Brief Communication

Electrophysiological Properties of Mutant $Na_v1.7$ Sodium Channels in a Painful Inherited Neuropathy

Theodore R. Cummins,[1] Sulayman D. Dib-Hajj,[2,3,4] and Stephen G. Waxman[2,3,4]

[1]Department of Pharmacology and Toxicology, Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, Indiana 46202, [2]Department of Neurology and [3]Center for Neuroscience and Regeneration Research, Yale University School of Medicine, New Haven, Connecticut 06510, and [4]Rehabilitation Research Center, Veterans Administration Connecticut Healthcare System, West Haven, Connecticut 06516

Although the physiological basis of erythermalgia, an autosomal dominant painful neuropathy characterized by redness of the skin and intermittent burning sensation of extremities, is not known, two mutations of $Na_v1.7$, a sodium channel that produces a tetrodotoxin-sensitive, fast-inactivating current that is preferentially expressed in dorsal root ganglia (DRG) and sympathetic ganglia neurons, have recently been identified in patients with primary erythermalgia. $Na_v1.7$ is preferentially expressed in small-diameter DRG neurons, most of which are nociceptors, and is characterized by slow recovery from inactivation and by slow closed-state inactivation that results in relatively large responses to small, subthreshold depolarizations. Here we show that these mutations in $Na_v1.7$ produce a hyperpolarizing shift in activation and slow deactivation. We also show that these mutations cause an increase in amplitude of the current produced by $Na_v1.7$ in response to slow, small depolarizations. These observations provide the first demonstration of altered sodium channel function associated with an inherited painful neuropathy and suggest that these physiological changes, which confer hyperexcitability on peripheral sensory and sympathetic neurons, contribute to symptom production in hereditary erythermalgia.

Key words: **dorsal root ganglion; hyperpolarization; voltage clamp; tetrodotoxin sensitive; neuropathic pain; skeletal sodium channel**

Introduction

Sensory neurons in dorsal root ganglia (DRG) express multiple voltage-gated sodium channels including $Na_v1.7$ (Klugbauer et al., 1995; Sangameswaran et al., 1997), $Na_v1.8$ (Akopian et al., 1996; Sangameswaran et al., 1996), and $Na_v1.9$ (Dib-Hajj et al., 1998; Tate et al., 1998), which play important roles in regulating their excitability (Matzner and Devor, 1994; Cummins et al., 1998, 1999; Renganathan et al., 2001). $Na_v1.7$ is selectively expressed in DRG and sympathetic ganglia (Black et al., 1996; Toledo-Aral et al., 1997) and is abundant in small-diameter DRG neurons (Black et al., 1996, 2004), including nociceptors (Djouhri et al., 2003a). Recombinant $Na_v1.7$ produces a fast-inactivating tetrodotoxin-sensitive (TTX-S) current (Klugbauer et al., 1995; Sangameswaran et al., 1997) and displays slow repriming and slow closed-state inactivation that poise it to respond to small, slow depolarizations (Cummins et al., 1998; Herzog et al., 2003).

It is now well established that dysregulated expression of sodium channel genes, for example $Na_v1.3$, can produce changes in sodium currents within spinal sensory neurons that contribute to neuropathic pain (Cummins and Waxman, 1997; Black et al., 1999; Hains et al., 2004). Recently, $Na_v1.7$ expression in DRG neurons has been shown to increase after carrageenan-induced inflammation of rat hindpaw (Black et al., 2004). The dynamic regulation of $Na_v1.7$ suggests that this channel contributes to neuronal hyperexcitability leading to inflammatory pain.

In contrast to dysregulated sodium channel expression, to date there have been no demonstrations of changes in sodium currents attributable to mutations associated with pain. Familial primary erythermalgia is a rare, dominantly inherited painful neuropathy that is manifested as burning pain and redness of the extremities (van Genderen et al., 1993). Layzer (2001) hypothesized that sensitized C-fibers and the axon reflex underlie these symptoms. A segment of chromosome 2, which is known to contain sodium channel genes, has been linked to primary erythermalgia (Drenth et al., 2001). Subsequently, Yang et al. (2004) showed that two independent mutations in SCN9A, which encodes $Na_v1.7$, are linked to this disorder. The two substitutions produce a change of isoleucine 848 to threonine (I848T) and leucine 858 to histidine (L858H).

