Pain as a channelopathy

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Mendelian heritable pain disorders have provided insights into human pain mechanisms and suggested new analgesic drug targets. Interestingly, many of the heritable monogenic pain disorders have been mapped to mutations in genes encoding ion channels. Studies in transgenic mice have also implicated many ion channels in damage sensing and pain modulation. It seems likely that aberrant peripheral or central ion channel activity underlies or initiates many pathological pain conditions. Understanding the mechanistic basis of ion channel malfunction in terms of trafficking, localization, biophysics, and consequences for neurotransmission is a potential route to new pain therapies.

Introduction

Pain serves to protect the body from harm and promote healing of damaged tissues. Chronic pain, however, remains a major clinical challenge, which, if unmet, significantly diminishes quality of life in the affected individuals. The genetics of human pain has been the subject of intense study in the past decade. Substantial evidence indicates that a large component of the pain experience, such as acute pain thresholds or efficacy of analgesics, is inherited (1). The involvement of channelopathies in human pain conditions has been highlighted by evidence from analysis of pain phenotypes in transgenic animal models (see below). Aberrant channel expression has also been linked to chronic pain evoked by physical insults (2). Hence understanding the ion channels involved in the pathophysiology of human pain conditions could provide opportunities for the development of novel therapeutic agents as well as furthering our insights into the functioning of the nervous system.

Biophysical properties of ion channels can determine nociceptor excitability, and hence abnormal channel function or expression could lead to chronic or neuropathic pain. Pain initiated in the periphery or viscera is detected by a specialized subset of sensory neurons called nociceptors that convey the information to the CNS, where pain is generated. Noxious stimuli activate receptor complexes in the nociceptor terminals to initiate action potentials that are transmitted along the length of the axons to the dorsal horn of the spinal cord (Figure 1). The identity of noxious transducers has been partially catalogued and includes GPCRs and ligand-gated ion channels, including several members of the transient receptor potential (TRP) family (Figure 1). Depolarization of the membrane results in the opening of voltage-gated Na^+ channels that conduct the flow of Na^+ ions down the electrochemical gradient into the cells, resulting in the rapid regenerative upstroke of action potential. Shortly after activation (in milliseconds), Na^+ channels inactivate — i.e., enter a nonconducting state — while K^+ channels activate to repolarize the membrane, "priming" Na^+ channels for the next action potential. The time and voltage dependence of activation and inactivation processes modulate duration and frequency of action potentials in nociceptors. The Na^+ channels $Na_v1.7$ (*SCN9A*) and $Na_v1.8$ (*SCN10A*) have been shown to be important in nociceptive pathways (3–5). As importantly, slowly inactivating Na channels contribute to sub-threshold potentials that determine whether a spike is generated in response to a depolarizing noxious stimulus. $Na_v1.9$, preferentially expressed by nociceptors, has slow activation and inactivation kinetics that allow it to amplify response to sub-threshold stimuli (6). $Na_v1.7$ has fast activation and inactivation kinetics but is also able to respond to slow depolarizations because of the properties of the channel in the closed state, and hence can amplify sub-threshold potentials. Thus the biophysical properties of ion channels can determine nociceptor responses to noxious stimuli and ultimately the level of pain experienced. Many inherited human sodium channelopathies impact the activation and inactivation of these channels, resulting in altered neuronal response to stimuli (7).

In this Review, we provide a synopsis of monogenic channelopathy–associated human pain syndromes (Table 1). Although they are extremely rare, study of these familial pain syndromes has provided a unique insight into the ion channels involved in human pain. In addition, we discuss transgenic animal models that have broadened our knowledge of the functional role of ion channels in pain transduction and the mechanisms of pathological pain. Translating data obtained from animal models to human pain pathology remains challenging, because there are subtle differences in pain mechanisms between mice and humans. For instance, antagonists of substance P acting at the NK1 receptor are analgesic in mice but not humans (8). The use of transgenic mouse models is nonetheless generally useful in advancing the molecular understanding of pain sensation and the development of novel therapeutics, because there are broad similarities in pain processing in mice and humans (9).

