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HYPEREXCITABILITY OF BLADDER AFFERENT NEURONS ASSOCIATED WITH REDUCED EXPRESSION OF POTASSIUM CHANNEL KV1.4 A–SUBUNIT IN RATS WITH SPINAL CORD INJURY

Hypothesis / aims of study
Hyperexcitability of C-fibre bladder afferent pathways has been proposed as an important pathophysiological basis of neurogenic detrusor overactivity with spinal cord injury (SCI). However, the functional and molecular mechanisms inducing hyperexcitability of C-fibre bladder afferent neurons after SCI are not fully elucidated. We therefore examined changes in electrophysiological properties of bladder afferent neurons obtained from spinal transected rats, especially focusing on voltage-gated potassium (K^+) channels and the expression levels of α–subunits, which can form A-type K^+ (K_A) channels. Activation of K_A channels is known to reduce excitability of capsaicin-sensitive C-fibre bladder afferent neurons from spinal intact rats [1].

Study design, materials and methods
Freshly dissociated L6-S1 dorsal root ganglia (DRG) neurons were prepared from female spinal intact and spinal transected (4 weeks after T9-T10 transection) SD rats. Whole cell patch-clamp recordings were performed on individual bladder afferent neurons, which were labelled by retrograde axonal transport of a fluorescent dye, Fast Blue (FB) injected into the bladder wall 7 days prior the dissociation. Since the majority (80%) of C-fibre bladder afferent neurons are known to be sensitive to capsaicin, capsaicin-sensitive neurons were selected for evaluation. The expression levels of Kv1.2 and 1.4 α–subunits were evaluated using immunohistochemical methods.

Results
Capsaicin-sensitive bladder afferent neurons from spinal transected rats exhibited increased cell excitability evidenced by lower thresholds for spike activation (-26.4±1.3mV) and the increased number of action potentials (4.7±0.7 spikes) during a 800 msec depolarizing pulse compare to spinal intact rats (-21.8±0.9mV and 1.3±0.1 spikes, respectively) (Fig. 1). The peak density of slowly-inactivating K_A currents during membrane depolarizations to 0mV in capsaicin-sensitive bladder afferent neurons of spinal transected rats was significantly smaller (38.1±4.6 pA/pF) than that from spinal intact rats (68.6±6.3 pA/pF) (Fig. 2), and the inactivation curve of the K_A current was displaced to more hyperpolarized levels by ~10mV after spinal transection (Fig. 3). On the other hand, the sustained delayed-rectifier K^+ current density was not altered after spinal transection (Fig. 2). The expression of Kv1.4 α–subunits, which can form K_A channels, was reduced in bladder afferent neurons from spinal transected rats compared to spinal intact rats (Fig. 4).

Interpretation of results
These results indicate that: (1) capsaicin-sensitive bladder afferent neurons in spinal transected rats show hyperexcitability as evidenced by lower thresholds for spike activation and tonic firing pattern, (2) the density of slowly-inactivating K_A currents was reduced and the inactivation curve of K_A currents for spinal transected rats was displaced to more hyperpolarized levels in comparison with spinal intact rats, (3) the expression of Kv1.4 α-subunits in bladder afferent neurons was decreased after spinal transection. Thus, it is assumed that the excitability of capsaicin-sensitive C-fiber bladder afferent neurons is increased in association with reductions in K_A current size and Kv1.4 α–subunit expression in spinal transected rats.

Concluding message
The reduction in K_A channel activity due to downregulation of the Kv1.4 α–subunit could contribute to hyperexcitability of C-fibre bladder afferent pathways, leading to detrusor overacitivity in SCI. Thus, the Kv1.4 α–subunit could be a potential molecular target for treating OAB due to neurogenic detrusor overactivity.

