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Research findings reveal potential to reverse cancer-related nerve pain

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A study providing new information about neuropathic pain afflicting some 90 percent of cancer patients who have had nerve damage caused by tumors, surgery, chemotherapy or radiation indicates gene therapy as a possible treatment.

The study in rats showed transfer of a gene known as KCC2 into the spinal canal restored chloride levels gone awry after nerve injury. Results from the research at The University of Texas MD Anderson Cancer Center, were published in the May 5 online issue of *Cell Reports*.

The results also could have implications for treatment of chronic pain due to diabetic neuropathy and spinal cord injury since neuropathic pain caused by these conditions is associated with reduced KCC2 activity.

"We found that delivery of KCC2 produced a complete and long-lasting reversal of nerve injury-induced pain hypersensitivity by restoring chloride homeostasis," said Hui-Lin Pan, M.D., Ph.D., professor of Anesthesiology and Perioperative Medicine. "This information significantly advances our understanding of these processes and provides a promising gene therapy strategy for treating unmanageable neuropathic pain."

The proper balance of chloride, a mineral crucial for nerve cell function, is thrown off kilter by nerve damage associated with surgery or the toxic aspects of standard chemotherapies. This causes the inhibitory neurotransmitters GABA and glycine to become less effective and

increases activity by excitatory nerve receptors known as NMDA receptors.

"Diminished synaptic inhibition by GABA and glycine and increased NMDA receptor activity are two key mechanisms underlying neuropathic pain," said Pan. "However the reciprocal relationship between the two is unclear. By using KCC2 gene transfer, we were able to restore chloride balance which also unexpectedly normalized NMDA receptor activity increased by nerve injury."

Chronic neuropathic pain is a major, debilitating clinical challenge that is difficult to treat. Existing analgesics including anti-depressants, opioids and gabapentinoids have limited efficacy and often produce intolerable side effects.

"The development of highly effective patient treatments with minimal effects is urgently needed," said Pan. "Our study addressed the need to change the intracellular concentration of chloride which can profoundly alter the strength and polarity of GABA and glycine."

Pan's study provided direct evidence that disrupted chloride homeostasis plays a critical role in regulation of NMDA receptors in neuropathic pain and that nerve injury increases NMDA receptor activity in the spinal cord by disrupting chloride levels.

Provided by University of Texas M. D. Anderson Cancer Center