9 Nerve growth factor-mediated Na+ channel plasticity of bladder afferent neurons in mice with spinal cord injury

Eur Urol Suppl 2019; 18(1);e14

Gu B. [1], Ni J.S. [1], Yoshimura N. [2]

[1]Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Dept. of Urology, Shanghai, China, [2]University of Pittsburgh, School of Medicine, Dept. of Urology, Pittsburgh, United States of America

Introduction & Objectives: It has been reported that nerve growth factor (NGF) is a crucial mediator involved in the emergence of bladder dysfunction after spinal cord injury (SCI). Specifically, NGF are overexpressed in the bladder and spinal cord after SCI and neutralization of NGF can reduce non-voiding contractions (NVCs), improve voiding efficiency and reverse the hyperexcitability of bladder afferent neurons. Na+ current is a dominant factor of neuronal excitability. Previous studies demonstrated that Nav channels existed in bladder afferent neurons and a transition from tetrodotoxin(TTX)-resistant to TTX-sensitive of Na+ current was found after SCI. Here, we aim to investigate the effect of NGF neutralization on Na+ channel plasticity of bladder afferent neurons in mice with spinal cord injury.

Materials & Methods: Thirty-sixth female C57/BL6 mice were randomly divided into three groups: Spinally intact (SI) group, SCI group and SCI+Ab group. SCI was conducted by transection at the Th8/9 level. In SCI+Ab group, anti-NGF antibodies (10 μg•kg-1 per hour) were administered subcutaneously for 2 weeks by osmotic pump. Bladder afferent neurons were labelled with Fluoro-gold (FG), injected into the bladder wall three weeks after SCI. Four weeks after SCI, L6-S1 dorsal root ganglion (DRG) neurons were dissociated and whole cell patch clamp recordings were performed on FG-labelled neurons. Action potential (AP) and Na+ current were recorded before and after TTX intervention. L6-S1 DRGs were harvested for immunofluorescence staining of Nav1.7 and Nav1.8.

Results: The whole-cell patch clamp recordings showed that TTX could partly inhibit AP and Na+ current of bladder afferent neuron in SI mice, which are almost completely inhibited in SCI mice. Total and TTX-sensitive Na+ current increased and TTX-resistant current decreased in SCI mice, which indicated a transition of Na+ channels from TTX-resistant to TTX-sensitive subtypes. These changes can be partially reversed by NGF-antibody treatment. Immunofluorescence results showed that Nav 1.7 increased and Nav 1.8 decreased in FG-labelled bladder afferent neurons in SCI mice compared to SI mice, which was partially reversed in SCI+Ab mice.

Conclusions: Foregoing results indicate that NGF mediates the Na+ channel plasticity that TTX-resistant subtypes (Nav 1.8) changed to TTX-sensitive subtypes (Nav 1.7), and this might be an underlying mechanism of bladder overactivity after SCI. Besides, NGF-targeting therapies could be effective for treatment of neurogenic bladder dysfunction after SCI.