We investigated the effect of the I848T and L858H mutations on the biophysical properties of $hNa_v1.7$. Both mutations cause a significant hyperpolarizing shift in the $V_{1/2}$ of activation of the mutant channel, which was accompanied by a larger ramp current. Our data are consistent with a role of $Na_v1.7$ in DRG neuron hyperexcitability in erythermalgia.

Materials and Methods

Plasmids. The plasmid carrying the human $Na_v1.7$ cDNA insert was described previously (Klugbauer et al., 1995). The TTX-S determinant res-

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Correspondence should be addressed to Dr. Stephen G. Waxman, Department of Neurology, LCI 707, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510. E-mail: stephen.waxman@yale.edu.

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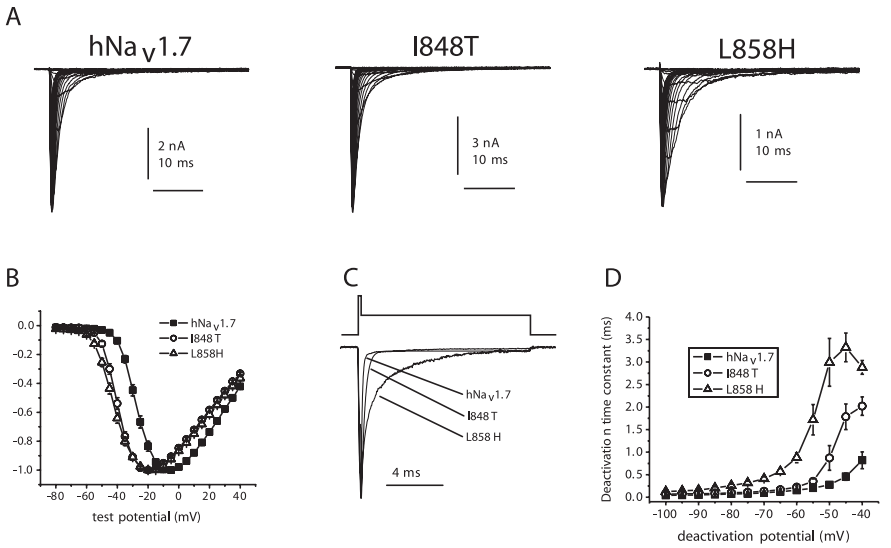

Figure 1. The I848T and L858H mutations of $hNa_v1.7$ alter activation and deactivation. *A*, Current traces recorded from representative HEK293 cells expressing either wild-type $hNa_v1.7$ or mutant channels, I848T or L858H. Cells were held at −100 mV, and currents were elicited with 50 msec test pulses to potentials ranging from −80 to 40 mV. *B*, Normalized peak current–voltage relationship for wild-type (filled squares; $n = 29$), I848T (open circles; $n = 27$), and L858H (open triangles; $n = 27$) channels. *C*, Representative tail currents of WT, I848T, and L858H channels. Cells were held at −100 mV and depolarized to −20 mV for 0.5 msec, followed by a repolarization to −50 mV to elicit tail currents. *D*, Time constants for tail current deactivation at repolarization potentials ranging from −40 to −100 mV for wild-type (filled squares; $n = 7$), I848T (open circles; $n = 7$), and L858H (open triangles; $n = 7$) $hNa_v1.7$ channels. Time constants were obtained with single exponential fits to the deactivation phase of the currents. Error bars represent SE.

idue of $Na_v1.7$, tyrosine 362, was changed by site-directed mutagenesis to a serine to render the channel resistant to TTX ($Na_v1.7_R$) (Herzog et al., 2003). The I848T and L858H were individually introduced into $Na_v1.7_R$ using the Quick Change XL site-directed mutagenesis kit (Stratagene, La Jolla, CA) with two mutagenic primers that were designed according to the manufacturer recommendations.