Inherited primary erythermalgia

The first human pain disorder mapped to an ion channel mutation was erythromelalgia (erythermalgia) (10). Familial or primary erythermalgia is an autosomal dominant disorder in which the affected individuals experience intermittent burning pain and redness in the extremities triggered by warm stimuli or exercise (reviewed in ref. 11). Interestingly, in some affected individuals, following the early onset in childhood, the severity of the associated pain and the affected areas progress with age (e.g., ref. 12). Analgesics and sedatives are only partially helpful, but effective pain relief has been achieved by repeated immersion of hands and feet in ice water, which invariably leads to skin lesions and further complications (13). A genome-wide search in five kindreds with varying degrees of erythermalgia found a linkage with the disease to chromosome 2q (14). Analysis of a Chinese family with erythermalgia further narrowed the region to chromosome 2q24.2–2q24.3. This region on human chromosome 2q contains the genes *SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, and *SCN9A*, which code for isoforms of voltage-gated sodium channel α-subunits. Yang and colleagues reasoned that the symp-

Conflict of interest: The authors have confirmed that no conflict of interest exists.

Citation for this article: *J Clin Invest.* 2010;120(11):3745–3752. doi:10.1172/JCI43158.

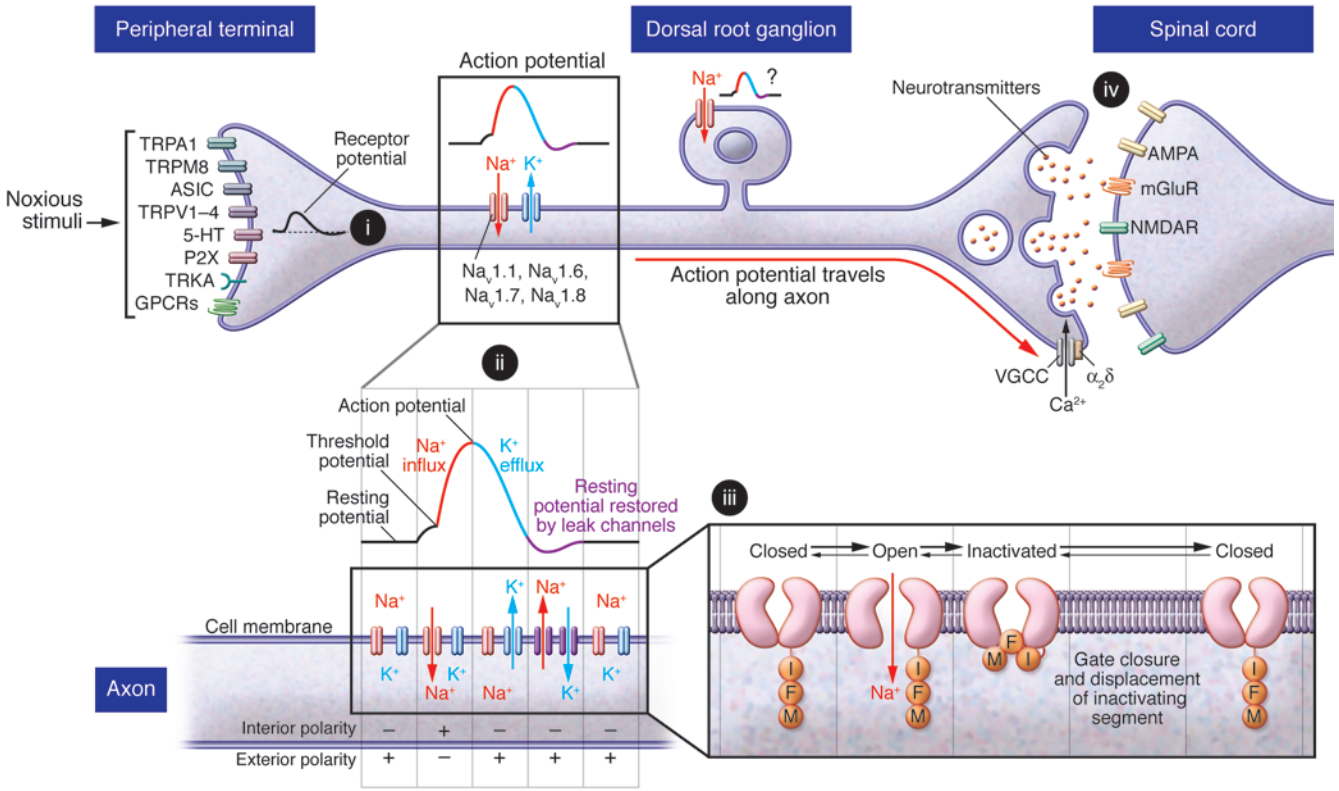

Figure 1
Schematic of ion channels in nociceptor function. The cell bodies of nociceptors are contained within the dorsal root ganglia and terminate as free endings in peripheral tissues. The peripheral terminals respond to noxious stimuli or tissue damage through receptors and ion channels including TRP channels, acid-sensing ion channels (ASIC), serotonin (5-HT) receptors, ATP-gated P2X receptors, tyrosine kinase receptor A (TRKA), and numerous GPCRs that indirectly activate ion channels. Receptors at the terminals respond to noxious stimuli such as heat or pressure (i). When a defined threshold of depolarization is reached, voltage-gated sodium channels are activated and an action potential is generated (ii). During an action potential, an IFM-inactivating segment moves to block the channel within 0.5–1 ms (iii). In this inactivated state, the channel cannot be opened. Meanwhile, potassium channels open, acting to repolarize the membrane. As the membrane repolarizes, the sodium channel gate is closed and inactivating segment is displaced, returning the sodium channel to a resting closed state (iii). This process is repeated to propagate the action potential along the axon (ii). The action potential is