The protein that makes us remember pain

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(PhysOrg.com) -- New research by scientists in Arizona in the US has demonstrated that an enzyme makes the body remember and remain sensitive to pain after an injury has healed.

Research in 2006 by Professor Todd C. Sacktor of the State University of New York Downstate Medical Center found that the protein kinase M zeta (PKMzeta) appears at the synapses (gaps between neurons) and must be continually recreated at the synapses. If it disappears, so do memories of the pain. Sacktor's team were able to irreversibly erase memories of pain in rats by using a chemical called zeta-inhibiting peptide (ZIP) which inhibits PKMzeta. In later research the showed that extra PKMzeta affected the brains of rats by boosting old memories.

Now new research by Marina Asiedu and Dipti Tillu and colleagues from the University of Arizona Medical School has shown that PKMzeta is also responsible for the lingering pain and sensitivity felt after an injury. The researchers knew that when pain is experienced the neurons carrying the pain signals develop stronger connections, especially in the dorsal horn section of the spinal cord. The same thing happens in the brain when we learn something new, and so they decided to test the hypothesis that PKMzeta is involved in both processes.

The team injected mice in the paw with Interleukin-6 (IL-6), a protein that produces mild swelling and makes the paw more sensitive for up to three days. They later injected prostaglandin E2 (PGE2) into the paw, and the mice reacted to the chemical, but only if they had previously been injected with IL-6. If the mice were injected with ZIP at the same

time as IL-6 or up to three days afterwards, their paws never became more sensitive to PGE2, indicating they had not developed a memory for the pain. When they injected a protein that mimics PKMzeta, the sensitivity returned.

Researchers in Korea made similar discoveries for chronic pain in research published in 2010. Dr Xiang-Yao Li and colleagues found that PKMzeta creates memories in chronic pain caused by nerve damage, and in this research they found the protein affects the anterior cingulated cortex (ACC) part of the brain. An injection of ZIP was found to ease the pain, but only for a few hours and not permanently.

If the protein kinase M zeta produces the same effects in humans, new treatments could be developed that target PKMzeta to treat severe or chronic pain, and conditions such as central neuropathic pain syndrome, in which people retain the memory of a pain long after the injury has healed. PKMzeta may also play a role in other conditions such as addictions and post traumatic stress disorder.

More information: Spinal Protein Kinase M ζ Underlies the Maintenance Mechanism of Persistent Nociceptive Sensitization, *The Journal of Neuroscience*, 4 May 2011, 31(18): 6646-6653; doi:10.1523/JNEUROSCI.6286-10.2011

Abstract

Sensitization of the pain pathway is believed to promote clinical pain disorders. We hypothesized that the persistence of a sensitized state in the spinal dorsal horn might depend on the activity of protein kinase M ζ (PKMζ), an essential mechanism of late long-term potentiation (LTP). To test this hypothesis, we used intraplantar injections of interleukin-6 (IL-6) in mice to elicit a transient allodynic state that endured ~3 d. After the resolution of IL-6-induced allodynia, a subsequent intraplantar injection of prostaglandin E2 (PGE2) or intrathecal injection of the

metabotropic glutamate receptor 1/5 (mGluR1/5) agonist DHPG (dihydroxyphenylglycol) precipitated allodynia and/or nocifensive responses. Intraplantar injection of IL-6 followed immediately by intrathecal injection of a PKMζ inhibitor prevented the expression of subsequent PGE2-induced allodynia. Inhibitors of protein translation were effective in preventing PGE2-induced allodynia when given immediately after IL-6, but not after the initial allodynia had resolved. In contrast, spinal PKMζ inhibition completely abolished both prolonged allodynia to hindpaw PGE2 and enhanced nocifensive behaviors evoked by intrathecal mGluR1/5 agonist injection after the resolution of IL-6-induced allodynia. Moreover, spinal PKMζ inhibition prevented the enhanced response to subsequent stimuli following resolution of hypersensitivity induced by plantar incision. The present findings demonstrate that the spinal cord encodes an engram for persistent nociceptive sensitization that is analogous to molecular mechanisms of late LTP and suggest that spinally directed PKMζ inhibitors may offer therapeutic benefit for injury-induced pain states.

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