Transfections. The $hNa_v1.7$ channels were cotransfected with the human $\beta1$ and $\beta2$ subunits (Lossin et al., 2002) into human embryonic kidney (HEK293) cells using the calcium phosphate precipitation method. HEK293 cells were grown under standard tissue culture conditions (5% CO_2; 37°C) in DMEM supplemented with 10% fetal bovine serum. The calcium phosphate–DNA mixture was added to the cell culture medium and left for 3 hr, after which the cells were washed with fresh medium. Sodium currents were recorded 40–72 hr after transfection.

Whole-cell patch-clamp recordings. Whole-cell patch-clamp recordings were conducted at room temperature (~21°C) using an EPC-10 amplifier and the Pulse program (v 8.5; HEKA Elektronik, Lambrecht/Pfalz, Germany). Fire-polished electrodes (0.8–1.5 MΩ) were fabricated from 1.7 mm VWR Scientific (West Chester, PA) capillary glass using a Sutter Instruments (Novato, CA) P-97 puller. Average access resistance was 1.4 ± 0.4 MΩ (mean ± SD; $n = 85$). Voltage errors were minimized using 80% series resistance compensation; the capacitance artifact was canceled using computer-controlled circuitry of the patch-clamp amplifier. Linear leak subtraction was used for all voltage-clamp recordings. Recordings were always started 3 min after establishing the whole-cell configuration. Membrane currents were filtered at 5 kHz and sampled at 20 kHz. The pipette solution contained the following (in mM): 140 CsF, 1 EGTA, 10 NaCl, and 10 HEPES, pH 7.3. The standard bathing solution was the following (in mM): 140 NaCl, 3 KCl, 1 $MgCl_2$, 1 $CaCl_2$, and 10 HEPES, pH 7.3. Data were analyzed using Pulsefit (HEKA Elektronik) and Origin (Microcal Software, Northampton, MA) software. Data sets used for statistical analysis were checked for normal distributions using a Shapiro–Wilks normality test.

Unless otherwise noted, statistical significance was determined ($p < 0.05$) using an unpaired *t* test. Results are presented as mean ± SEM and error bars in the figures represent SEs.

Results

Wild-type (WT) $hNa_v1.7_R$ and the two mutant derivative channels I848T and L858H were transiently expressed along with hβ-1 and hβ-2 subunits in HEK293 cells. Figure 1*A* shows representative whole-cell currents. Although similar peak current densities were recorded from cells expressing WT (318 ± 43 pA/pF; $n = 29$) and I848T (350 ± 37 pA/pF; $n = 27$) channels, the current densities recorded from cells expressing L858H channels were significantly smaller (174 ± 30 pA/pF; $n = 27$). The voltage dependence of activation was examined using a series of depolarizing test pulses from −100 mV. Mutant channels activated at potentials 10–15 mV more negative than WT channels (Fig. 1*B*). The midpoint of activation (estimated by fitting the data with a Boltzman function) was significantly more negative for I848T currents (−38.4 ± 1.0 mV; $n = 27$) and L858H currents (−37.9 ± 0.9 mV; $n = 27$) than for WT currents (−24.6 ± 1.1 mV; $n = 29$). Although the midpoint of activation was almost identical for I848T and L858H channels, the threshold for activation appeared to be ~5 mV more negative for L858H channels than for I848T channels.

The kinetics of deactivation, which reflects the transition from the open to the closed state, of WT and mutant channels was also examined by eliciting tail currents at a range of potentials after briefly activating the channels (at −20 mV for 0.5 msec). Altered deactivation of skeletal muscle sodium channels is thought to contribute to the pathophysiology of paramyotonia congenita (Featherstone et al., 1998). I848T and L858H currents exhibited slower kinetics of deactivation (Fig. 1*C*). The time constant of deactivation (measured with single exponential fits) was slower at potentials ranging from −100 mV to −40 mV for the mutant channels. Interestingly, the effect on deactivation was much greater with the L858H mutation than with the I848T mutation at all deactivation voltages tested. For example, the deactivation time constants for I848T and L858H channels at −50 mV were approximately threefold and ~10-fold, respectively, larger than that of WT channels.

