PAIN

Converging on LTP

Anxiety disorders are common in individuals with chronic pain and the development of such pain is more likely in people with anxiety. The anterior cingulate cortex (ACC) is implicated in both conditions, although the underlying neurobiological relationship between pain and anxiety is unclear. Now, Koga *et al.* show in mice that chronic pain and anxiety may be mechanistically linked by a presynaptic form of long-term potentiation (LTP) that occurs at synapses in the ACC.

LTP can be induced in the ACC by the activation of postsynaptic NMDA receptors, with the expression of such LTP being largely mediated by postsynaptic enhancement of AMPA receptor (AMPAR) responses, and evidence suggests that this mechanism is involved in pain perception. However, *ex vivo* studies have revealed that peripheral nerve injury, which can lead to chronic pain, causes enhanced excitatory transmission in the ACC that also involves enhanced glutamate release. This led the authors to examine whether a presynaptic form of LTP in the ACC contributes to chronic pain.

To determine whether presynaptic LTP can be induced at synapses in the ACC, the authors stimulated mouse brain slices that included the ACC using a protocol that is known to induce presynaptic LTP in the amygdala. Stimulation in layer 5/6 increased the amplitudes of evoked excitatory postsynaptic currents (eEPSCs) in layer 2/3 pyramidal neurons in the ACC for at least 1 hour, indicating that presynaptic LTP had been induced.

The authors examined the underlying mechanisms of such LTP and found that genetic deletion of the gene encoding the GLUK1 kainate receptor (KAR) subunit reduced presynaptic LTP in the ACC, and application of a GLUK1 KAR agonist induced presynaptic LTP. These findings show that GLUK1-containing KARs are necessary and sufficient for presynaptic LTP induction in the ACC.

The authors also found that pharmacological blockade of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels before stimulation blocked the induction of presynaptic LTP and that HCN channel inhibition after LTP expression reduced eEPSCs to baseline levels. Thus, HCN channels are necessary for the induction and maintenance of presynaptic LTP at synapses in the ACC.

The authors next examined the effects of chronic pain on presynaptic LTP. In mouse models of chronic inflammatory or neuropathic pain, they were unable to induce presynaptic LTP. However, they reasoned that the apparent absence of presynaptic LTP could have resulted from a saturation of this mechanism and tested this possibility by applying an HCN channel inhibitor to slices taken from mice that underwent nerve injury (a model of chronic pain). This treatment reduced eEPSCs in ACC neurons activated by the injury, suggesting that chronic pain had indeed activated and saturated presynaptic LTP. Interestingly, such LTP could also not be induced in mouse models of anxiety.

Finally, the authors examined whether presynaptic LTP might explain the increase in anxiety that often accompanies chronic pain. To do so, they microinjected an HCN channel inhibitor into the ACC of mice with nerve injury and showed that, in two different anxiety-like behaviour paradigms, these animals had lower levels of anxiety than saline-injected nerve injury controls. They also exhibited a reduction in mechanical allodynia, confirming the importance of presynaptic LTP in the development of chronic pain.

Together, these findings suggest that induction of a form of presynaptic LTP at synapses in the ACC may, at least in part, explain the interaction between chronic pain and anxiety at the clinical level.

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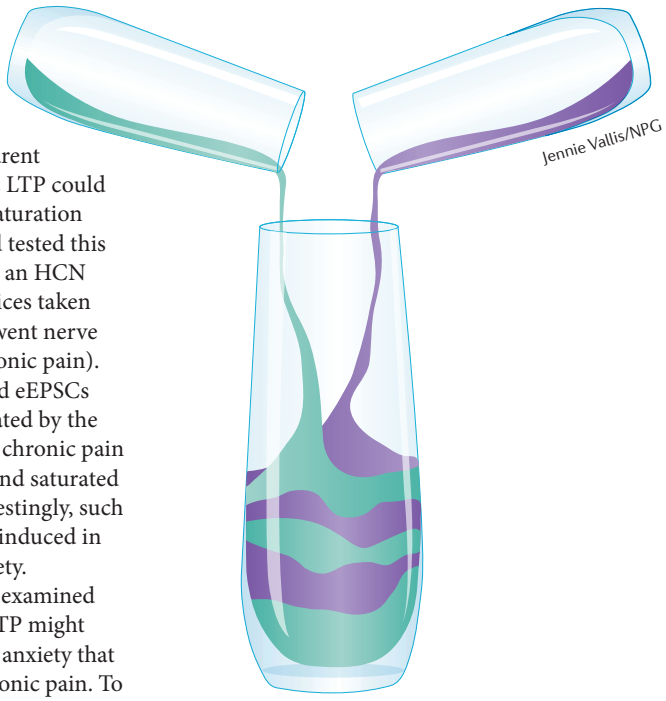

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