propagated along the axon to the presynaptic terminals synapses with second-order neurons in the dorsal horn. Calcium influx through voltage-gated calcium channels (VGCC) triggers the release of neurotransmitters such as glutamate from presynaptic terminals (iv). Glutamate activates ionotropic AMPA, NMDA receptor (NDMAR), and metabotropic glutamate receptors (mGluR) on the postsynaptic terminals in the spinal cord, and the signal is transmitted through the ascending pathways to higher centers in the brain.

toms associated with primary erythermalgia are reminiscent of changes in excitability seen in the CNS channelopathies linked to mutations in *SCN1A*, such as generalized epilepsy with febrile seizures (15), and identified two independent missense mutations (L858H and I848T) in the *SCN9A* gene that are linked to erythermalgia and are not present in unaffected individuals (10). *SCN9A* codes for $Na_v1.7$, a voltage-gated, tetrodotoxin-sensitive (TTX-sensitive) sodium channel with high-level expression in the nociceptors and sympathetic ganglia (16, 17). Analysis of the mutant channels showed a gain-of-function phenotype marked by a hyperpolarizing shift in the activation of the channel, slower deactivation, and an increase in ramp current in response to slow depolarizing ramps (18). The consequence of this gain-of-function phenotype is hyperexcitability of the nociceptors and reduced thresholds for the activation of action potentials, which would contribute to the pain and heat associated with erythermalgia. The etiology of the redness and swelling accompanying pain in erythermalgia is not known but likely involves hypoexcitability of the sympathetic neurons innervating the microvasculature of the affected limbs (19). There are now ten independent mutations in *SCN9A* linked to varying severity erythermalgia, all of which exhibit a hyperpolarizing shift in activation and slowed inactivation (20).

Paroxysmal extreme pain disorder

A second pain disorder linked to gain of function in $Na_v1.7$, paroxysmal extreme pain disorder (PEPD), formerly known as familial rectal pain, is a rare autosomal dominant inherited disorder characterized by episodic pain manifested in early childhood. The distinguishing feature of PEPD is the excruciating pain and flushing, usually with a burning quality, experienced by the patient in the anorectal region (rectal pain) or around the eyes (ocular attacks) and submandibular region. The severity of the attacks generally diminishes with age but in some patients may persist into adulthood (see ref. 21 for a review of clinical symptoms). A genome-wide linkage search followed by a mutational analysis of the *SCN9A*