The fast-inactivation time constant, which provides a measure of the open-to-inactivated transition, was estimated using m^3h Hodgkin and Huxley type fits to the current data. The time constants for fast inactivation between −40 and −20 mV were smaller for the mutant channels than for WT channels (Fig. 2*A*). However, the time constants of the three channels were similar at more depolarized potentials.

In contrast to the dramatic differences in the voltage dependence of activation, the voltage dependence of steady-state fast inactivation was similar for WT, I848T, and L858H (Fig. 2*B*). The midpoint of fast inactivation (measured with 500 msec prepulses) was not significantly different for WT (−73.6 ± 1.1 mV; $n = 20$), I848T (−75.8 ± 1.1 mV; $n = 19$), and L858H (−76.1 ± 1.2 mV; $n = 17$) channels. The steady-state fast-inactivation curve for L858H channels deviated from that of the other channels at negative voltages (e.g., between −120 and −80 mV). This

is likely attributable to differences in slow inactivation (see below).

Defective slow inactivation of skeletal muscle sodium channels has been proposed to play a role in hyperkalemic periodic paralysis, and therefore, we also examined the voltage dependence of steady-state slow inactivation of $hNa_v1.7$ currents. Thirty second prepulses, followed by 100 msec recovery pulses to −120 mV to allow recovery from fast inactivation, preceded the test pulse (to 0 mV for 20 msec) to determine the fraction of current available. Dramatic differences were observed for slow-inactivation properties of WT, I848T, and L858H currents (Fig. 2*C*). Surprisingly, the L858H mutation substantially enhanced slow inactivation of $hNa_v1.7$. This enhancement of slow inactivation is likely to account for the enhanced inactivation of L858H currents observed at negative potentials with the steady-state fast-inactivation protocol (Fig. 2*B*). In contrast, the I848T mutations impaired slow inactivation of $hNa_v1.7$ channels. At 0 mV, only 67 ± 6% of I848T channels ($n = 8$) are slow inactivated (determined from the fraction of channels available for activation as measured in Fig. 2*C*) compared with 84 ± 4% of WT channels ($n = 8$) and >97 ± 2% of L858H channels ($n = 7$). For both mutants, the percentage of channels that were slow inactivated at 0 mV was significantly different than for WT channels. Therefore, the two mutations identified in the $Na_v1.7$ channels of patients with primary erythermalgia have differential effects on slow inactivation of $hNa_v1.7$ channels.

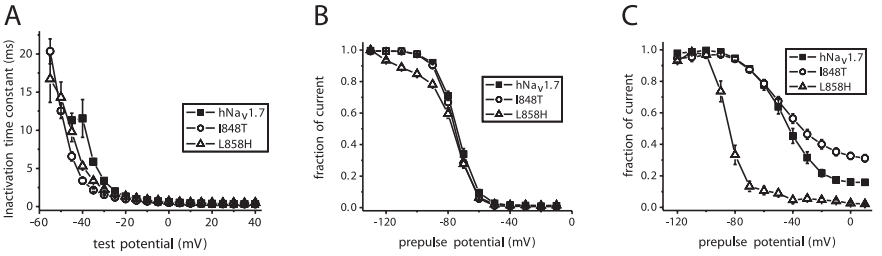

Figure 2. The I848T and L858H mutations differentially alter inactivation of $hNa_v1.7$. *A*, Fast inactivation kinetics as a function of voltage for wild-type (filled squares; $n = 8$), I848T (open circles; $n = 8$), and L858H (open triangles; $n = 8$) $hNa_v1.7$ channels. Currents elicited as described in Figure 1*A* were fit with Hodgkin-Huxley type m^3h model to estimate the inactivation time constants. *B*, Comparison of steady-state fast inactivation for wild-type (filled squares; $n = 20$), I848T (open circles; $n = 19$), and L858H (open triangles; $n = 17$) $hNa_v1.7$ channels. Currents were elicited with test pulses to 0 mV after 500 msec inactivating prepulses. *C*, Comparison of steady-state slow inactivation for wild-type $hNa_v1.7$ (filled squares; $n = 9$), I848T (open circles; $n = 8$), and L858H (open triangles; $n = 9$) $hNa_v1.7$ channels. Slow inactivation was induced with 30 sec prepulses, followed by 100 msec pulses to −120 mV to allow recovery from fast inactivation. A test pulse to 0 mV for 20 msec was used to determine the fraction of current available. Error bars represent SE.

