From genes to pain: \( \text{Na}_\text{v}1.7 \) and human pain disorders

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Gain-of-function mutations or dysregulated expression of voltage-gated sodium channels can produce neuronal hyperexcitability, leading to acute or chronic pain. The sodium channel \( \text{Na}_\text{v}1.7 \) is expressed preferentially in most slowly conducting nociceptive neurons and in sympathetic neurons. Gain-of-function mutations in the \( \text{Na}_\text{v}1.7 \) channel lead to DRG neuron hyperexcitability associated with severe pain, whereas loss of the \( \text{Na}_\text{v}1.7 \) channel in patients leads to indifference to pain. The contribution of \( \text{Na}_\text{v}1.7 \) to acquired and inherited pain states and the absence of motor, cognitive and cardiac deficits in patients lacking this channel make it an attractive target for the treatment of neuropathic pain.

Introduction

Dysregulated expression of several-sodium channel isoforms has been associated with chronic pain induced by trauma, inflammation or metabolic disorders (e.g. diabetes) and blocking of sodium channels can ameliorate pain symptoms [1–4]. However, one particular sodium channel isoform, \( \text{Na}_\text{v}1.7 \), has emerged as a major focus in studies on pain, in large part because recent studies have identified \( \text{Na}_\text{v}1.7 \) as a key contributor to nociceptive neuronal excitability, which is linked to three human pain disorders [5–7]. In this article, we review the status of research on \( \text{Na}_\text{v}1.7 \) as a major contributor to pain, which points to this channel as an attractive target for the development of new therapeutics to treat neuropathic pain of different etiologies.

Discovery and tissue distribution of \( \text{Na}_\text{v}1.7 \)

\( \text{Na}_\text{v}1.7 \) is one of the nine pore-forming \( \alpha \)-subunits (\( \text{Na}_\text{v}1.1–1.9 \)) that comprise the voltage-gated sodium-channel family [8]. Robust levels of \( \text{Na}_\text{v}1.7 \) transcripts and protein have been detected only in dorsal-root ganglia (DRG) neurons and sympathetic ganglion neurons [9–13] (Figure 1a), although not at significant levels in the CNS [10,12]. However, low levels of transcripts and currents that were attributed to this channel have been detected in smooth myocytes [14–16] and in non-excitable cells, including metastatic breast and prostate tumor cells, the PC12 cell line and erythrocytes [10,17–20]. \( \text{Na}_\text{v}1.7 \) is produced by most neurons within sympathetic ganglia [e.g. superior cervical ganglion (SCG) neurons] (Figure 1a). Within DRGs, \( \text{Na}_\text{v}1.7 \) is present in both A\( \beta \)-type and C-type DRG neurons [21]; however, it is concentrated preferentially in small diameter neurons (Figure 1a) and, importantly, in 85% of functionally identified nociceptors [21].

The subcellular distribution of \( \text{Na}_\text{v}1.7 \) in myelinated axons is not well documented. By contrast, \( \text{Na}_\text{v}1.7 \) is distributed uniformly in the soma and along unmyelinated C-fibers within the sciatic nerve [13,22]. Additionally, this channel accumulates within the neurite tips of DRG and trigeminal ganglion neurons in culture [10] (Figure 1b), suggesting that \( \text{Na}_\text{v}1.7 \) might translocate to, and accumulate at, nerve endings in vivo, consistent with the role of this channel in amplifying generator potentials [23].

Electrophysiological properties of \( \text{Na}_\text{v}1.7 \)

\( \text{Na}_\text{v}1.7 \) produces a fast activating and inactivating current that is sensitive to nanomolar concentrations of tetrodotoxin (TTX-S) [11,17]. Unlike the other TTX-S voltage-gated sodium channels, however, \( \text{Na}_\text{v}1.7 \) channels recover (reprime) slowly from fast inactivation [23,24] (Figure 1c,d). Also, \( \text{Na}_\text{v}1.7 \) is characterized by slow closed-state inactivation, which permits it to pass a current (ramp current) in response to small slow depolarizations [23,24] (Figure 1e). The ability of \( \text{Na}_\text{v}1.7 \) to respond to ramp stimuli suggests that it might act as a ‘threshold’ channel, amplifying generator potentials and thus setting the gain in nociceptors where it is coexpressed with \( \text{Na}_\text{v}1.8 \) (see later).

