Neurobiology: a channel sets the gain on pain.

A channel sets the gain on pain

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Nerve impulses that convey pain signals to the brain are produced by sodium channels in the neuronal membrane. Studies on people who are unable to feel pain identify one specific sodium channel as essential to the process.

*"God...*shouts*in ourpain. It ishis megaphone..."*

- C.S.Lewis

Pain can be useful - when it warns us that a hot object is burning us, for instance. Yet the amelioration of pain is essential to modern medicine, permitting surgery to take place and making many illnesses more bearable. Even so, some pain does not respond to current treatments; in particular neuropathic pain, which can occur in the absence of noxious stimuli following injury to the nervous system, and some types of inflammatory pain. II):.this issue, Cox et al. (page 894)1describe a rare, inherited mutation that renders the people tarrying it unable to feel any pain. The mechanism behind this deficit could aid the search for novel painkillers.

Where does pain come from, and how can we understand it so that we can tame it? Painful stimuli are conveyed in the form of trains of electrical impulses. These impulses travel from nociceptive (pain-signalling) dorsal root ganglion (DRG) neurons originating in the body's periphery, through ascending spinal pathways to the brain. Ion channels in the cell membranes of these nociceptive neurons, including several different types of sodium channel, collaborate to produce such nerve impulses, although the relative

roles of the different channels are not fully understood.

Ten different genes encode ten versions (isoforms) of the sodium-channel protein that all share a common structure but have different constituent amino-acid sequences.

One of these genes, SCN9A, encodes a sodium channel known as Na,,1.7,which is preferentially expressed at high levels in two types of neuron: nociceptive DRG neurons and sympathetic ganglion neurons, which are part of the involuntary, or 'autonomic: nervous system2.

Na,,1.7is deployed at the endings of pain sensing nerves (the nociceptors), close to areas where the impulse is initiated2.Stimulation of the nociceptor "nerve endings produces' generator potentials' - small changes in the voltage across the neuronal membranes. The Na,,1.7 channel amplifies these membrane depolarizations and when the membrane potential difference reaches a certain threshold, the neuron fires.

Clues that Na,,1.7 is involved in pain came from the observation4 that DRG neurons in animal models of inflammatory pain show increased expression of Na,,1.7. Also, mice genetically engineered to lack Na,,1.7 specifically in their nociceptors show markedly reduced responses to inflammatory pains.The painful inherited human neuropathy known as erythromelalgia, in which sufferers experience a severe burning pain in response to mild warmth, is due to mutations6-8in Na,,1.7 that cause excessive channel activity. This suggests that Na,,1.7 sets the gain on pain signalling in humans.

Cox et al.I have now discovered SCN9A mutations that cause a loss of Na,,1.7 function in three families from Pakistan. Their observations link loss of Na"l. 7 function with a congenital inability to experience pain, adding to the evidence indicting this sodium channel as an essential participant in human nociception. The profound insensitivity to pain in. members of these families is remarkable because nociceptors contain many sodium-channel isoforms, so the remaining isoforms might have been expected to support at least some degree of nociception,

even though Na,,1.7 is out of action.

The Na,,1.7 channel is present in some nonnociceptive DRG neuronsll, as well as in nociceptors. However, the people described by Cox *et ai.* have no apparent deficits in non-nociceptive sensory functions, such as the ability to perceive touch, warmth, cold, tickle, pressure,or the position of their limbs (propripception).

This raises the question of whether Na,,1.7 channels have different roles in nociceptive and non-nociceptive DRG neurons. The pain insensitivity in these people seems to be more severe than the deficits seen in the mice lacking Na,,1.7 in their nociceptorss. So perhaps there are changes in upstream nociceptive centres in the spinal cord or brain of these people that contribute to their insensitivity to pain. Na,,1.7 is present not only in DRG neurons, but also in sympathetic ganglion neurons2. But although total deletion of Na,. 1.7 in mice results in perinatal deaths, the people lacking functional Na,.1.7 showed no signs of dysfunction in their sympathetic ganglion neuronsl. Some mutations of Na,.1.7 seen in erythromelalgia depolarize both nociceptors and sympathetic ganglion neurons. Consistent with different functional roles in the two cell types, these mutations produce hypoexcitablity in sympathetic ganglion neurons (because membrane depolarization inactivates all the sodium channels) and hyperexcitability in nociceptors (due to the selective presence of sodium channels that are relatively resistant to inactivation once depolarized)J2. Whether the absence of autonomic dysfunction in the families described by Cox et al.Jisdue to different functional roles ofNa,.1.7 in sympathetic and nociceptive neurons, or to redundancy of sodium-channel subtypes in sympathetic neurons, is not known. It might also be due to increased sensitivity of upstream neurons induced by sympathetic hypoactivity, or to compensatory increases in the expression of other sodium-channel isoforms in the autonomic

neurons (as can occur in other neuronal types in which mutations result in loss of other channelsl3).

The association of pain insensitivity with loss of function of a specific type of sodium channel might have therapeutic implications. Because Na,.1.7 is not present in cardiac muscle or neurons in the central nervous system, subtype-specific blockers of Na,.I.7 should not, in principle, have direct actions on these cells and so should have less-severe side-effects than current

pain medications. Although Na,.1.7 channels

are present in sympathetic neurons as well as nociceptors, the observations in the people studied by Cox et al. suggest that it may be possible to ameliorate pain by blocking Na,.I. 7 without producing autonomic side-effects. Whether Na,.I. 7 blockers can abolish acute nociceptive signalling, thereby providing protection from pain similar to that afforded by local anaesthetics, but with fewer side-effects, remains to be determined. Also unknown is whether Na,.I. 7 blockers can ameliorate chronic neuropathic or inflammatory pain without loss of the protection provided by acute nociception. If either of these possibilities turns out

to be the case, it might be possible to develop a new generation of drugs that can effectively mute the megaphone of pain.

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