Sodium Channels in Normal and Pathological Pain

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Key Words

erythromelalgia, paroxysmal extreme pain disorder, congenital insensitivity to pain, sensory neurons, sympathetic neurons

Abstract

Nociception is essential for survival whereas pathological pain is maladaptive and often unresponsive to pharmacotherapy. Voltage-gated sodium channels, $Na_v1.1$–$Na_v1.9$, are essential for generation and conduction of electrical impulses in excitable cells. Human and animal studies have identified several channels as pivotal for signal transmission along the pain axis, including $Na_v1.3$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, with the latter three preferentially expressed in peripheral sensory neurons and $Na_v1.3$ being upregulated along pain-signaling pathways after nervous system injuries. $Na_v1.7$ is of special interest because it has been linked to a spectrum of inherited human pain disorders. Here we review the contribution of these sodium channel isoforms to pain.

Contents

Nociceptors: pain- or damage-sensing neurons

Inherited sodium channelopathies: pathologies linked to mutations in sodium channels

Na_v1: voltage-gated sodium channel subfamily 1

TTX: tetrodotoxin

DRG: dorsal root ganglion

INTRODUCTION

Nociception is the physiological system for the perception of pain, and thus it contributes to survival because it warns of impending harm. Signaling along the pain axis from peripheral receptors to higher-order brain centers optimally discriminates potentially harmful from innocuous stimuli. If pain is inappropriately magnified or prolonged, or occurs in the absence of appropriate external stimuli, it is pathological. The responses of nociceptors to stimuli are encoded by action potentials, whose genesis and propagation are dependent on voltage-gated sodium channels, and it is thus not surprising that aberrant expression patterns of channels and inherited sodium channelopathies have been linked to neuropathic and inflammatory pain. Here we review current knowledge of sodium channels that are preferentially expressed along the pain-signaling pathways.

Nine pore-forming sodium channel α-subunits ($Na_v1.1$–$Na_v1.9$, referred to as channels hereinafter), encoded by the *SCN1A-SCN5A* and *SCN8A-SCN11A* genes, have been identified in mammals, and their expression is spatially and temporally regulated (Catterall et al. 2005). These channels are large polypeptides (1700–2000 amino acids) that fold into four domains (DI–DIV), each domain including six transmembrane segments, linked by three loops (Catterall 2000). Different channels gate with different kinetics and voltage-dependent properties (Catterall et al. 2005), with six channels sensitive to block by nanomolar concentrations of tetrodotoxin (TTX-S), and three channels resistant to this blocker (TTX-R) (**Table 1**) (Catterall et al. 2005). Because channel properties are cell-type dependent and sodium channel properties can be modulated in a cell type–specific manner (for example, see Cummins et al. 2001, Choi et al. 2007), these channels should, whenever practicable, be studied within neurons in which they are normally expressed. Methods to study sodium channels within peripheral sensory neurons (Dib-Hajj et al. 2009b) have yielded important information about the contribution of individual sodium channels to electrogenesis within these neurons (Rush et al. 2006).

SODIUM CHANNELS IN DRG NEURONS

Dorsal root ganglia (DRG) house neurons of diverse sensory modalities that require precise electrogenic tuning. DRG neurons can express up to five sodium channels (Black et al. 1996, Dib-Hajj et al. 1998b), more than in any other neuronal cell type. Adult DRG neurons can express the TTX-S channels $Na_v1.1$, $Na_v1.6$, and $Na_v1.7$, and the TTX-R channels $Na_v1.8$

Table 1 Sodium channels preferentially expressed in peripheral neurons

Channel	Expression in peripheral sensory neurons	TTX sensitivity	Physiological attributes
$Na_v1.3$	Normally expressed during embryogenesis, but continues to be expressed in sympathetic neurons in adult Upregulated in DRG neurons after injury	S Kd = 1.8–4nM	Rapid repriming Produces large ramp current Produces persistent current Amplifies small depolarizing inputs
$Na_v1.7$	Preferentially expressed in DRG and sympathetic neurons	S Kd = 4.3–25nM	Slow repriming Produces large ramp current Amplifies small depolarizing inputs
$Na_v1.8$	Selectively expressed in DRG neurons	R Kd = 40–60 μM	Depolarized voltage-dependence for activation and inactivation. Rapid repriming Produces majority of current during AP upstroke Supports repetitive firing in response to depolarizing input Different slow-inactivation properties in $IB4^+$ and $IB4^-$ DRG neurons
$Na_v1.9$	Selectively expressed in small-diameter nonpeptidergic DRG neurons	R Kd = 40 μM	Hyperpolarized voltage-dependency of activation Slow activation kinetics Ultra slow inactivation Broad overlap between activation and fast-inactivation Amplifies and prolongs small depolarizations close to resting membrane potential Depolarizes resting potential of DRG neurons

and $Na_v1.9$ (as well as $Na_v1.5$ at low levels) (**Figure 1**). $Na_v1.1$ and $Na_v1.6$ expression is common to central nervous system (CNS) and peripheral nervous system (PNS) neurons, whereas $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are specific to PNS neurons.