Contribution of \( \text{Na}_\text{v}1.7 \) to pain: animal studies

The contribution of \( \text{Na}_\text{v}1.7 \) to acquired channelopathies is best documented in animal studies of inflammatory pain [25]. Peripheral-tissue inflammation causes a significant increase in the amplitude of the TTX-S current in DRG neurons [25]. The increased TTX-S current density following inflammation is paralleled by an increase in \( \text{Na}_\text{v}1.7 \) transcript and \( \text{Na}_\text{v}1.7 \) protein levels and the relative increase in \( \text{Na}_\text{v}1.7 \) levels is more robust than that of \( \text{Na}_\text{v}1.3 \), the other TTX-S channel that is upregulated under
these conditions [25,26]. Nerve growth factor (NGF), which is an important inflammatory cytokine [27], might contribute to the upregulation of Nav1.7 under inflammatory conditions because NGF is known to upregulate Nav1.7 transcript and Nav1.7 protein levels [10,28,29]. Increased Nav1.7 levels in DRG neurons following inflammation might contribute to neuronal hyperexcitability, which is associated with pain behavior.

The role of Nav1.7 in inflammatory pain signaling is supported by knock-down and knockout studies in mice. Knocking-out Na\textsubscript{v}1.7 in DRG neurons abrogates inflammation-induced mechanical and thermal hyperalgesia [30]. Knock-down of Na\textsubscript{v}1.7 in primary afferents in vivo by a viral antisense construct prevents thermal hyperalgesia in mice injected with complete Freund’s adjuvant in their hindpaw [31]. The cumulative evidence has shown that Na\textsubscript{v}1.7 has a key role in inflammatory pain, although knockout studies in mice have suggested that Na\textsubscript{v}1.7 is less important in neuropathic pain [32]. However, a role for Na\textsubscript{v}1.7 in acute and chronic neuropathic pain in humans can be inferred from recent studies of human patients, as will be discussed in the next section.

**Contribution of Na\textsubscript{v}1.7 to pain: human studies**

Inherited sodium channelopathies underlie several neurological and muscular diseases [33–36], however, until recently, they had not been linked to inherited painful neuropathies. This changed in 2004 when the painful syndrome erythromelalgia (also called erythermalgia) was associated in two Chinese families with two independent mutations in SCN9A, the gene that encodes Na\textsubscript{v}1.7 [37]. Since 2004, several more mutations in SCN9A (Figure 2) have been linked to inherited erythromelalgia [5,38]. Additionally, other mutations in SCN9A have been linked to inherited paroxysmal extreme pain disorder (PEPD) [7] and, more recently, individuals with complete loss of functional Na\textsubscript{v}1.7 have been reported to be ‘indifferent’ to pain [6,39,40] (Figure 2).

**Inherited erythromelalgia**

**Clinical phenotype**

Life-long symptoms of early-onset (as early as 1 year-old) inherited erythromelalgia are characterized by episodes of burning pain triggered by mild warmth or exercise, together with erythema and mild swelling in the hands and feet, and sometimes in the ears or face [41–44]. The frequency and severity of pain episodes increase with age, with each episode lasting minutes to hours. Typically, patients with early-onset inherited erythromelalgia do not report autonomic abnormalities, such as orthostatic hypotension or gastrointestinal symptoms. Neurological examinations are otherwise normal, consistent with normal MRI brain scans and results from sensory- and motor-nerve conduction studies. The combination of the release of vasodilating peptides, substance P and calcitonin gene-related peptide by hyperactive C-fibers and impaired
cutaneous vasoconstriction caused by hypoexcitable sympathetic neurons (see later for discussion) might contribute to the erythema in patients with heritable erythromelalgia [38]. Partial relief of symptoms comes from cooling the affected extremities.

Genetic basis
Linkage analysis identified the disease locus on chromosome 2 (2q31–32) [45], where a cluster of voltage-gated sodium-channel genes, including SCN9A, is known to exist and, subsequently, the molecular target was identified as Na$_{v}$1.7 [37]. To date, a total of nine mutations affecting highly conserved residues have been identified in Na$_{v}$1.7 (Figure 2). Na$_{v}$1.7-related inherited erythromelalgia has been reported in patients of diverse ethnic origin and geographical locations and penetrance of these mutations appears to be complete [37,46–51]. De novo mutations have been found in some early-onset patients with asymptomatic parents [37,49,50]. Indeed, two independent mutations (I848T and L858F) in two sporadic early-onset erythromelalgia cases from China [37,49] have also been reported from multigeneration French (I848T) and Canadian (L858F) families [47].