Table 1
Human monogenic channelopathy-associated pain syndromes

Disorder	Gene (protein)	Independent mutations	Alteration in channel function	Mouse model	Predicted pathophysiology	Refs.
FHM1	*CACNL1A4* (Cav2.1 α1A)	R192Q, S218L, R583Q, V714A, D715E, K1336E, T666M, V1457L, W1684R, V1696I, 0T, I1811L	Gain of function: increased whole cell currents at more negative potentials, enhanced open channel probability	R192Q and S218L knock-in mice	Decreased threshold for CSD in the knock-in mice	30, 41, 56
FHM2	*ATP1A2* (Na^+/K^+ ATPase α2)	G301R, T376M, L764P, W887R, T345A, A606T, R689Q, M731T, R763H, X1021R, R383H, R689Q, M731T, R763H, R834Q	Compromised pump action, including partial or complete loss of function, reduced turnover, but also alterations in affinity for K^+	*Atp1a2*$^{+/-}$ (*Atp1a2*$^{-/-}$ mice are not viable); CSD not tested	Increased K^+ in extracellular space	30, 50
FHM3	*SCN1A* (Nav1.1)	Q1489K, L1649Q, L263V	Various; Q1489K and L1649Q: partial or complete loss of function; L263V: gain of function	–	Neuronal hyperexcitability	30, 95
FEPS	*TRPA1* (TRPA1)	N855S	Gain of function: 5-fold increase in activation current at resting membrane potential	*Trpa1*$^{-/-}$ mice have reduced cold pain sensitivity	Altered nociceptor function	65, 96
PEPD	*SCN9A* ($Na_v1.7$)	R996C, V1298D, V1299F, I1461T, T1464I, and M1627K, A1632E, F1462V	Gain of function: impaired inactivation leading to persistent sodium currents	–	Nociceptor hyperexcitability, prolonged action potentials and repetitive neuronal firing	20, 97
CIP	*SCN9A* ($Na_v1.7$)	F259X, R277X, Y328X, S459X, E693X, I767X, R830X, W897X, I1235-, F1200-, R1488X , K1659X, W1689X, Q693X (due to c.4366-7del)	Loss of function: premature termination of protein, frameshift or splicing alterations	Nociceptor specific $Na_v1.7$-null mice have increased mechanical and thermal pain threshold (3)	Compromised nociceptor function	3, 20, 97
PE	*SCN9A* ($Na_v1.7$)	Q10R, I136V, F216S, S241T, N395K, V400M, L823R, I848T, L858H, L858F, A863P, V872G, F1449V	Gain of function: hyperpolarizing shift in the voltage dependence of channel activation, slowed deactivation, increased ramp currents in some mutants	–	Nociceptor hyperexcitability	20, 97

PE, primary erythermalgia.

gene identified eight mutations in eleven families and two sporadic cases (22). Two of the mutations identified (I1461T and F1462V) are present in the highly conserved IFM motif in the linker region between domains III and IV, with a third mutation (T1464I) adjacent to the IFM motif. The three IFM residues are critical for the fast inactivation of sodium channels (Figure 1) (23). Another four mutations were found in the S4-S5 linker region of domains III and IV (V1298F, V1298D, V1299F, and M1627K). Functional analysis of three mutant channels revealed a reduction in fast inactivation, which gives rise to a persistent current not present in the wild-type channel (22). The non-inactivating (persistent) $Na_v1.7$ currents are thought to cause PEPD syndrome by promoting repetitive firing of action potentials in nociceptors, leading to paroxysmal pain (see ref. 20 for review). Carbamazepine, which is effective in controlling the symptoms in some PEPD patients, effectively blocks the persistent current in the T1464I mutation, adjacent to the IFM motif, but is ineffective in reversing the negative activation potential in the primary erythermalgia mutant channel I848T (10, 22). The insensitivity of the I848T mutant channel to carbamazepine could explain why individuals with erythermalgia do not benefit from the treatment, suggesting that the two conditions may be caused by different underlying mechanisms. Although the presentation of different symptoms linked to mutations in different parts of the same gene is a feature of some channelopathies, it would be interesting to know whether a compound heterozygote with both erythermalgia- and PEPD-causing mutations would present the symptoms of both conditions. Estacion et al. described an A1632E missense mutation in a patient presenting with both erythermalgia- and PEPD-like symptoms (24). In this case, the mutation that lies in the S4-S5 linker region of domain IV results in fast inactivation, deactivation, and a persistent inward current similar to PEPD mutations. It is likely, then, that although the spectrum of hyperexcitability caused by the mutations in *SCN9A* contributes to the broad pain symptoms manifested in erythermalgia and PEPD, other polymorphisms or mechanisms are determining factors of the severity of the symptoms exhibited in each syndrome. For instance, alternative splicing of *SCN9A* exon 5 alters the impact of the I1461T PEPD-linked mutation on the inactivation and ramp currents of the channel (25).