Finally, we examined the currents induced in $hNa_v1.7$ channels by slow ramp depolarizations. Significantly larger currents were elicited with slow ramp (0.2 mV/ms) depolarizations from −100 to +20 mV by either I848T or L858H channels compared with WT channels (Fig. 3). The ramp currents (expressed as a percentage of peak current) were 1.8 ± 0.2% for I848T channels ($n = 19$), 2.6 ± 0.3% for L858H channels ($n = 16$), and 0.6 ± 0.1% for WT channels ($n = 16$). The ramp currents in cells expressing I848T and L858H channels were pronounced between −70 and −40 mV (Fig. 3) and thus could contribute to subthreshold depolarizations and the initiation of action potentials.

Discussion

Voltage-gated sodium channels mediate an increase in Na^+ permeability during depolarization of membrane potential that underlies action potential electrogenesis. Although dysregulated sodium channel expression contributes to the pathophysiology of neuropathic pain (Matzner and Devor, 1994; Waxman et al., 2000), mutations of voltage-gated sodium channel α-subunits, which underlie a number of human and animal disorders (for review, see Goldin, 2001; Keating and Sanguinetti, 2001; Meisler et al., 2001; Cannon, 2002), were not associated with painful neuropathies until Yang et al. (2004) identified two mutations in SCN9A, the gene encoding $Na_v1.7$, in patients with primary erythermalgia. In this study, we have characterized the functional consequences of these two $hNa_v1.7$ mutations, I848T and L858H.

The I848T and L858H mutations are located in the S4–S5 linker region of domain II (DIIS4–S5) of the channel. Biophysical analysis of the mutant channels revealed several differences compared with wild-type $hNa_v1.7$. Both mutations significantly shifted the voltage dependence of activation in the hyperpolarizing direction. Deactivation of $hNa_v1.7$ was also slowed by both mutations, although the effect was much larger with the L858H mutation. Both mutations also significantly increased the size of ramp currents produced by $hNa_v1.7$ channels in response to slow depolarizations between −70 and −40 mV, a range that probably encompasses resting potential of sensory neurons (Harper and Lawson, 1985; Caffrey et al., 1992). These changes in the functional properties of $hNa_v1.7$ are likely to contribute to increased excitability of spinal sensory neurons that express $Na_v1.7$ and may underlie the abnormal pain sensations in patients with inherited erythermalgia.

The I848T and L858H mutations shifted the voltage dependence of activation of $hNa_v1.7$ by almost 15 mV in a hyperpolarizing direction. A shift of this magnitude is expected to decrease the threshold for action potential generation in sensory neurons and increase neuronal excitability. Both mutations also significantly slowed the rate of deactivation of $hNa_v1.7$. Impaired deactivation of skeletal muscle sodium channels ($Na_v1.4$) has been hypothesized to contribute to abnormal muscle excitability (predominantly myotonia) in patients with paramyotonia congenita (Featherstone et al., 1998). Many of the $Na_v1.4$ mutations that cause myotonia slow both the rate of fast inactivation and deactivation, and in computer simulations, this combination can induce a destabilization of repolarization after an action potential, leading to "myotonic runs" (Featherstone et al., 1998). Unlike these $Na_v1.4$ mutations, the $hNa_v1.7$-I848T and -L858H did not slow the rate of fast inactivation, and therefore the $hNa_v1.7$ mutations might not destabilize repolarization.

