Painful and painless channelopathies

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The discovery of genetic variants that substantially alter an individual's perception of pain has led to a step-change in our understanding of molecular events underlying the detection and transmission of noxious stimuli by the peripheral nervous system. For example, the voltage-gated sodium ion channel $Na_v1.7$ is expressed selectively in sensory and autonomic neurons; inactivating mutations in *SCN9A*, which encodes $Na_v1.7$, result in congenital insensitivity to pain, whereas gain-of-function mutations in this gene produce distinct pain syndromes such as inherited erythromelalgia, paroxysmal extreme pain disorder, and small-fibre neuropathy. Heterozygous mutations in *TRPA1*, which encodes the transient receptor potential cation channel, can cause familial episodic pain syndromes, and variants of genes coding for the voltage-gated sodium channels $Na_v1.8$ (*SCN10A*) and $Na_v1.9$ (*SCN11A*) lead to small-fibre neuropathy and congenital insensitivity to pain, respectively. Furthermore, other genetic polymorphisms have been identified that contribute to risk or severity of more complex pain phenotypes. Novel models of sensory disorders are in development—eg, using human sensory neurons differentiated from human induced pluripotent stem cells. Understanding rare heritable pain disorders not only improves diagnosis and treatment of patients but may also reveal new targets for analgesic drug development.

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Introduction

Rapid growth is taking place in the discovery of rare genetic variants associated with mendelian disorders of pain perception. Progress has been made because of enhanced ascertainment of patients with pain disorders, greatly improved phenotyping, and new sequencing and bioinformatics technologies. In some individuals, gene mutations lead to insensitivity to pain, whereas in others, mutations lead to increased pain perception. Many variants reside in genes encoding ion channels, which play an important part in determining the excitability and function of nociceptors. Restricted expression of these molecules in sensory neurons, and their pivotal role in chronic and acute pain states, means that these genetic findings are now being translated into analgesic drug discovery programmes.

Chronic pain represents a substantial health burden, affecting one in five people in Europe; for 40% of these individuals, treatment is inadequate.[1] Common acquired chronic pain states are associated with altered expression and dysfunction of ion channels. Application of modern genomics to persistent pain states is challenging because of the complexity of phenotyping and the large cohort sizes needed; early findings suggest, however, that variants in ion channels modulate the risk, severity, and persistence of pain after injury. In this Review, we discuss recent advances in the understanding of the molecular basis of nociception, describe the clinical features and genetics of mendelian disorders of pain perception, and highlight the role of ion channels in acquired pain syndromes.

Ion-channel function in nociceptors

The term nociceptor was originally coined to describe sensory neurons that detect high-threshold stimuli causing—or with the potential to cause—tissue injury.[2] Such stimuli include extremes of temperature, mechanical force, or chemicals (eg, acid or prostaglandins).[3,4] The soma of nociceptors resides in dorsal root or trigeminal ganglia, and the neurons have unmyelinated or small-diameter myelinated axons. Nociceptors have a pseudo-unipolar morphology; a peripheral terminal innervates a target organ, such as skin, and a central terminal provides connectivity to the dorsal horn of the spinal cord (figure 1A–1C). During the past two decades, rapid advances have been made in our understanding of how nociceptors detect signals and transmit them to the CNS, leading to the perception of pain. Such nociceptor input from the periphery is subject to extensive processing and modulation within the CNS, such that perceived pain is dependent on environmental context, emotional factors, attentional mechanisms, and past experience.[9] Here, we will focus on the role of nociceptors, rather than central processing.