Congenital insensitivity to pain

Congenital insensitivity to pain (CIP) is defined as the inability to feel pain from birth, while all other sensory modalities remain intact, and is associated with a number of hereditary sensory and autonomic neuropathies (HSANs), including HSAN4 and HSAN5 (26, 27). In both cases, mutations (in *NTRK1* for HSAN5 and *NGFB* for HSAN4) result in complete loss of nociceptors. Cox et al. (28) reported three families in which nonsense mutations in *SCN9A* were linked to insensitivity to pain (i.e., channelopathy-associated CIP). Unlike in other HSANs where the nociceptors are lost, the central and peripheral nervous system appears intact in the affected individuals. Three independent homozygous mutations were identified in the affected individuals — S459X, I767X, and W897X — all of which result in a loss of function in the $Na_v1.7$ channel when expressed in a heterologous expression system (28). Goldberg et al. reported nine other loss-of-function mutations in *SCN9A* in nine families of seven nationalities (29). In all families, motor responses, autonomic responses, and the ability to detect sensory stimuli were unaffected, which suggests an important role for $Na_v1.7$ in nociception as predicted by a tissue-specific *Scn9a*-knockout mouse model (3, 29). $Na_v1.7$ global-knockout mice die shortly after birth owing to an inability to feed because of anosmia (F. Zufall, personal communication), and humans with null mutations are also anosmic (29). However, the complete insensitivity to pain in individuals with CIP underscores the absolute requirement of $Na_v1.7$ function for nociception in humans.

Familial hemiplegic migraine

Migraine is a debilitating neurovascular pain disorder of episodic headaches that affects more than 10% of the population (30). There is a body of evidence suggesting that headache pain is primarily due to activation of the trigeminovascular system innervating the meningeal and superficial cortical blood vessels and projecting to the trigeminal nucleus caudalis in the brain stem (31). The mechanism of headache pain initiation during a migraine attack remains controversial; however, there is evidence for involvement of both peripheral sensitization of meningeal nociceptors and central sensitization of medullary dorsal horn neurons in the process (reviewed in ref. 31).

In cases where migraine is associated with aura, the aura is thought to be generated by the phenomenon of cortical spreading depression (CSD), which is characterized by a self-propagating short burst of depolarization that moves throughout the cortex (32). In individuals with migraine with visual disturbances, it is postulated that CSD originates from the occipital lobe of the brain and propagates toward the frontal cortex (33, 34). There is evidence that the wave of astroglia depolarization may lead to vascular alterations and eventual inflammation and pain (35). Photophobia is a common affliction of migraine patients, but the mechanism via which light exacerbates migraine pain has been enigmatic. Recently, a subset of inherently photosensitive retinal ganglion cells (ipRGCs) has been shown to innervate the dura-sensitive neurons in the posterior thalamus, the activity of which is modulated by light (36). Interestingly, a study of a small cohort of patients suggested that photic exacerbation of migraine headache is only preserved in blind persons who retain the ability to perceive light (36).

The genetic analysis of familial clustering as well as twin studies have indicated that there is a significant genetic component underlying the etiology of migraine headaches (37). Familial hemiplegic migraine (FHM) is a rare autosomal dominant form of migraine with aura that is associated with moderate to severe motor weakness (hemiplegia), ataxia, and seizures. Although genetic studies on the common form of migraine have not yielded specific candidate genes, indicating a polygenic etiology, studies in FHM have identified three genes linked to the disease (reviewed in ref. 30).

The first gene identified (associated with FHM1) was *CACNL1A4*, located on chromosome 19p3, which codes for the α1 subunit of the $Ca_v2.1$ neuronal voltage-gated calcium channel (38, 39). Currently there are 25 known mutations in *CACNL1A4* associated with FHM1, all of which are missense mutations (30). $Ca_v2.1$ has a wide expression pattern in the CNS, at presynaptic terminals and the somatodendritic membrane, where it plays a role in fast synaptic transmission by contributing to Ca influx and neurotransmitter release (reviewed in ref. 40). The majority of the mutations result in a gain-of-function phenotype where the activation threshold for the channel is reduced, resulting in conditions that would favor initiation and propagation of CSD. This is confirmed by two knock-in mouse models of the disease carrying the human FHM1 R192Q or S218L mutations, which showed a reduced threshold and increased velocity of CSD progression through the cortex (41–43). Increased

current density in cerebellar granule cells and enhanced neurotransmission at the neuromuscular junction were observed in the knock-in mice. However, a loss-of-function phenotype in $Ca_v2.1$ α1–null hippocampal neurons overexpressing mutant channels has also been reported (44). This loss of function particularly affects the ability of the channel to mediate inhibitory synaptic transmission, suggesting a differential effect of FHM1 mutant channels on inhibitory and excitatory transmission (45).