Familial adult-onset erythromelalgia has been described recently in a family from the USA in which coding mutations of Na$_{v}$1.7 were excluded as the causative factor [52]. Thus, it is possible that mutations in noncoding regions of the SCN9A gene that cause increased expression of the channel or indeed other target genes might cause inherited erythromelalgia. Cases of sporadic adult-onset erythromelalgia, which cannot be attributed to underlying vascular disorders or to side-effects of medications, might be caused by less penetrant mutations. The contribution of polymorphic sites in Na$_{v}$1.7 to the adult-onset form of the disease awaits functional analyses in native neurons; these sites might represent less penetrant mutations or could modify channel stability.

Molecular pathophysiology
To date, whole-cell voltage-clamp studies have shown that all of the inherited erythromelalgia mutations cause a lowering of the threshold for activation of Na$_{v}$1.7. Many of the mutations slow deactivation, which is the transition of the channel from the open to closed state, and increase the ramp response of the channel [46,49,50,53–56]. For example, the I848T mutation causes Na$_{v}$1.7 channels to activate at a lower stimulus threshold (Figure 3a,b,e) and increase their response to small, slow depolarizations of the cell membrane [54] (Figure 3g). Each of these changes can contribute to DRG neuron hyperexcitability. Several mutations have been studied in a similar manner and have shown hyperpolarizing shifts in the voltage dependence of channel activation but alter other biophysical properties in a mutation-dependent manner [49,50,53–56].
The shift in activation voltage dependence (Figure 3e), with or without the change in steady-state inactivation (Figure 3f), is predicted to increase the window current produced by Nav1.7, which might cause a depolarizing shift in the resting membrane potential (RMP) of neurons [50]. Indeed, both L858H and A863P mutant Nav1.7 channels cause a 5 mV depolarizing shift in the RMP of DRG neurons [13,50]. Depolarization of the RMP brings DRG neurons closer to threshold for Nav1.8 channels [57,58], which produce a majority of the current underlying the upstroke of the all-or-none action potential in small DRG neurons [59,60]. Thus, the mutant Nav1.7 channels might lower the current threshold for the generation of all-or-none action potentials, without altering the voltage threshold at which the action potential takes off. Current-clamp experiments in DRG neurons in which mutant Nav1.7 channels are expressed support this model (Figure 4).

Paroxysmal extreme pain disorder

Clinical phenotype

A different set of mutations in Na$_{v}$1.7 has been associated with another autosomal dominant painful disorder, PEPD [7], which was known as familial rectal pain previously [61–63]. PEPD is characterized by life-long pain episodes, accompanied by tonic posturing and immediately followed by flushing of the lower limbs, in a uni- or bi-lateral fashion, which start within the first days after birth and are triggered by defecation or probing of the anal or genital areas. The frequency of the rectal-pain episodes decreases with age; ocular and mandibular pain are sometimes triggered by cold or irritants, becoming more prominent complaints. In contrast to inherited erythromelalgia, which is generally refractory to pharmacological treatment, PEPD patients respond to treatment with carbamazepine with almost complete cessation of spontaneous or induced attacks [7,61,63].

Genetic basis

Eight mutations in Na$_{v}$1.7 have been linked to PEPD and are segregated with the disease in affected families [7] (Figure 2). One patient has been shown to carry two mutations: a R996C substitution that is inherited from his affected father and a second de novo mutation V1298D [7]. This patient has more severe symptoms compared with his father and with patients in another family carrying the R996C mutation alone.

Molecular pathophysiology

The location of PEPD mutations in Na$_{v}$1.7 (Figure 2), within the fast-inactivation peptide in L3 and the S4–S5 linkers in domains III and IV, which act as the receptor for flushing of the lower limbs, in a uni- or bi-lateral fashion, which start within the first days after birth and are triggered by defecation or probing of the anal or genital areas. The frequency of the rectal-pain episodes decreases with age; ocular and mandibular pain are sometimes triggered by cold or irritants, becoming more prominent complaints. In contrast to inherited erythromelalgia, which is generally refractory to pharmacological treatment, PEPD patients respond to treatment with carbamazepine with almost complete cessation of spontaneous or induced attacks [7,61,63].

