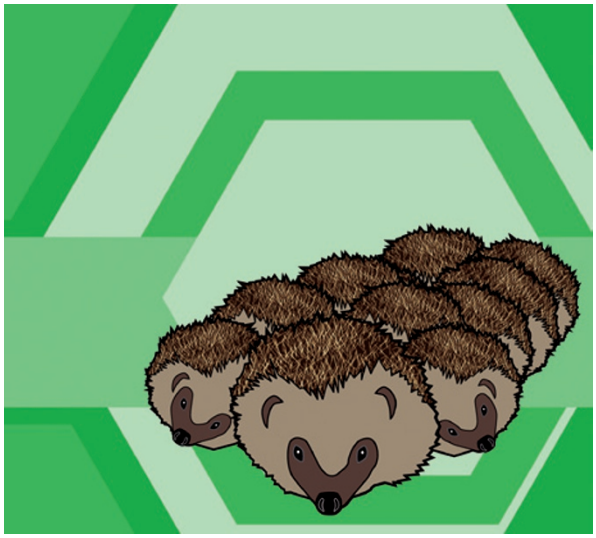
Nature Reviews Neuroscience | AOP, published online 5 October 2011; doi:10.1038/nrn3124

PAIN

A prickly solution?



The Hedgehog (HH) signalling pathway is best known for its roles in development. Now, a study by Galko and colleagues reveals that this protein is also involved in pain signalling. Reporting in *Current Biology*, the authors show that in both flies and rats, inhibition of HH signalling reduces nociceptive hypersensitivity.

Tissue damage often results in exaggerated pain responses to noxious stimuli (hyperalgesia) and to non-noxious stimuli (allodynia). These responses usually cease when the tissue is repaired, but in some cases they can persist, resulting in chronic pain. Current analgesics are associated with undesirable adverse effects such as tolerance and dependence, highlighting the need to identify new mediators of nociceptive signalling.

The authors examined the nocifensive withdrawal behaviour of *Drosophila melanogaster* larvae bearing a temperature-sensitive allele of the hedgehog gene (*hh*) following ultraviolet irradiation damage. These flies failed to develop thermal allodynia and hyperalgesia, suggesting that *hh* is required for nociceptive sensitization. Through genetic disruption of HH signalling in fly nociceptive sensory neurons, the authors showed that components of the canonical HH signalling pathway — such as the receptors Patched and Smoothened, the transcriptional activator Cubitus interruptus and HH transcriptional targets Engrailed and Decapentaplegic — mediate nociceptive sensitization following tissue damage. In agreement with these findings, they also found that ectopic HH signalling leads to thermal allodynia and hyperalgesia in the absence of tissue damage.

Eiger, the *D. melanogaster* orthologue of tumour necrosis factor, has previously been implicated in the development of thermal allodynia. However, the authors showed that thermal allodynia that was induced by the ectopic overexpression of Eiger in the absence of tissue damage was not affected by inhibition of HH signalling (and vice versa), indicating that Eiger and HH act in parallel signalling pathways. Furthermore, they showed that the effects of HH and Eiger were mediated through different transient receptor potential channels. The effects of ectopic expression of Eiger or HH on allodynia required the receptor Painless, but unlike Eiger, HH induced hyperalgesia through activation of transient receptor potential cation channel subfamily A member 1 (TRPA1).

Finally, the authors investigated whether the role of HH signalling in nociceptive sensitization is conserved in mammals. Interestingly, pharmacological blockade of HH signalling in rats with cyclopamine, a specific inhibitor of sonic hedgehog signalling, blocked the development of analgesic tolerance to morphine and synergistically augmented the effects of morphine analgesia in standard assays of inflammatory and neuropathic pain. These findings suggest that in mammals, modulation of nociceptive signalling by HH affects opioid receptor signalling, which could have important implications for novel pain treatments.

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ORIGINAL RESEARCH PAPER Babcock, D. T. *et al.* Hedgehog signalling regulates nociceptive sensitization. *Curr. Biol.* 27 Sep 2011 (doi:10.1016/j.cub.2011.08.020)