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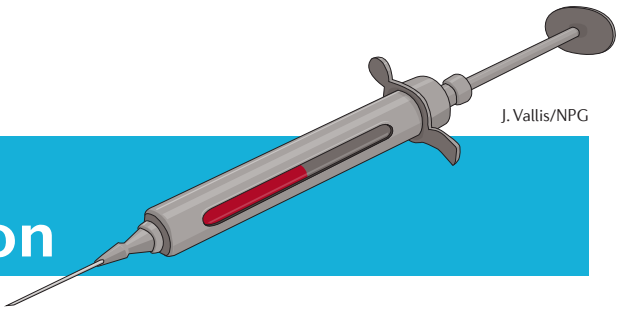

J. Vallis/NPG

PAIN

A painful addiction

> a longer lasting central sensitization might remain in the spinal cord ... that ... was being masked by a compensatory, homeostatic increase in tonic MOR activity

Chronic pain is associated with central sensitization — a state of chronic hyper-responsiveness in spinal cord pain pathways that involves enhanced NMDA receptor (NMDAR) signalling. Chronic pain is known to be partially tempered by the endogenous opioid system because administration of opioid antagonists such as naloxone hydrochloride (NLX) or naltrexone (NTX) increases hyperalgesia in humans and animals. Corder *et al.* show that after resolution of acute inflammatory pain, central sensitization of pain pathways persists but is masked by endogenous opioid signalling.

The authors used several mouse models of pain, including the unilateral injection of complete Freund's adjuvant (CFA) into the hindpaw plantar region. In the CFA model, recovery from inflammatory hyperalgesia, spontaneous pain and affective pain occurs within 10 days.

The authors found that NTX administration 21 days after CFA (CFA-21d) reinstated hyperalgesia, as did intrathecal administration of CTOP, a selective blocker of the μ-opioid receptor (MOR). The authors reasoned that although the acute inflammatory response in CFA-21d mice had subsided, a longer lasting central sensitization might remain in the spinal cord for more than 6 months and that this was being masked by a compensatory, homeostatic increase in tonic MOR activity.

MOR signals via $G\alpha_{i/o}$-type G proteins and inhibition of $G\alpha_{i/o}$ signalling with pertussis toxin reinstated hyperalgesia in CFA-21d mice. Selective MOR activation in spinal cord slices from CFA-21d mice led to an increase in the binding between $G\alpha_{i/o}$ and its substrate GTP-γ-S but not in sham-operated control mice. The antinociceptive effects of intrathecal administration of the MOR agonist DAMGO were enhanced in CFA-21d mice compared with those in controls. The neutral receptor antagonist 6-β-naltrexol abolished the ability of NTX to produce hyperalgesia, and the inverse agonist β-FNA reduced basal GTP-γ-S binding. Together, these findings indicate that injury transforms the MOR into a state of constitutive activity (which the authors term MOR_{CA}) that provides analgesic signals in the absence of the endogenous ligand. The authors next sought to determine whether MOR_{CA} was masking NMDAR-mediated central sensitization. Co-administration of NTX and glutamate resulted in larger increases in intracellular calcium in spinal cord laminae I and II of CFA-21d mice than that of glutamate alone, and this effect was blocked by administration of the NMDAR antagonist MK-801. This suggests that MOR_{CA} suppresses NMDAR-mediated calcium signalling in CFA-21d mice.

NMDARs are known to activate adenylyl cyclases (ACs), and the authors found that, in CFA-21d mice, NTX administration produced an overshoot in the cyclic AMP response that did not occur in controls, and this effect was abolished by MK-801. These data support the notion of an AC-mediated central sensitization pathway that is increased in CFA-21d mice and kept in check by MOR_{CA}.

Increased AC activity and MOR_{CA} is also associated with opiate addiction and dependence, and NTX-produced behaviours that are characteristic of opiate withdrawal, including jumping, paw tremors and hyperlocomotion. These findings reveal an unexpected role for the endogenous opioid system in tempering chronic pain mechanisms and also for producing a form of 'endogenous opioid dependence' that is unmasked by MOR inhibition.

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ORIGINAL RESEARCH PAPER Corder, G. *et al.* Constitutive μ-opioid receptor activity leads to long-term endogenous analgesia and dependence. *Science* **341**, 1394–1399 (2013)