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PAIN

A new trick for opioids?

Continuous low doses of opioids such as morphine are often prescribed for the management of severe pain symptoms, but this treatment does not undo the changes in pain signalling pathways that underlie chronic pain. In a new paper published in *Science*, a team led by Drdla-Schutting and Sandkühler reveals that these drugs have previously undiscovered potential for use in the treatment of chronic pain by showing that an acute high dose of an opioid agonist is able to reverse plasticity at pain-transmitting synapses in the rat spinal cord.

Long-term potentiation (LTP) at synapses between the sensory fibres (C-fibres) that detect painful stimuli and secondary neurons in the dorsal horn of the spinal cord is thought to contribute to the development and maintenance of chronic pain symptoms, such as hyperalgesia. μ-opioid receptor (MOR) agonists exert their painkilling effects by dampening transmission at these synapses; however, whether they could also be used to reverse LTP was unknown.

The authors examined the effects of intravenous administration of a brief, high dose of the short-acting MOR agonist remifentanil in several models of spinal LTP in adult rats. They found that remifentanil suppressed the potentiated responses of C-fibres that were induced by low- or high-frequency stimulation of these fibres or by subcutaneous application of capsaicin. The effects lasted well beyond the duration of remifentanil treatment, suggesting that the drug could reverse (or 'depotentiate') the LTP induced by these stimuli. Furthermore, an identical dose could reverse LTP even when given 4 hours after the LTP-inducing stimulus, showing that it is effective in both the induction and maintenance phases of LTP. High-dose remifentanil was also able to reduce behavioural symptoms of hyperalgesia caused by subcutaneous injection of capsaicin.

Next, the authors considered the mechanisms underlying the depotentiation of C-fibre synapses by remifentanil. They found that calcium-dependent signalling via NMDA receptors and type 1 metabotropic glutamate receptors was essential for the remifentanil-induced depotentiation. Furthermore, high-dose remifentanil treatment reversed some of the modifications of AMPA receptor subunits (including phosphorylation of glutamate receptor 1 (GluR1) subunits and dephosphorylation of GluR2 subunits) that are thought to contribute to LTP at C-fibre synapses.

These findings suggest that a new therapeutic strategy for chronic pain should be explored by further studies. It is possible that acute, high doses of opioids, rather than the more usual prolonged low doses, could be used as a relatively simple and cheap strategy to not only manage the symptoms of pain but also to reverse some of the molecular changes that lead to chronic pain.

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> an acute high dose of an opioid agonist is able to reverse plasticity at pain-transmitting synapses

ORIGINAL RESEARCH PAPER Drdla-Schutting, R. *et al.* Erasure of a spinal memory trace of pain by a brief, high-dose opioid administration. *Science* **335**, 235–238 (2012)