ANALGESICS

Pain control at the periphery

Cannabinoid receptor 1 (CB_1) and CB_2 are expressed throughout the nervous system and are known to play a part in analgesia. However, the mechanisms underlying this effect in the periphery, including the identity of the endogenous ligand, are poorly understood. Now, Piomelli and colleagues report the development of a small molecule that is restricted to peripheral tissues and inhibits pain signalling by increasing the levels of the endocannabinoid anandamide. These findings suggest an approach to treat pain that would avoid the psychotropic effects of drugs that target central cannabinoid signalling.

The authors began by chemically modifying a CNS-penetrating inhibitor of fatty acid amide hydrolase (FAAH), the enzyme that degrades anandamide, at residues that would not affect the compound's biological activity. Intraperitoneal administration of a hydroxylated derivative, termed URB937, to mice and rats inhibited FAAH activity and increased anandamide levels in peripheral tissues but not in the brain. Biochemical assays revealed that URB937 was actively extruded from the CNS by a transporter system at the blood–brain barrier.

Next, the authors tested the effect of the compound in various rodent models of pain. Injection of acetic acid into the peritoneal cavity of mice caused writhing, which was reduced by administration of URB937. The effect of the compound was blocked by infusion of the CB_1 antagonist rimonabant but not a CB_2 antagonist, suggesting that the drug-induced increase in levels of anandamide elicited analgesia through activation of CB_1 receptors. Similarly, in mouse models of neuropathic pain and peripheral inflammation, URB937 attenuated thermal and mechanical hyperalgesia.

How does a peripherally active compound affect pain perception? To investigate a possible effect on central processing of nociceptive signals, the authors measured the expression of FOS, an indicator of neuronal activity, in the spinal cord of rats that were administered formalin into the hind paw to induce persistent pain. These rats showed higher FOS expression in regions of the dorsal horn that are implicated in nociceptive processing than vehicle-treated rats and, importantly, this effect was attenuated by co-injection of URB937. The authors therefore proposed that increased activation of peripheral CB_1 receptors resulting from URB937 treatment regulates the transmission of emerging pain signals from peripheral afferent terminals to the spinal cord and the brain.

Cannabinoid signalling has a role in diverse physiological functions, most notably appetite and locomotion. The authors therefore tested the effect of URB937 on feeding and spontaneous movement in mice, and found that it had no effect on these processes. Together, these studies suggest a means to exploit an endogenous pain-killing mechanism while avoiding the unwanted side effects of central cannabinoid receptors.

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ORIGINAL RESEARCH PAPER Clapper, J. R. *et al.* Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. *Nature Neurosci.* **13**, 1265–1270 (2010)
FURTHER READING Di Marzo, V. Targeting the endocannabinoid system: to enhance or reduce? *Nature Rev. Drug Discov.* **7**, 438–455 (2008)