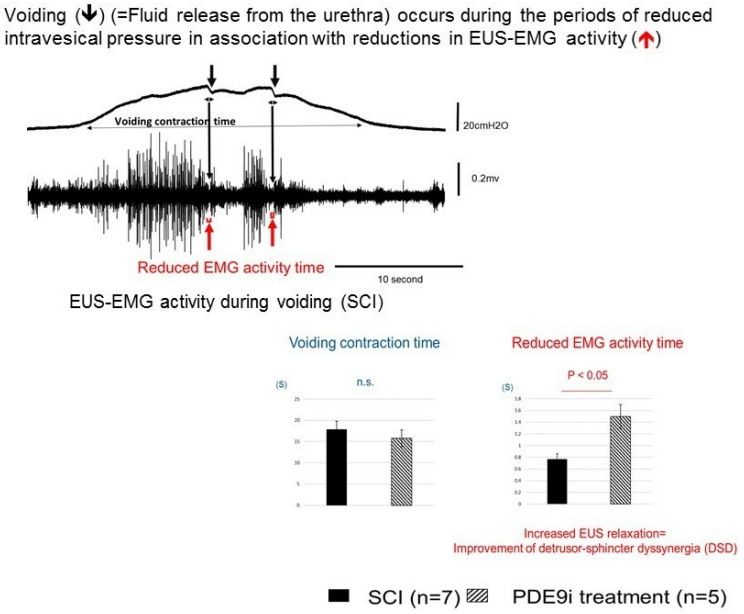
Introduction & Objectives: Phosphodiesterase type 9 (PDE9) is one of novel isozymes, which is expressed in brain, skeletal muscle and urinary tract. Recently, PDE9 inhibitors (PDE9i) have received much attention as potential therapeutics for the treatment of neurological diseases such as Alzheimer's disease. However, it remains to be elucidated whether PDE9 is involved in LUTD induced by SCI. Therefore, we investigated the effects of a PDE9i to clarify the role of PDE9 in storage and voiding dysfunction using SCI mice.

Materials & Methods: C57BL/6N mice were used, and SCI was induced by complete transection of the Th8/9 spinal cord. Two weeks after SCI, PDE9i (PF-04447943; 5mg/kg/day) or saline (treatment or control group, respectively) was administered daily by i.p. injection for 14 days. Four weeks after SCI, urodynamic studies were performed under an awake condition. L6 dorsal root ganglia (DRG), urethral, bladder muscle and mucosal specimens were obtained from PDE9i and saline-treated SCI mice as well as saline-treated normal (spinal intact) mice to evaluate the levels of PDE9, TRPV1, TNFα and VEGF transcripts by real-time PCR

Results: Compared to saline-treated SCI mice, non-voiding contractions during bladder filling were significantly reduced and voiding efficiency was significantly improved in PDE9i-treated SCI mice. PDE9i reverses SCI-induced detrusor-sphincter dyssynergia (DSD), evident as a reduction of sphincter EMG activity time during bladder contractions (Figure 1).The of TRPV1 mRNA levels in DRG and bladder muscle were increased in SCI mice vs. spinal intact mice, and significantly decreased after PDE9i treatment in SCI mice. The TNFα mRNA levels in urethra, bladder muscle and mucosa were increased in SCI mice vs. spinal intact mice, and significantly decreased after PDE9i treatment in SCI mice. PDE9 transcripts were identified in L6 DRG and bladder tissues.



Conclusions: PDE9 inhibition ameliorated SCI-induced detrusor overactivity and inefficient voiding/DSD, along with significant reductions in TRPV1, a C-fiber afferent marker, and TNFa, a proinflammatory cytokine, in mice. Thus, PDE9 could be a therapeutic target for storage and voiding LUTD after SCI.