

PAIN

The pain of integrins

Although chronic pain is a common problem, progress in treating it has been relatively slow. Advances in our understanding of neuropathic and inflammatory pain are important if new therapeutic targets are to be identified. In the *European Journal of Neuroscience*, Dina and colleagues describe a potential role for integrins in mediating this kind of pain.

Integrins are adhesion molecules that are expressed on primary afferent neurons. They bind to elements of the extracellular matrix (ECM) and interact with signalling systems that are known to mediate hyperalgesia. Inflammation and nerve injury cause changes in the ECM around peripheral nerves that might provide important signals to integrins. So, the authors investigated whether integrins were involved in the sensitization of nociceptors that leads to hyperalgesia in animal models of inflammatory and neuropathic pain.

Dina *et al.* used several methods to interfere with normal integrin signalling in rats, and found that by doing so they could block the development of hyperalgesia. However, there seems to be more than one pathway through which integrins can influence pain.

Fragments of laminin, or antibodies against the integrin subunits that are involved in binding to laminin, blocked hyperalgesia induced by injection of prostaglandin E₂ (PGE₂), but not that induced by injection of adrenaline (epinephrine).

The laminin peptides also blocked the induction of hyperalgesia in a slower-acting model of inflammatory pain, the injection of carrageenan. On the other hand, fragments of fibronectin, or antibodies against the subunits of integrin that are needed for binding fibronectin, prevented the induction of hyperalgesia by adrenaline, but not by PGE₂ or by carrageenan.

The β₁ integrin subunit is involved in the binding of both laminin and fibronectin. When rats were treated with antibodies against this subunit, neither adrenaline nor PGE₂ induced hyperalgesia. The same effect was obtained by treatment with antisense oligodeoxynucleotides that knocked down the expression of the β₁ subunit. The knockdown also prevented hyperalgesia in a model of neuropathic pain caused by the chemotherapeutic drug taxol, and could reverse hyperalgesia if given after taxol treatment.

This evidence that specific integrin subunits are involved in pathways that cause pain when stimulated by different substances should add to our growing understanding of the mechanisms of chronic pain. It might also lead to the development of new therapies for the many patients who are affected by inflammatory or neuropathic pain.

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References and links

ORIGINAL RESEARCH PAPER Dina, O. A. *et al.* Integrin signalling in inflammatory and neuropathic pain in the rat. *Eur. J. Neurosci.* **19**, 634–642 (2004)

IN BRIEF

SENSORY PHYSIOLOGY

K_v1.3 channel gene-targeted deletion produces 'super-smeller mice' with altered glomeruli, interacting scaffold proteins, and biophysics.

Fadool, D. A. *et al. Neuron* **41**, 389–404 (2004)

Mice with a targeted deletion of the voltage-dependent K⁺ channel K_v1.3 are found to have a heightened sense of smell, with a threshold for odour detection that is 1,000- to 10,000-fold lower than the wild type. Anatomically, they have smaller olfactory glomeruli than wild-type mice, and more of them. Potassium currents in olfactory bulb neurons from the K_v1.3^{-/-} mice have slower inactivation and a modified voltage dependence, and are not modulated by activators of receptor tyrosine signalling cascades.

NEUROLOGICAL DISORDERS

Diffusion tensor MRI of early upper motor neuron involvement in amyotrophic lateral sclerosis.

Sach, M. *et al. Brain* **127**, 340–350 (2004)

It is difficult to assess the involvement of upper motor neurons during the early stages of amyotrophic lateral sclerosis (ALS). Sach and colleagues show that diffusion tensor imaging can identify changes that are related to upper motor neuron involvement in patients with ALS before they show clinical symptoms related to corticospinal tract lesions.

NEURAL MODULATION

Selective D2 receptor actions on the functional circuitry of working memory.

Wang, M. *et al. Science* **303**, 853–856 (2004)

D2 dopamine receptors have been implicated in various cognitive and motor functions. To clarify the functions of these receptors, Wang *et al.* recorded from prefrontal cortical neurons in monkeys performing an oculomotor task while applying selective D2 agonists and antagonists through iontophoresis. They found that D2 receptors modulate saccade-related activity, whereas D1 receptors modulate memory-related activity.

GENE EXPRESSION

Stochastic yet biased expression of multiple *Dscam* splice variants by individual cells.

Neves, G. *et al. Nature Genet.* 1 February 2004 (10.1038/ng1299)

The *Drosophila* homologue of *Dscam* is essential for axon guidance and undergoes alternative splicing to generate 38,016 possible isoforms. Neves *et al.* used single-cell RT-PCR to investigate the expression of *Dscam* in single photoreceptors. The authors find that individual photoreceptors express 14–50 mRNAs from the possible range of *Dscam* isoforms, and that populations of photoreceptor subtypes express broad but distinctive subsets of *Dscam*. They propose that the *Dscam* repertoire of a cell could provide a mechanism for generating unique cell identity in the nervous system.