Both ligand-gated and voltage-gated ion channels have a pivotal role in the processes of detection and transmission of high-threshold stimuli by nociceptors (figure 1D–1F). An example is the transient receptor potential (TRP) family of ion channels.[10] TRPV1 was the first to be linked to nociception and is a non-selective cation channel activated by noxious heat, capsaicin (the active ingredient in chilli peppers), and low pH.[11,12] Several TRP channels were shown subsequently to be expressed by sensory neurons. Every TRP channel is attuned to detect specific physical and chemical stimuli, ranging from innocuous warming (TRPV3) to high temperatures (TRPV2). TRPA1 is activated by noxious cold and various environmental irritants—eg, mustard, cinnamon, wasabi, and acrolein (the active component of tear gas).[13–16] Although TRPA1 is not the noxious mechanotransducer (the identity of which remains a mystery), it amplifies the response to high-threshold mechanical stimuli.[17] Subpopulations of nociceptors express ion channels in complex patterns, either in combination or in a mutually exclusive fashion, and these differences in expression ultimately determine the physiological heterogeneity of nociceptors. For example, some nociceptors respond to noxious thermal, mechanical, and chemical stimuli (polymodal nociceptor)

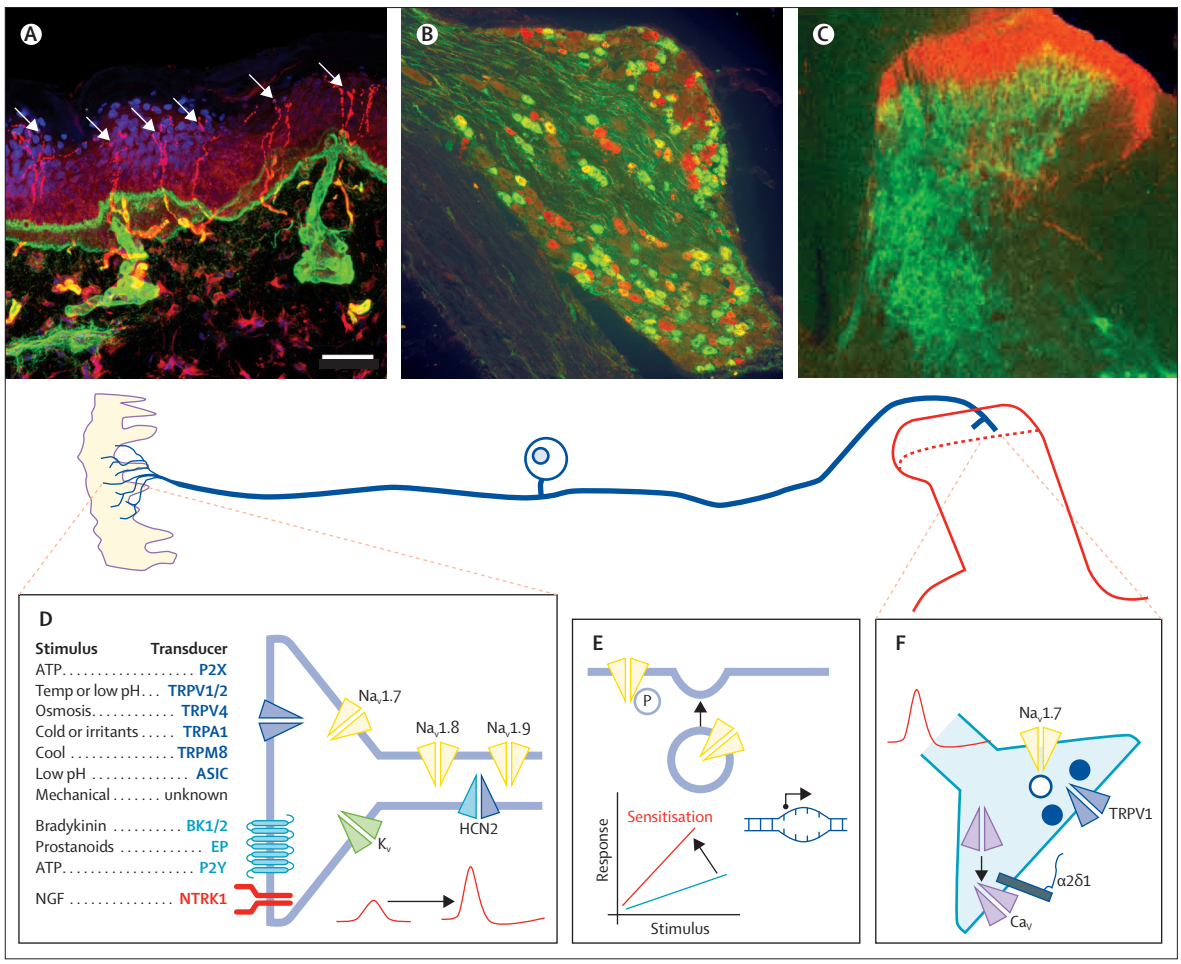

Figure 1: **Structure and functional components of a nociceptor**
Nociceptors provide connectivity between peripheral targets (in this case, skin) and the dorsal horn of the spinal cord. (A) Peripheral nociceptor terminals (arrows) are seen as free nerve endings (immunollabelled with PGP9.5, red) crossing the basement membrane (collagen IV, green) into human epidermis. (B) Cell bodies of distinct populations of nociceptors reside within dorsal root ganglia and differ by histochemical characteristics, ion-channel expression, connectivity, and functional properties. Nociceptors can be divided into two roughly equal populations: those that express neuropeptides (immunolabelled with CGRP, red); and those that bind isolectin B4 (green).[5] (C) Nociceptors project to superficial laminae of the dorsal horn (immunolabeled with CGRP, red), by contrast with low-threshold myelinated afferent fibres that project to deeper laminae (labelled with cholera toxin, green). (D) A stylised view of a nociceptor terminal, showing just some of the ligand-gated ion channels (blue), G-protein-coupled receptors (light blue), and tyrosine kinase receptors (red) by which these neurons transduce extremes of temperature (Temp), low pH, and various chemical stimuli. The voltage-gated sodium channels (Na_v; yellow) have a key role in responding to small depolarisations and action-potential generation. Voltage-gated potassium channels (K_v; green) are important breaks on excitability.