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Sodium channels in neuropathic pain—friend or foe?

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Neuropathic pain syndromes remain a major therapeutic challenge, despite considerable research efforts during the past few decades. Many hypotheses about the mechanisms of pain generation have been formulated, and two important questions have been raised. First, why is there so much variation in somatosensory phenotypes? Second, why, given the same type of nerve lesion, does only a subgroup of patients develop a chronic pain state? Recent findings indicate that genetic variability of ion channels in the nociceptive system might provide some answers.

In a Case Study in this issue, Novella *et al.* describe a rare inherited mutation of the *SCN9A* gene, which encodes the neuronal sodium channel $Na_V1.7$. This channel is preferentially expressed at high levels in nociceptive and sympathetic neurons (Dib-Hajj SD *et al.* [2005] *Brain* 128: 1847–1854). The mutation has been shown to alter the threshold of activation of $Na_V1.7$, resulting in temperature-dependent hyperexcitability of pain-signaling neurons (Han C *et al.* [2007] *Mol Pain* 3: 3); the clinical phenotype was primary erythromelalgia. Erythromelalgia exhibits a unique clinical profile characterized by bilateral presentation of skin redness and burning pain located distally on extremities, which is triggered by warmth and relieved by cooling. Novella *et al.* have elegantly combined a genome-wide linkage search with *in vitro* voltage and current-clamp recordings of human embryonic kidney cells and dorsal root ganglion neurons transfected with mutant *SCN9A*. This approach enabled them to unravel the pathogenesis of erythromelalgia at the molecular as well as the electrophysiological level.

Sodium channels are pivotal to the challenge that we face in tackling neuropathic pain. Ectopic spontaneous activity in primary afferent neurons following nerve injury is matched by increased expression of voltage-gated sodium channels (Devor M *et al.* [1993] *J Neurosci* 13: 1976–1992). This hyperactivity induces fundamental changes in the PNS and CNS, including peripheral and central sensitization (Baron R [2006] *Nat Clin Pract Neurol* 2: 95–106). These mechanisms lead to the characteristic symptoms of neuropathic pain, namely burning pain, pain attacks and evoked pain. Accordingly, sodium channel blocking agents, such as carbamazepine and lidocaine, are effective for treating neuropathic pain.

Sodium channels are pivotal to the challenge that we face in tackling neuropathic pain

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Several missense mutations in the *SCN9A* gene have been shown to be responsible for the unique clinical picture of erythromelalgia, but interestingly other mutations of the same gene lead to entirely different phenotypes. $Na_V1.7$ mutations are responsible for the inherited 'paroxysmal extreme pain disorder' or PEPD (Fertleman CR *et al.* [2006] *Neuron* 52: 767–774). PEPD, previously known as familial rectal pain, is characterized by paroxysms of rectal, ocular or submandibular pain with flushing. Molecularly, PEPD is characterized by deficits in sodium channel fast inactivation. In contrast to the autosomal dominant gain-of-function mutations in erythromelalgia and PEPD, homozygous nonsense mutations in the *SCN9A* gene can cause a loss of $Na_V1.7$ function. For example, three recently described Pakistani families presented with an autosomal recessive congenital analgesia without neuropathy, which was attributed to a loss-of-function mutation in *SCN9A* (Cox JJ *et al.* [2006] *Nature* 444: 894–898).

Will it be possible to 'befriend' the painful sodium channels and use channel-subtype-specific antagonists as a pain treatment? Can $Na_V1.7$ blockers ameliorate chronic neuropathic or inflammatory pain without loss of the protection provided by acute nociception? $Na_V1.7$ sodium channels are not present in cardiac muscle or CNS neurons, and this fact might be exploited to minimize adverse effects of sodium channel blockers. If these possibilities are correct, we could develop a new generation of mechanism-based drugs that can mute the roar of pain effectively.