New molecular mechanism of neuropathic pain in mice

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A research group from Hiroshima University demonstrated that the downregulation of spinal astrocyte connexin43 (Cx43) expression causes sustained neuropathic pain following peripheral nerve injury. Controlling the Cx43 expression using pharmacological approaches or gene therapy might serve as novel therapeutic strategies ameliorate neurological disorders in general and neuropathic pain in particular.

The downregulation of spinal astrocyte connexin43 (Cx43) expression causes sustained neuropathic pain following peripheral nerve injury. The inflammatory cytokinetumor necrosis factor (TNF) mediates the downregulation of Cx43 expression, which leads to decreased expression of the glutamate transporter GLT-1 and enhanced glutamatergic neurotransmission. Targeting the recovery of Cx43 function using pharmacological approaches or gene therapy might serve as novel therapeutic strategies ameliorate neurological disorders in general and neuropathic pain in particular.

Spinal cord astrocytes are critical in the maintenance of neuropathic pain. Cx43 expressed on spinal dorsal horn astrocytes modulates synaptic neurotransmission, but its role in nociceptive transduction has yet to be fully elaborated.

Several types of Cx have been identified in the spinal cord. Cx43 is preferentially and mainly expressed in astrocytes, and altered astrocytic Cx43 expression is associated with various neurological disorders such as the neuroinflammation observed in multiple sclerosis. However, the relationship between astrocytic Cx43 expression level and changes in pain perception is controversial.

A research group from Hiroshima University investigated the effects of altered spinal astrocytic Cx43 expression and pain-related behavior following peripheral nerve injury. They found that in the spinal cord, an inflammatory event following nerve injury resulted in the release of cytokines such as TNF and induced the downregulation of astrocytic Cx43 and GLT-1 expression, resulting in increased excitatory synaptic activity.

"When downregulated Cx43 expression is restored by adenovirus vector expressing Cx43 in mouse model, reversed mechanical hypersensitivity was observed," stated Dr. Norimitsu Morioka. "In addition, downregulated GLT-1 was reversed by restoration of Cx43 by adenovirus vector expressing Cx43. It is possible that Cx43 directly regulates GLT-1 expression and function".

The precise molecular mechanisms involving Cx43-mediated GLT-1 downregulation require further investigation. These results indicate the importance of spinal astrocyte Cx43 are essential for maintenance of neuropathic pain following peripheral nerve injury and suggested modulation of Cx43 as a novel target for developing analgesics for neuropathic pain.

More information: "Tumor necrosis factor-mediated downregulation of spinal astrocytic connexin43 leads to increased glutamatergic neurotransmission and neuropathic pain in mice," *Brain, Behavior, and Immunity*, DOI: 10.1016/j.bbi.2015.06.015

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