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Molecular pathophysiology

The location of PEPD mutations in Na$_{v}$1.7 (Figure 2), within the fast-inactivation peptide in L3 and the S4–S5 linkers in domains III and IV, which act as the receptor for
this gate [64], suggested an effect on channel fast inactivation. Three mutations (I1461T, T1461I and M1627K) were characterized by Fertleman et al. [7] in whole-cell patch-clamp studies. As expected, the I1461T and T1461I mutations impair fast inactivation of the mutant channels and produce a substantial persistent current, with no effect on channel activation [7]. By contrast, M1627K, which is located in the domain IV S4-S5 linker (Figure 2) does not show a similar deficit in fast inactivation or an increase in persistent current [7] (Figure 3c). Instead, the M1627K mutation causes a significant shift in the voltage dependence of steady-state fast inactivation of Na1,7 (Figure 3f) and the time constant for fast inactivation becomes almost voltage independent. The depolarizing shift in the voltage dependence of fast inactivation is predicted to contribute to enhanced window currents with the M1627K mutation.

Impaired fast inactivation enables more sodium current to flow through the mutant channel, which could be linked to repetitive firing in hyperexcitable DRG neurons [7]. Hyperexcitability of DRG neurons that produce PEPD mutant Na1,7 channels, however, has not been demonstrated experimentally. Although the mechanism for increased sodium current through mutant Na1,7 channels [lower threshold for channel activation in inherited erythromelalgia mutations (Figure 3e) and impaired fast inactivation in PEPD mutations (Figure 3c,f)] might differ, the net outcome is similar: DRG neuron hyperexcitability. A major difference, however, between the two cases is the dramatic response of PEPD patients to treatment with carbamazepine [7,61,63], whereas treatment with nonselective sodium-channel blockers is less effective in patients with inherited erythromelalgia [41,50].

Carbamazepine is a use-dependent inhibitor of sodium channels that binds to inactivated channels preferentially and, as a result, can enhance inactivation [65]. Carbamazepine-induced enhancement of inactivation and stabilization of the inactivated state might counteract the impaired inactivation caused by the PEPD mutations, thus accounting for the effectiveness that has been reported in patients with PEPD. By contrast, most inherited erythromelalgia mutations do not alter channel inactivation and carbamazepine would not be expected to be more effective...
on these mutant channels than on wild-type channels (Box 1).

PEPD, similar to other diseases of ion channels, could be caused by a genetic defect at more than one locus. Indeed, five families with PEPD have wild-type Na$_\text{v}$.1.7-coding sequence [7]. The absence of a missense mutation in Na$_\text{v}$.1.7 does not preclude other changes that might underlie the disease; for example, mutations that enhance the rate of transcription of SCN9A or the stability of the channel transcripts. These mutations are harder to detect and validate than missense mutations. However, SCN9A has been excluded as the cause of PEPD in a family large enough to carry out linkage analysis [7]. Therefore, mutations in other targets might, in some cases, cause PEPD.

**Channelopathy-associated congenital indifference to pain (CIP)**

**Clinical phenotype**

Patients with congenital insensitivity (or indifference) to pain (CIP) show varying degrees of deficits in sensing, perceiving and reacting to painful stimuli but their other sensory modalities are intact [66,67]. The designation of patients as ‘insensitive’ or ‘indifferent’ to pain is a subject of controversy that has led to the use of the term channelopathy-associated CIP for a subset of these patients with null mutations in Na$_\text{v}$.1.7 [6] (but see [39]). Typically, these patients present with a history of not experiencing any form of pain anywhere on their bodies, even after burns, bone fractures or severe injuries to their lips and tongues, and they do not experience visceral pain [6,39,40]. Despite the fact that Na$_\text{v}$.1.7 is produced within sympathetic ganglion neurons [9–13], patients with channelopathy-associated CIP do not show apparent deficits in autonomic function, such as whole-body thermoregulation or cardiac or respiratory rhythm, and have a normal axon-reflex response to histamine [6,39]. Interestingly, channelopathy-associated CIP patients have deficits in the sense of smell [39].

**Genetic basis**

Different forms of CIP have been linked genetically to several targets, including genes encoding NGF and its receptor [66]. However, characterization of the molecular defect in channelopathy-associated CIP awaited linkage analysis, which led to the identification of null mutations in SCN9A [6,39,40].

Homozygous single-nucleotide nonsense mutations and compound heterozygous mutations, which include nonsense mutation on one allele and a deletion mutation of coding or intronic sequences on the second allele, have been identified (Figure 2). Three loss-of-function mutations in SCN9A were identified initially in unrelated consanguineous Pakistani families [6]. Subsequently, several other mutations, including deletions in coding sequence that truncate the protein and deletion of intronic sequences that suggest splicing defects, were identified in ethnically diverse patients [39]. Surprisingly, these cases included patients who were born into families that are apparently non-consanguineous, which suggests a de novo mutation of one of the alleles and the inheritance of the second mutant allele from one of the parents, who would be an asymptomatic carrier. This observation suggests that SCN9A-related CIP might underlie some cases of idiopathic CIP in non-consanguineous families.

