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Gene Therapy Targeting Chloride Homeostasis Reverses Cancer-Related Neuropathic Pain

Lingyong Li*

Department of Anesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, Houston, USA

***Corresponding author:** Lingyong Li, Center for Neuroscience and Pain Research, Department of Anesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; **E-mail:** lingyongli@yahoo.com

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Chronic neuropathic pain is a major, debilitating clinical problem that remains difficult to treat, and over 90 percent of cancer patients who have had nerve damage caused by tumors, surgery, chemotherapy or radiation are suffered from neuropathic pain [1]. Because of our limited understanding of the mechanisms underlying neuropathic pain, the existing analgesics for neuropathic pain are not very effective and are associated with various side effects. Gene therapy strategies may target specific chronic pain mechanisms in a tissue-specific manner to be used to correct the abnormal functional proteins, modulate the activity of signal transduction pathways or overproduce various therapeutic secreted proteins.

The loss of synaptic inhibition by γ-aminobutyric acid (GABA) and glycine due to K^+-Cl^- co-transporter 2 (KCC2) down-regulation and the increase of glutamate-mediated input and N-methyl-D-aspartate receptor (NMDAR) activity in the spinal dorsal horn are the two major mechanisms underlying chronic neuropathic pain. Our recent study found lentivirus-mediated overexpression of KCC2 restored KCC2 activity by the depolarizing shift the reversal potential of GABA-mediated currents in spinal cord horn and DRG neurons caused by nerve injury. We also found that restoring KCC2-mediated inhibition caused a large decrease in the amplitude of NMDAR-mediated excitatory postsynaptic currents of dorsal horn neurons and in the frequency of miniature EPSCs in dorsal horn neurons of spinal nerve ligation (SNL) rats. Moreover, a single intrathecal injection of lentivirus over expressing KCC2 reversed nerve injury-induced tactile allodynia and mechanical hyperalgesia for at least 8 weeks. Our findings suggest that restoring KCC2-mediated spinal inhibition produces long-lasting relief of nerve injury-induced chronic pain through NMDARs, and virus-mediated over expression of KCC2 at spinal level offers a promising gene therapy for treating chronic neuropathic pain.

Neuropathic pain mechanisms are complex, and it remains unclear to what extent the reduced spinal KCC2-mediated synaptic inhibition contributes to neuropathic pain. Our data showed that restoring KCC2 function in the spinal dorsal horn by virus-mediated overexpression of KCC2 not only restore intracellular Cl^- level and increase GABA/glycine synaptic inhibition, but also reduces the glutamatergic synaptic input to spinal dorsal horn neurons and decrease the NMDA receptor-mediated excitability of spinal dorsal horn neurons. These results suggest that nerve injury-induced spinal NMDAR activity may be activity dependent, maintained by a sustained glutamatergic input from primary afferents after nerve injury, and the reduction of KCC2-dependent firing activity may contribute to the potentiation of NMDARs. Thus we propose that spinal pain information processing is mediated by a convergent feed-forward mechanism: peripheral injury (KCC2 activity reduce) leads to a decrease in inhibitory postsynaptic currents in superficial dorsal horn neurons, and the disinhibition increases release of glutamatergic neurotransmitters and activate the NMDAR, which increases the excitability of the output neuron and facilitate the transmission of pain messages to the brain.

In addition to spinal cord injury-induced spasticity and pain, similar changes in KCC2 expression have been also demonstrated in the spinal dorsal horn as a prominent feature of inflammation, metabolic nerve injury and even opioid-induced hyperalgesia. Our findings indicate that gene therapy targeting KCC2 reverses SNL-induced pain hypersensitivity long-lastingly, suggesting the virus-mediated overexpression of KCC2 based approach in spinal level is a promising way for these clinical conditions.

Reference

1. Li L, Chen SR, Chen H, Wen L, Hittelman WN, et al. (2016) Chloride Homeostasis Critically Regulates Synaptic NMDA Receptor Activity in Neuropathic Pain. Cell Rep 15: 1376-1383.