De Fusco et al. identified a second locus linked to FHM (FHM2) in an Italian family that had missense mutations in the *ATP1A2* gene encoding the Na^+/K^+ ATPase α2 subunit (46). Although mutations in *ATP1A2* are not strictly channelopathies, Na^+/K^+ pumps are responsible for the maintenance of the bulk ionic concentrations of Na^+ and K^+ across the membrane, which are critical for the function of Na channels in the generation and propagation of action potentials in neurons. In addition, maintenance of such gradients is critical for regulation of membrane potential, Na-dependent transport of calcium and amino acids, as well as the reuptake of neurotransmitters in the CNS. There are now 15 *ATP1A2* mutant alleles that have been linked to FHM2, most of which are predicted to cause moderate alterations in pump function (Table 1) (47).

In mammals there are four Na^+/K^+ ATPase α subunits that combine with auxiliary β and γ subunits to form functional pumps. Interestingly, the α2 subunit is only expressed in neurons in neonatal brain; in the adult, expression is restricted mainly to astrocytes (48, 49), which may be relevant to the childhood onset and severity of the disease in affected individuals. Two independent mouse models of *ATP1A2* loss of function have been generated, and in both the homozygous mutants die shortly after birth from breathing failure (50, 51). *ATP1A2* heterozygous mutants do not appear to experience seizures but did exhibit enhanced conditioned fear/anxiety behaviors (50). The mechanism underlying the pathophysiology of FHM2 may include increased extracellular K^+ concentration due to altered pump action or an increase in intracellular Ca^{2+} concentrations that leads to CSD (46, 52).

A genome-wide linkage analysis of three pedigrees with FHM provided evidence for a third disease-causing locus (FHM3), and sequence analysis showed cosegregation of a Q1489K missense mutation in *SCN1A* with disease phenotype in all three families (53). This mutation is in the highly conserved region of the sodium channel responsible for fast inactivation and hence is predicted to cause a gain-of-function phenotype with slowed recovery from fast inactivation (53). Gain-of-function mutations in *SCN1A* have been linked to childhood epilepsy or generalized epilepsy with febrile seizures, and childhood seizures have been reported in some affected individuals in families with FHM3 (53). Further analysis of the Q1489K mutant has shown that the mutant channel features a loss-of-function as well as a gain-of-function phenotype (54). The ability to initiate but not sustain neuronal hyperexcitability could explain the low prevalence of seizures in FHM3 families (53–55). So far, five FHM3 mutations have been identified, all of which are missense mutations (Table 1) (53, 55–57). It is yet to be determined whether the etiology of FHM3 and childhood seizures both result from sodium channelopathies affecting the brain.

Spectrum of human SCN9A-related channelopathies

An intriguing aspect of human $Na_v1.7$ channelopathies is that gain-of-function mutations result in localized pain (erythermalgia and PEPD), often with a burning quality, whereas loss-of-function mutations result in a global insensitivity to all modalities of pain numbers (20). It remains unclear why such gain-of-function mutations only affect certain areas of the body. Differences in the number of $Na_v1.7$-expressing sensory neurons that innervate the limbs from different segments of spinal cord may underlie this inconsistency. Further, it has been reported that an SNP within the *SCN9A* gene (rs6746030) could modulate pain experience in conditions such as osteoarthritis (58). Although $Na_v1.7$ is highly expressed in the sympathetic nervous system of rodents, a loss of function in humans does not appear to have a major functional consequence for the autonomic nervous system (29). Interestingly, the gain-of-function mutations in erythermalgia and PEPD are linked to autonomic alterations (skin flushing in individuals with erythermalgia). This apparent contradiction may reflect a rescue of phenotype by other sodium channels in CIP (29).

The extent of *SCN9A*'s contributions to human neurophysiology may yet be expanded further by the finding that mutations in this gene are potentially linked to generalized febrile seizures (FS) and may act as modifiers in Dravet syndrome (59). Singh et al. have reported a linkage between *SCN9A* mutations and febrile seizures in a large family with 21 affected individuals (FEB3 or GEFSP7). They further showed using a mouse knock-in model that susceptibility to kindling, an animal model of epilepsy, is the likely mechanism underlying FS (59). The consequence of these mutations in *SCN9A* for channel function have not been reported, and the link between CNS abnormalities and *SCN9A* mutations remains unclear; however, the spectrum of syndromes associated with mutations in $Na_v1.7$ defines this channel as a critical player in altered neuronal excitability linked to human pathologies.