Fig.1

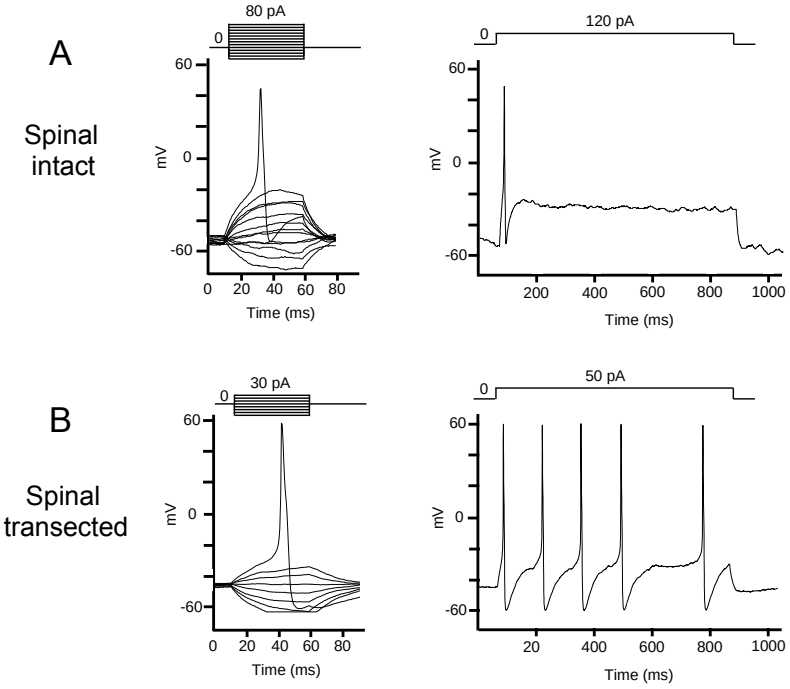


Fig.2

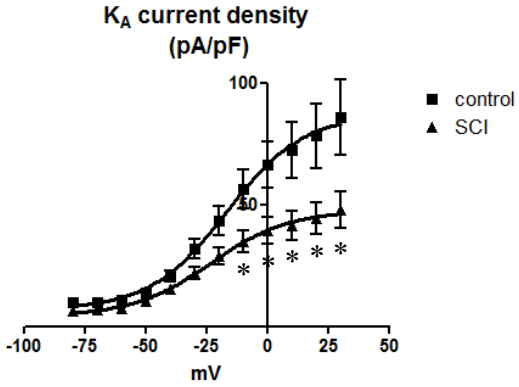


Fig.3

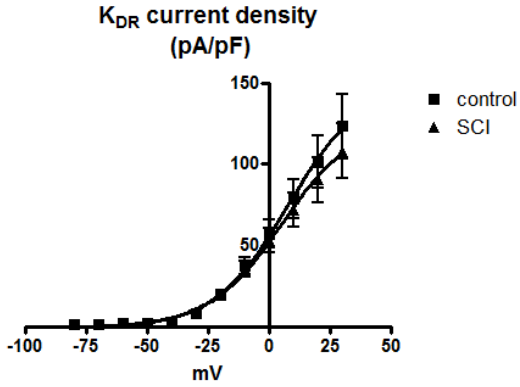
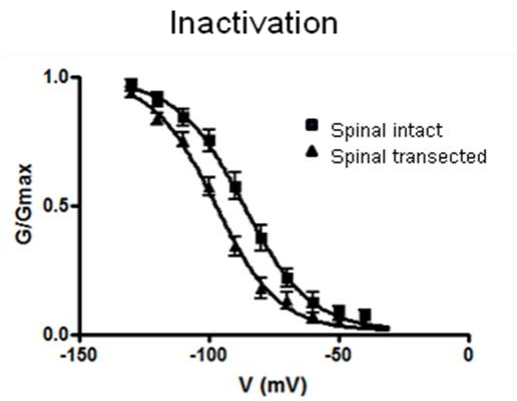
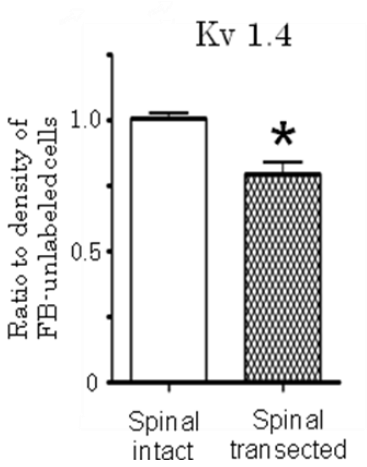


Fig.4





References
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Disclosures
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