**Molecular pathophysiology**

Homozygous null mutations or the compound heterozygous loss-of-function mutations in Na$_\text{v}$.1.7 would be expected to cause the complete loss of Na$_\text{v}$.1.7 current in all of the neurons in which this channel is normally expressed. Consistent with this prediction, truncations of Na$_\text{v}$.1.7 channel protein that are caused by the null mutations S459X, I767X and W897X prevent the formation of functional channels [6] (Figure 3d,h). The deletion of an intronic sequence in one of the alleles in a compound heterozygous case might inhibit normal splicing completely or reduce the efficiency of correct splicing significantly, thus reducing the level of full-length channel; parents of patients with channelopathy-associated CIP and heterozygous siblings experience no sensory deficit, indicating that the null mutations of Na$_\text{v}$.1.7 do not produce clinically significant haploinsufficiency.

The complete knockout of Na$_\text{v}$.1.7 by the null mutations does not appear to impair other sensory modalities (with the exception of smell, as mentioned earlier). This suggests that truncated Na$_\text{v}$.1.7 channel proteins do not interfere with the function of the other sodium-channel isoforms that might be expressed within the same neuron. Persistence of the deficit of pain sensibility into adulthood (at least within the pool of patients reported to date)
suggests that the role of \( \text{Na}_{\text{v}1.7} \) in nociception is not redundant and cannot be substituted by other channels, such as the sensory neuron-specific channels \( \text{Na}_{\text{v}1.8} \) and \( \text{Na}_{\text{v}1.9} \) [39]. The lack of detectable autonomic deficits suggests that other channels might compensate for the loss of \( \text{Na}_{\text{v}1.7} \) within sympathetic ganglion neurons [39]. Among a number of unanswered questions (Box 2), it remains to be seen if aversion to noxious stimuli in growing patients with channelopathy-associated CIP [6] represents learned behavior or is the result of compensatory upregulation of another channel or an alternative pain pathway that might be regulated developmentally.

**Implications for physiology of nociception and for SCN9A-related pathophysiology in sympathetic neurons**

Small DRG neurons, most of which are nociceptive, express multiple sodium channels, including \( \text{Na}_{\text{v}1.7} \) and \( \text{Na}_{\text{v}1.8} \)

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**Box 2. Outstanding questions**

1. What are the age-dependent triggers of adult-onset inherited erythromelalgia?
2. Why is global \( \text{Na}_{\text{v}1.7} \) KO lethal in mice but not in humans and why is there no global sympathetic dysfunction in inherited erythromelalgia or PEPD patients?
3. Why are inherited erythromelalgia symptoms absent over the trunk and why does PEPD cause pain that is focused on perirectal, jaw and periocular regions?
4. Do mutations in noncoding regions of SCN9A (e.g. in the promoter) cause erythromelalgia or PEPD?
5. Can \( \text{Na}_{\text{v}1.7} \)-specific blockers be developed as treatments for erythromelalgia and PEPD?
6. Will \( \text{Na}_{\text{v}1.7} \)-specific blockers be useful in the treatment of non-inherited pain?

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**Figure 5.** The L858H mutation decreases firing frequency in transfected P2 rat SCG neurons and the phenotype is rescued by the coexpression of \( \text{Na}_{\text{v}1.8} \). (a) Representative SCG neuron expressing wild-type \( \text{Na}_{\text{v}1.7} \) fires six action potentials in response to a 950 ms input of 40 pA from RMP (approximately \(-45 \text{ mV}\)). (b) Representative SCG neuron expressing L858H fires only two action potentials, with reduced overshoot, in response to a 100 pA current injection from RMP (approximately \(-40 \text{ mV}\)). When the cell was held at \(-60 \text{ mV}\) to overcome the depolarization of RMP caused by L858H, it produced four action potentials in response to an identical stimulus (inset). (d) Representation of the cell membrane of SCG and DRG neurons showing the different complement of voltage-gated sodium channels that is present in the two different neurons. (d) The \( \text{Na}_{\text{v}1.8} \) sodium channel (green) has markedly depolarized voltage-dependence, compared with TTX-sensitive sodium channels, which include \( \text{Na}_{\text{v}1.1}, \text{Na}_{\text{v}1.3}, \text{Na}_{\text{v}1.6} \) and \( \text{Na}_{\text{v}1.7} \) (black). (e) Action-potential overshoot in SCG neurons transfected with the L858H erythromelalgia-mutant channel (red trace) was reduced significantly compared with that in neurons transfected with wild-type \( \text{Na}_{\text{v}1.7} \) (blue trace). The action potential overshoot was restored to wild-type levels when \( \text{Na}_{\text{v}1.8} \) was coexpressed with L858H (green trace). Modified, with permission, from Rush et al. [13].