The broader implication of similar changes in sodium channel function and the relationship to pathophysiology of a spectrum of heritable syndromes such as episodic pain, epilepsy, myotonia, and periodic paralysis could be of potential importance for drug development efforts. Although the majority of Na channelopathies described to date involve alterations in inactivation kinetics of the channel, it is unclear whether a common pathophysiology results from this phenotype. Jarecki and colleagues have suggested that resurgent sodium currents could provide a common pathophysiological mechanism for human gain-of-function sodium channelopathies (60). Normally sodium channels do not conduct currents during the repolarization phase following an action potential and cannot reopen until hyperpolarized for many milliseconds. Resurgent currents, however, open during repolarization, allowing for the rapid firing of another action potential. These neurons could then fire bursts of action potentials in response to depolarizing stimuli. As resurgent currents have only been described in a few neuronal cell types, further studies into the prevalence of these currents in other neuronal and non-neuronal tissues are needed to determine whether they have a widespread pathological role in sodium channelopathies (61).

Familial episodic pain syndrome

There is increasing evidence for the involvement of TRP channels in all aspects of mammalian sensory physiology, including vision, hearing, gustation, olfaction, and chemosensation (62). Evidence for involvement in pain transduction and inflammatory pain has been accumulating from mouse knockout studies (see below and ref. 63). Although at least 14 instances of monogenic human disorders have been mapped to TRP channelopathies (64), the first human TRP channelopathy underlying a pain syndrome has only recently been reported (65) describing a Colombian family with familial episodic pain syndrome (FEPS) (65). A missense mutation,

N855S, in the *TRPA1* gene was linked to the syndrome. Biophysical analysis of the mutant channel revealed a gain-of-function phenotype, where the channel exhibited a five-fold increase in activation current (by cold or chemical stimuli) at normal resting potential (65). The exact mechanistic link between the channelopathy and FEPS remains to be elucidated, but the involvement of TRPA1 in cold sensitization in mouse models does suggest a defect in the peripheral nociceptors due to a gain-of-function mutation in *TRPA1*. Despite strong evidence from transgenic studies suggesting functional involvement of TRP channels in pain pathways, TRPA1 is the first instance of a TRP channelopathy linked to a heritable human pain disorder. However, the advent of genome-wide association studies (GWASs) will likely illuminate how other TRP channel mutations contribute to human pain states (65).

Visceral pain

Visceral pain is characterized by poor localization and pain referral to dermatomes distant from the damaged viscera. One of the most common forms of visceral pain and abdominal discomfort is irritable bowel syndrome (IBS). Several studies have concluded that there is strong genetic component in the incidence of IBS (familial IBS), and many candidate genes have been investigated, although no strong association with any of the candidate genes, such as *P2X3* or *TRPV1*, has been found (66). The observation that families with *SCN5A*-related cardiac channelopathies report much higher incidence of abdominal pain than a control population has led to the hypothesis that sodium channelopathies may be a contributing cause in the pathogenesis of functional bowel disorders (67). The $Na_v1.5$ voltage-gated sodium channel encoded by *SCN5A* is expressed in human jejunal epithelial cells and interstitial cells of Cajal (68). In a study of an IBS cohort, one patient with a family history of IBS exhibited a loss-of-function G298S missense mutation on a background of a common H558R polymorphism in *SCN5A* (69). The G298S mutation results in a reduction in the current density, slowing of the activation kinetics, and possibly reduced mechanosensitivity of the channel on H558R background (69). Further studies are needed to establish an association of *SCN5A* channelopathies with IBS symptoms.

