Researchers identify root of chronic pain as potential new drug target

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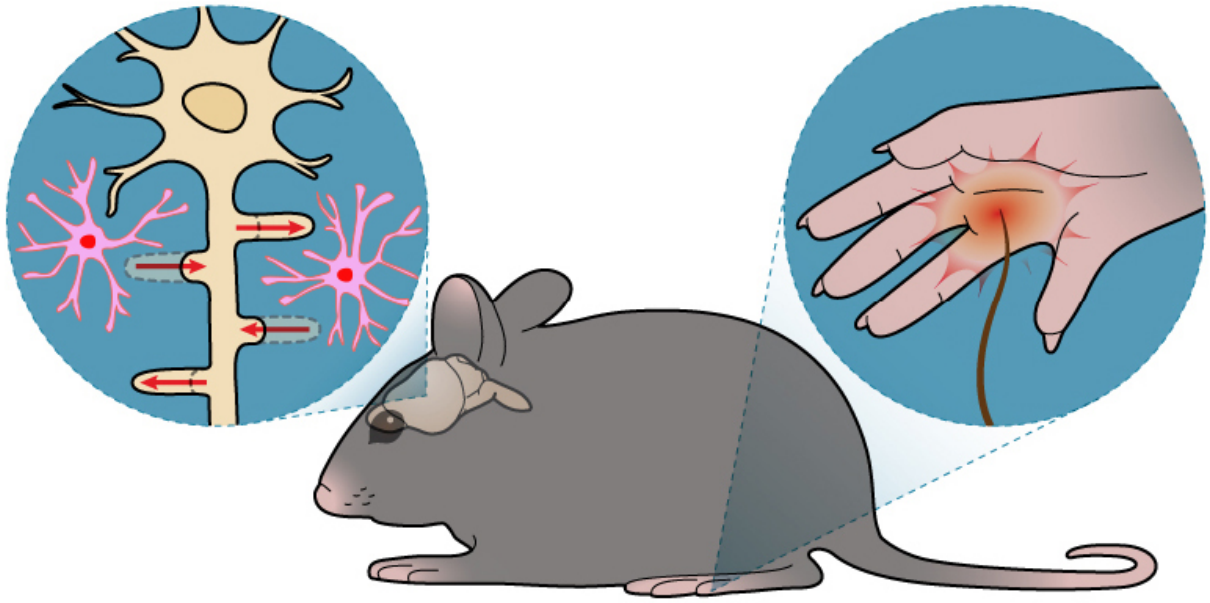

NIPS-led researchers measured the heightened pain response when mice with a leg nerve injury were poked on the underside of a hind paw with a fine filament. Simultaneous live imaging of calcium ions in the brain's S1 cortex showed that certain signaling pathways were activated in astrocytes, a type of cell that helps neurons. Certain signaling pathways in S1 astrocytes were activated and triggered S1 cortex rewiring, contributing to mechanical hypersensitivity (allodynia). Such astrocyte-mediated changes in the brain may provide new clues for novel therapeutic strategies for treating debilitating mechanical allodynia. Credit: NIPS/NINS

When we are in pain, we reach for painkillers as we try to "turn off" the pain. Unfortunately, this does not always work, and this problem has prompted researchers around the world to seek the "main switch" that can promptly and effectively conduct this switching off.

Pain comes in many forms; one is allodynia, which is pain that is greatly amplified by even the slightest sensations, such as light, touch, or warmth. Current treatments to alleviate allodynia are limited. The spinal cord and glial cells, which provide support and insulation between neurons and are the most abundant cell types in the central nervous system, are thought to play a crucial role in allodynia. However, the underlying cellular mechanisms of their involvement remained unsolved, until now.

An international team of researchers centered at the National Institute for Physiological Sciences (NIPS) has identified a sequence of events in the S1 cortex, a remote region of the brain not directly affected by spinal cord injury, that contribute to sustained mechanical allodynia. The findings are to be reported in *The Journal of Clinical Investigation*.

"Direct manipulation of the S1 cortex has been shown to relieve neuropathic pain in humans and animals. This suggests the S1 cortex might act as a sort of central processing unit within the brain networks that mediate and/or sustain chronic neuropathic pain," study first author Sun Kwang Kim explains. "We hypothesized that S1 astrocytes, a type of glial cell, may show functional changes following peripheral nerve injury , resulting in mechanical allodynia."

The researchers tested the hypothesis by conducting a series of experiments in mice with a leg nerve injury. Thin filaments were applied to the underside of a back paw, and the paw response to each application was measured. At the same time, live calcium ion imaging was used to track the corresponding activities of astrocytes in the S1 cortex. They

found that specific signaling pathways, including one that allowed an influx of calcium into the astrocytes, were activated only during the first week after injury and correlated spine turnover, and that blocking the pathways suppressed mechanical allodynia. Conversely, activating them resulted in long-lasting allodynia, even when there was no peripheral injury.

The results indicate that this "reawakening" of S1 astrocytes is a key trigger for S1 circuit rewiring, and that it contributes to neuropathic mechanical allodynia. "By revealing some of the underlying mechanisms, our study sug¬gests that cortical changes may move beyond their utility as just diagnostic tools and serve as potential targets for therapeutics," corresponding author Junichi Nabekura says. "Appreciation of these astrocyte-mediated changes in cortical synaptic connections requires a paradigm shift in our understanding of neuropathic pain pathophysiology; one that may result in novel therapeutic strategies for treating the debilitating effects of allodynia."

More information: Sun Kwang Kim et al. Cortical astrocytes rewire somatosensory cortical circuits for peripheral neuropathic pain, *Journal of Clinical Investigation* (2016). DOI: 10.1172/JCI82859

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