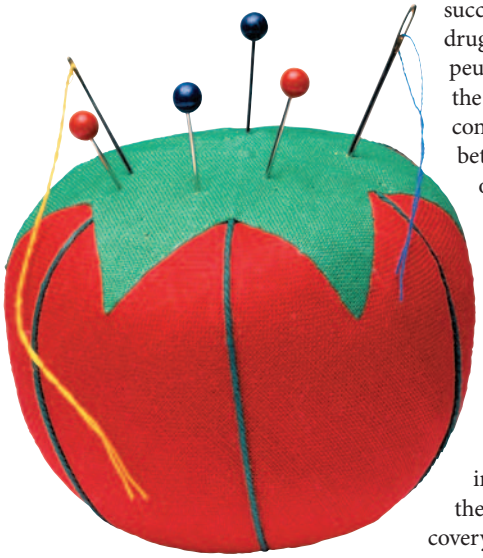
PAIN

Pinning down neuropathic pain



Neuropathic pain, a widespread chronic condition caused by injury to the nervous system, is one of the most difficult syndromes to treat successfully with drugs. New therapeutic approaches to the treatment of this condition require a better understanding of the molecular mechanisms that underlie its development. Lai and colleagues, reporting in *Nature Neuroscience*, have now uncovered an important piece of the puzzle. The discovery that dynorphin A, an opioid neuropeptide, promotes chronic pain through its agonist action at bradykinin receptors, could pave the way for new treatment options.

Many experimental models of chronic pain show significant and time-dependent regional elevation of dynorphin A, where it is known to mediate inhibitory effects on pain regulation by binding to opioid receptors. Dynorphin A also mediates excitatory effects by an unknown mechanism. Now further receptors for dynorphin A have been discovered. A des-tyrosyl fragment of dynorphin A (dynorphin A_{2-13}) with very low affinity for opioid receptors, was shown to induce Ca^{2+} influx by binding to B_1 and B_2 bradykinin receptors *in vitro* in embryonic dorsal root ganglia (DRG) and in a model cell line for peripheral sensory neurons. This led to the activation of L-type and P/Q type voltage-sensitive calcium channels, possibly by inducing bradykinin receptor coupling to the G_s–cAMP–PKA pathway.

Importantly, *in vivo* experiments demonstrated that administration of dynorphin A_{2-13} into the spinal canal of rats induced reversible hypersensitivity and hyperalgesia, an effect that was not observed in bradykinin-receptor-B_2-knockout mice. In a model of neuropathic pain induced by spinal nerve ligation (SNL), the bradykinin B_2 antagonist HOE 140 led to a reversal of the chronic pain state. SNL induced time-dependent upregulation of dynorphin, which has a delayed onset and reached its peak 7–10 days after injury. The reversal with HOE 140 was similarly time-dependent, with no effect at 2 days after SNL, but a complete block of injury-induced pain 7 days post-SNL. Combined with the analysis

ANALGESIA

Fast-track to pain relief

Current analgesics do not effectively control many severe pain states, so there is a need for novel therapeutics that alleviate this debilitating condition. LoVerme and colleagues, writing in the *Journal of Pharmacology and Experimental Therapeutics*, have shown that the peroxisome proliferator-activated receptor-α (PPARα) might represent a novel analgesic target, because agonists acting at this receptor produce rapid, broad-spectrum analgesia.

From a range of structurally diverse PPARα agonists, the authors identified compounds — GW7647, Wy-14643 and palmitoylethanolamide (PEA, a naturally occuring ligand) — that reduced early- and late-phase irritant-induced nociception. After intraplantar administration of PEA to mice, tissue levels of the drug were elevated in the injected paw but remained unchanged in the brain and spinal cord, indicating that PPARα agonists might inhibit pain behaviour through a peripheral mechanism. This was reinforced by the finding that intraplantar administration of GW7647 or PEA attenuated the sensitization of spinal-cord nociceptive neurons to peripheral noxious stimuli in rats.

> “The antinociceptive effects of PPARα agonists occurred within minutes of administration.”

Although PPARα is traditionally considered a nuclear receptor, the antinociceptive effects of PPARα agonists occurred within minutes of administration, an effect too rapid to be transcription-dependent. To elucidate the mechanism of action of PPARα agonists, the authors focused on K^+channels, which are involved in some actions of PEA and also in the regulation of pain sensitivity. By testing a series of K^+ channel blockers to modulate PPARα-mediated antinociception, the authors found that large conductance ($K_{Ca}1.1$) and intermediate conductance ($K_{Ca}3.1$) calcium-activated K^+ channels mediated the rapid antinociceptive response to PPARα agonists.

LoVerme and colleagues then examined the role of PPARα agonists in three pain models. In a mouse model of neuropathic pain, administration of GW7647 or PEA caused a rapid reversal of mechanical and thermal hyperalgesia, which was absent in neuropathic PPARα-null mice. Furthermore, GW7647 and PEA suppressed mechanical and thermal hyperalgesia in experimental arthritis and paw oedema — two mouse models of chronic inflammation. Unlike opiate analgesics, the use of PEA was not associated with the development of analgesic tolerance.

Although not all PPARα agonists demonstrated analgesic efficacy, this study suggests that certain PPARα agonists — many of which are currently in clinical development — could have potential therapeutic activity in chronic pain states.

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ORIGINAL RESEARCH PAPER LoVerme, J. *et al.* Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-α. *J. Pharmacol. Exp. Ther.* **319**, 1051–1061 (2006)