Genetic model studies of pain channelopathies

Ion channels involved in pain pathways identified in mutant mice have been recently catalogued (63), and a regularly updated database of mouse mutants is available (Pain Genes Database; ref. 70 and http://paingeneticslab.ca/4105/06_02_pain_genetics_database.asp). Modality-specific deficits of pain transduction have been identified in a number of transgenically modified mice (3, 71). The techniques used include imaging studies of sensory neurons in culture and electrophysiological analysis of isolated skin nerve preparations or noxious input into the spinal cord measured in anesthetized mice. Strikingly, deficits in aspects of sensory transduction detected at the cellular level do not always translate into robust behavioral phenotypes, supporting the view that there is redundancy in damage-sensing mechanisms. For example, the transient receptor potential channel TRPV1 is heat activated, but knockout mice that no longer express this channel show almost normal acute temperature responses (72). By contrast, deletion of voltage-gated Na^+ channels $Na_v1.7$ and $Na_v1.8$ lead to a loss of noxious mechanosensation measured behaviorally; these channels are not mechanosensors but are responsible for electrical signaling in the neurons that detect noxious pressure (4, 73). Interpreting behavioral data in animal models is thus challenging in terms of ascribing function to a particular channel, whose role may be indirect. Conditional knockouts are useful for ascribing function to sets of cells or in contexts where global gene deletion is lethal. Other approaches, for example, the use of antisense oligonucleotides or siRNA to block gene expression, have been extensively used to complement knockout studies. However, an additional complication occasionally arises from the fact that gene knockdown sometimes gives results different from those found with knockout mice. For example, gene knockdown using oligonucleotides shows that $Na_v1.8$ is important in rat neuropathic pain, but in $Na_v1.8$-knockout mice, neuropathic pain develops normally (74, 75). Despite these caveats, rodent model systems have provided insights into potential pain mechanisms (63, 76). However, there are many examples of unsuspected functions associated with ion channels in humans that appear to have a role in pain pathways in mice. For example, TRPV4 was found to have a role in noxious mechanosensation in mice (77, 78), but human *TRPV4* mutations have been linked to a range of disorders in humans including Charcot-Marie-Tooth syndrome 2C and late-onset deafness rather than a specific pain syndrome (79–81).

Pathological pain as a channelopathy

Although heritable pain channelopathies associated with somatic mutations occur, neuropathic pain may also arise from mis-expression of ion channels as a consequence of environmental insults (viral infection, toxic drugs, and physical trauma) (2). Many studies have focused on altered channel mRNA transcripts in the cell bodies of sensory or CNS neurons in pathological pain states (82). However, less is known about the expression of channel proteins, changes in functional activity, and trafficking of defined channels in damaged nerves. In a proteomic analysis of altered channel expression in rat and mouse neuromas, little evidence for altered levels of sodium channel α-subunit protein was obtained (83). Ectopic activity may reflect changes in localization and density of ion channels in damaged nerves rather than changes at the level of gene expression.

Analysis of neuropathic pain models in knockout mice has provided some insights into ion channels that are relevant to chronic pain states. Mechanical hypersensitivity and ectopic activity are attenuated in neuromas of $Na_v1.8$-knockout mice, which also show deficits in visceral and inflammatory pain sensation (84). The sodium channel $Na_v1.3$ is expressed at higher levels in the developing nervous system than in adults; its reexpression in damaged sensory neurons makes it a candidate for generating ectopia after nerve injury (85). Glial cell-derived growth factor (GDNF) can normalize the upregulation of $Na_v1.3$ expression and reverse neuropathic pain in animal models where neurons have been severed (86). However, $Na_v1.3$-knockout mice develop normal levels of neuropathic pain, suggesting that this channel has no causative role in these syndromes (87).

The calcium channel accessory subunit α2δ1 is upregulated 20-fold in damaged peripheral neurons and is the site of action of the analgesic drugs gabapentin and pregabalin (88, 89). Site-directed mutagenesis of a single amino acid in α2δ1 that abolishes gabapentin binding results in a complete loss of efficacy of the drug in the mutant knock-in mice (90). Trafficking of $Ca_v2.1$ channels into the cell membrane is facilitated by α2δ1, and the analgesic action of gabapentin in patients with neuropathic pain was assumed to reflect a lowered level of calcium channel expression (91). Interestingly, other actions of α2δ1 have recently been discovered. This calcium channel subunit is a receptor for the extracellular matrix family of thrombospondin proteins and

appears to play an important role in synaptogenesis, independent of its trafficking role (92). The relative significance of these two actions of α2δ1 in the pathogenesis of neuropathic pain is as yet unclear.

Summary

The central role of ion channels in chronic pain and in diseases of excitability such as epilepsy is underscored by the utility of similar drugs for both pathologies (93). The study of human heritable disorders of pain has suggested new analgesic drug targets, but many mouse knockout studies of ion channels implicated in pain have yet to be linked to human pain conditions (94). Results from ion channel gene deletion studies in mice are informative but highly dependent on a comprehensive analysis of phenotype. Understanding subtle changes in function and the levels and spatiotemporal patterns of ion channel expression holds the key to controlling neuronal excitability in altered pain states. Thus, information from monogenic human pain syndromes coupled to human pain GWASs, together with in-depth phenotyping of targeted mutant mouse models will help identify channels and regulatory genes that contribute to pathological pain.

Acknowledgments

Our work is supported by the Biotechnology and Biological Sciences Research Council, the Medical Research Council, the Wellcome Trust, and World Class University grant R31-2008-000-10103-0.

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