[6] The hyperpolarising activated cation channel HCN2 acts as a so-called pacemaker, modulating ectopic activity after nerve injury. (E) Altered ion-channel activity contributes to peripheral sensitisation, and mechanisms include stimulation of signalling pathways downstream of G-protein-coupled and tyrosine-kinase receptors and phosphorylation (P) events (upper left), altered trafficking to the membrane (centre), and, over longer periods, changes in transcription (lower right). (F) Central terminals are also important in nociceptive processing. $Na_v1.7$ might also have a role in determining ingress of action potentials to central terminals and neurotransmitter release. Transient receptor potential (TRP) channels are also expressed centrally and can modulate presynaptic activity.[7] The α2δ1 subunit is part of the voltage-gated calcium-channel complex (Ca_v; purple) and has an important role in trafficking of voltage-gated calcium channels to presynaptic terminals.[8] GABApentinoids bind to α2δ1 and impair this trafficking.

whereas others are insensitive to mechanical and thermal stimuli unless sensitised in the context of inflammation.[18] Transduction agents are important because they allow nociceptors to become sensitised after injury and inflammation through altered expression,[19] trafficking,[20] phosphorylation events,[21] or interaction with G-protein-coupled receptors,[13] sometimes leading to abnormal hypersensitivity and, ultimately, chronic pain states.

Voltage-gated sodium channels (Na_v) are key determinants of nociceptor excitability (figure 2). The channels $Na_v1.7$,[22] $Na_v1.8$,[23] and $Na_v1.9$[24] are all expressed preferentially in peripheral neurons but have different kinetics and show subtly distinct patterns of expression; all have been linked to pain. $Na_v1.7$ channels are expressed in the peripheral terminals of sensory neurons, along their axons, at the node of Ranvier of thin myelinated sensory neurons, within the neuronal soma of dorsal root ganglia, and at the central terminals of nociceptors in the superficial laminae of the spinal cord.[25,26] $Na_v1.7$ channels can produce a substantial ramp current in