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Although it might be intuitively obvious why gain-of-function mutations in Na<sub>1.7</sub> channels could cause hyperexcitability of sensory neurons in inherited erythromelalgia and PEPD, it is less obvious how the loss of Na<sub>1.7</sub> in channelopathy-associated CIP abrogates the pain response completely. The biophysical properties of Na<sub>1.7</sub> suggest that this channel might function to amplify generator potentials at nerve endings to transduce signals from thermo- or mechano-receptors [23]. The subcellular localization of this channel (Figure 1b) is consistent with this view [10,22]. Inevitably, it must be concluded that Na<sub>1.7</sub> has an essential role in the transmission of the signal from somatic- and visceral-pain receptors to higher-order brain centers; however, the absence of autonomic deficits in channelopathy-associated CIP patients suggests that the function of Na<sub>1.7</sub> within sympathetic neurons might be redundant.

Computer simulation studies of model neurons [56] have predicted that lowering the threshold for channel activation, as is the case in all of the inherited erythromelalgia mutant Na<sub>1.7</sub> channels studied thus far, can account for the hyperexcitable phenotype of DRG neurons. The effects of a larger ramp current and slower deactivation from the open state have not been evaluated in these simulation studies. By analogy to mutations in the cardiac channel Na<sub>1.5</sub>, which cause arrhythmias, and in neuronal channel Na<sub>1.1</sub>, which cause epilepsy, PEPD mutations that impair fast inactivation of Na<sub>1.7</sub> would be expected to increase repetitive firing, leading to hyperexcitability of DRG neurons housing the mutant channels [69].

By contrast, the expression of mutant Na<sub>1.7</sub> in sympathetic neurons of the SCG, which normally express several sodium channels, including Na<sub>1.7</sub>, causes hypexcitability [13] (Figure 5). Two related factors might explain the opposite cell type-dependent effect of the expression of mutant Na<sub>1.7</sub>: (i) sensory neurons express the TTX-R sodium channel Na<sub>1.8</sub>, whereas sympathetic neurons do not [13] (Figure 5c,d) and (ii) the expression of mutant Na<sub>1.7</sub> channels causes a depolarization of approximately 5 mV in the RMP of DRG [13,50] and SCG neurons [13]. SCG neurons express Na<sub>1.3</sub>, Na<sub>1.6</sub> and Na<sub>1.7</sub> but not Na<sub>1.8</sub>, channels [13]; a depolarization of the RMP would be expected to inactivate these channels, including the mutant Na<sub>1.7</sub> channels, which have relatively hyperpolarized steady-state inactivation [24,70] that causes a reduction in the action-potential overshoot and attenuates repetitive firing [13] (Figure 5e). Na<sub>1.8</sub> channels, however, have depolarized voltage dependence of activation and steady-state inactivation [57,58] compared with other sodium channels, including Na<sub>1.7</sub> (Figure 5d). Na<sub>1.8</sub> channels carry most of the inward sodium current underlying the action-potential upstroke in cells in which they are expressed and the presence of Na<sub>1.8</sub> within DRG neurons permits these cells to generate action potentials and sustain repetitive firing when depolarized [60,71], so that depolarization would not be expected to abolish action-potential firing in DRG neurons expressing erythromelalgia Na<sub>1.7</sub> mutants. The action potentials supported by Na<sub>1.8</sub> are followed by hyperpolarization of the neuronal membrane, which further contributes to the recovery of all sodium channels from inactivation. Indeed, the coexpression of Na<sub>1.8</sub> with Na<sub>1.7</sub> L858H mutant channels in SCG neurons [13] restores the action-potential overshoot of SCG neurons [13] (Figure 5e), consistent with the hypothesis that the presence of Na<sub>1.8</sub> in sensory neurons and its absence in sympathetic neurons underlies, at least partially, hyperexcitability in one cell type and hypexcitability in the other.

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