The mutant $hNa_v1.7$ channels produced significantly larger currents in response to slow ramp depolarizations than wild-type channels. Increased overlap between the inactivation and activation curves, resulting from the large negative shift in the voltage dependence of activation (Fig. 1*B*) and unchanged voltage dependence of steady-state inactivation (Fig. 2*B*), may underlie the larger ramp currents. Impaired deactivation, which indicates that the open-to-closed transition is altered, is also likely to contribute to the increased ramp current amplitudes. At negative potentials (less than −45 mV), the closing rate is much larger than the inactivation rate, and therefore channel openings are more likely to be terminated by deactivation than by inactivation in this voltage range (Vandenberg and Bezanilla, 1991). Vandenberg and Bezanilla (1991) suggested that the deactivation rate of sodium channels limits the ability of sodium channels to open and reopen at negative potentials. Thus, slowing the deactivation rate would

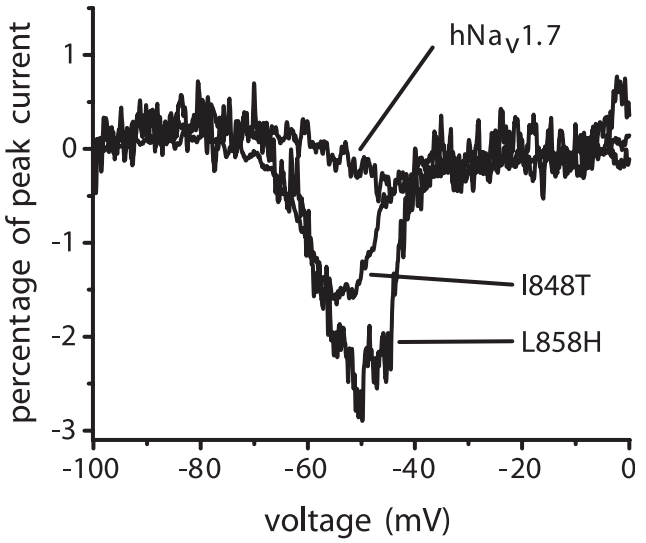

Figure 3. The I848T and L858H mutations enhance ramp currents of $hNa_v1.7$. Representative ramp currents elicited with 500 msec ramp depolarizations from −100 to 0 mV from HEK293 cells expressing wild-type, I848T, and L858H channels.

be expected to increase the number of openings and open times at negative potentials, and this could contribute to increased ramp current amplitudes. The fact that the L858H mutant exhibited the slowest deactivation kinetics and the largest ramp currents is consistent with this hypothesis. Because the ramp currents are evoked between −70 and −40 mV, close to the resting potential of DRG neurons (Harper and Lawson, 1985; Caffrey et al., 1992), the larger ramp currents in cells expressing mutant channels could amplify the response to small depolarizing inputs, increasing excitability. $Na_v1.7$ channels are expressed at high levels in small, mostly nociceptive, sensory neurons (Djouhri et al., 2003a), suggesting that changes in activation, deactivation, and ramp current amplitude contribute to pain in erythermalgia patients with the I848T and L858H mutations.

The amino acid sequence of domain II S4–S5 linker in $hNa_v1.7$ and $hNa_v1.4$ are identical (Yang et al., 2004) and are highly conserved when the sequence of all known sodium channels are aligned (data not shown). The conservation of this sequence suggests that the DIIS4–S5 linker plays a similar role in different sodium channels. The I848T mutation in erythermalgia (Yang et al., 2004) corresponds to the I693T mutation in $hNa_v1.4$ of patients with episodic muscle weakness (Cannon, 2002). The T704M mutation in $hNa_v1.4$ causes hyperkalemic periodic paralysis, another muscle disorder characterized by episodic weakness (Cannon, 2002). The L858 in $hNa_v1.7$ corresponds to L703 in $hNa_v1.4$, which is immediately adjacent to the T704 residue. Thus, DIIS4–S5 mutations in both $hNa_v1.7$ and $hNa_v1.4$ are associated with hereditary neurological and muscle disorders, which suggests that this linker contributes to the determination of biophysical properties of sodium channels including voltage dependence of activation and deactivation.

The functional consequences of the I693T and T704M mutations on $hNa_v1.4$ have been characterized after expression in HEK293 cells (Plassart-Schiess et al., 1998; Hayward et al., 1999; Bendahhou et al., 2002) and are similar to the effects of the I848T mutation on $hNa_v1.7$. All of these mutations shift the voltage dependence of activation in a hyperpolarizing direction. The $Na_v1.4$ mutations are thought to induce muscle weakness as a result of an enhanced persistent current (possibly attributable to window currents that result from the negative shift in the voltage dependence of activation) that depolarizes the muscle 5–10 mV, causing inactivation of the sodium currents and decreasing the ability of the muscle to fire action potentials (Lehmann-Horn et al., 1987; Cummins et al., 1993). The $hNa_v1.4$-I693T and $hNa_v1.4$-T704M mutations also significantly impair slow inactivation, and this impairment is thought to contribute to muscle weakness associated with these mutations (Ruff, 1994). However, whereas the I848T mutation impaired slow inactivation of $hNa_v1.7$, the L858H mutation of $hNa_v1.7$ enhanced slow inactivation. Because both mutations are associated with primary erythermalgia, this divergence might be interpreted as suggesting that slow inactivation is not important in its pathophysiology. Alternatively, there may be subtle differences in the symptoms of primary erythermalgia in patients with the I848T and L858H mutations attributable to the differential effect of the two mutations on slow inactivation.

Given that the I693T mutation in $Na_v1.4$ is associated with muscle weakness, how can the I848T mutation in $Na_v1.7$ be associated with increased pain sensations? One explanation may derive from the fact that whereas mature muscle cells express only $Na_v1.4$ channels, spinal sensory neurons express multiple sodium channel isoforms with distinct properties (Black et al., 1996). The $Na_v1.8$ channel, which is expressed at high levels in many (but not all) spinal sensory neurons, has a very depolarized voltage dependence of inactivation compared with other channels such as $Na_v1.4$ and $Na_v1.7$ (Akopian et al., 1996) and plays a critical role in action potential firing in sensory neurons (Renganathan et al., 2001). If the $Na_v1.7$-I848T mutation depolarizes the sensory neurons by 5–10 mV, as the $Na_v1.4$ mutations associated with muscle weakness are thought to do in muscle (Lehmann-Horn et al., 1987; Cannon, 2000), the $Na_v1.8$ channels are likely to still be available for activation. Depolarizations of similar magnitudes might produce reduced action potential activity in muscle but could lead to enhanced excitability in neurons that also express $Na_v1.8$ because these cells would be closer to threshold for activation of $Na_v1.8$ currents. Thus, mutations of identical residues in $Na_v1.7$ and $Na_v1.4$ that have similar effects on channel properties could have differential effects on excitability and cause distinct neurological disorders because of the presence of multiple sodium channels (including $Na_v1.8$ which is not present in muscle) in spinal sensory neurons.

Non-nociceptive neurons are less likely to express $Na_v1.8$ channels than nociceptive neurons (Djouhri et al., 2003b), and thus mutant $Na_v1.7$ channels could possibly differentially alter excitability in nociceptive and non-nociceptive neurons. Moreover, although $Na_v1.7$ currents exhibit similar properties in HEK293 cells and DRG neurons (Cummins et al., 1998; Herzog et al., 2003), it is also possible that the mutant and wild-type $Na_v1.7$ channels are differentially modulated in DRG neurons, and this might contribute to the disease phenotype. For example, our studies in HEK293 cells were done with coexpression of the $\beta1$ and $\beta2$ subunits, but DRG neurons also express other β subunits such as $\beta3$ (Shah et al., 2000) that could impact the current properties. $Na_v1.4$ and $Na_v1.7$ currents exhibit distinct properties (Cummins et al., 1998) and could be differentially modulated by β subunits, and this could also contribute to the different disease phenotypes.

Our results highlight the fact that analogous mutations in sodium channels can result in dramatically different phenotypes and suggest that this difference may be attributable to the ensemble of other sodium channels (or channel subunits) that are expressed together with the mutant channel within DRG neurons.

The changes in the electrophysiological properties of mutant $hNa_v1.7$ provide the first example of altered sodium channel function in a hereditary pain syndrome and suggest that targeting of sodium channels may provide a useful therapeutic strategy for this disorder.

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