$Na_v1.3$ is the major channel in embryonic neurons; in rodents, it is significantly reduced in neonates and is undetectable in adult DRG neurons (Waxman et al. 1994) and is at low levels in adult brain (Beckh et al. 1989). However, levels of $Na_v1.3$, comparable to other channels, are present in adult sympathetic ganglion neurons (Rush et al. 2006). $Na_v1.3$ channel expression is upregulated in axotomized rodent DRG neurons (Waxman et al. 1994, Dib-Hajj et al. 1996), as is discussed in detail below. The recent discovery of a mutation in $Na_v1.3$ linked to childhood epilepsy (Holland et al. 2008), however, is consistent with higher $Na_v1.3$ expression levels in human brains after birth (Whitaker et al. 2001), and suggests that $Na_v1.3$ may play a larger role in human than in rodent nociception.

Three channels, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, appear to have evolved relatively recently because their sequences have not been reported from nonmammalian species thus far. $Na_v1.7$ is expressed in sensory and sympathetic (Toledo-Aral et al. 1997), and myenteric (Sage et al. 2007) neurons, whereas $Na_v1.9$ is expressed in sensory and myenteric neurons (Dib-Hajj et al. 1998b, Rugiero et al. 2003), and $Na_v1.8$ only in sensory neurons (Akopian et al. 1996, Rugiero et al. 2003). $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, produced by functionally identified nociceptive neurons (Fang et al. 2002; Djouhri et al. 2003a,b), may have evolved a specialized sensory role in mammals, including pain, and are attractive targets for the development of new pharmaceutical agents to treat pain.

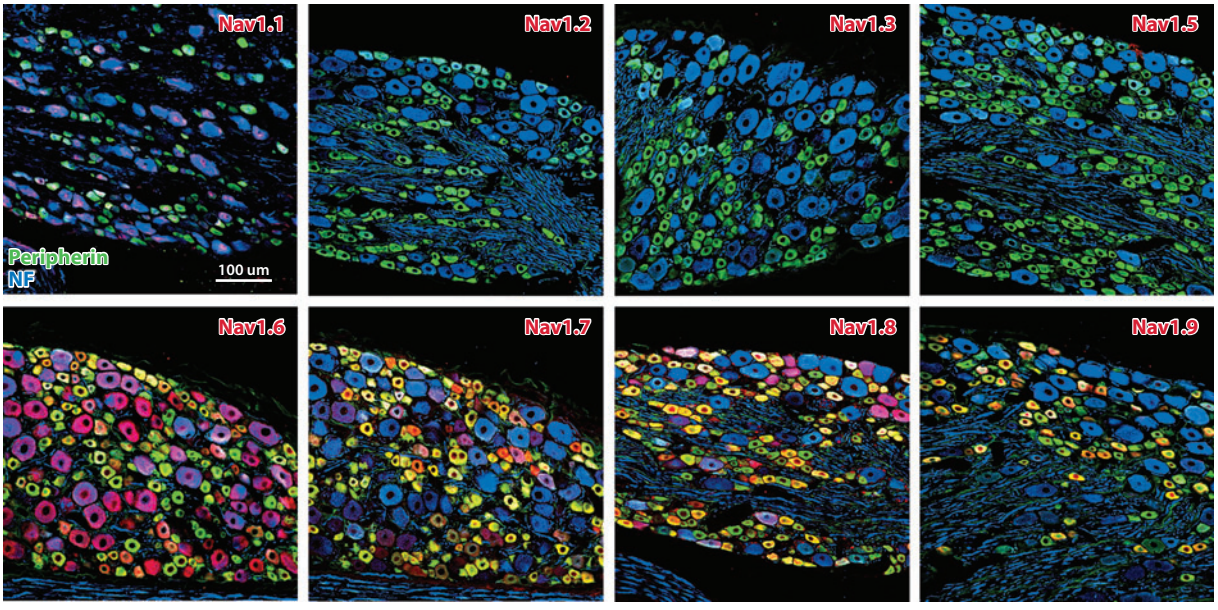

Figure 1

Five sodium channels are expressed in adult DRG neurons. Sodium channel isoforms $Na_v1.1$, $Na_v1.6$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ (*red*) are colocalized in DRG neurons expressing peripherin (*green*), a specific small neuron marker, and neurofilament (*blue*), a marker of medium and large neurons. $Na_v1.8$ is expressed preferentially in small and medium neurons, whereas $Na_v1.9$ is expressed exclusively in small neurons. $Na_v1.7$ is highly expressed in small neurons, but is also present in some large neurons. $Na_v1.6$ generally has expression in all size classes of neurons, whereas the limited $Na_v1.1$ expression is largely confined to large neurons. Colocalization of sodium channels with peripherin is depicted in yellow and with neurofilament in magenta.

NORMAL AND PATHOLOGICAL ELECTROGENESIS IN NOCICEPTORS

Neuropathic and inflammatory pain signals originate predominantly in peripheral sensory terminals, but are maintained by central sensitization. Sodium channel mutations or dysregulated expression within peripheral primary afferents and within CNS neurons along the pain-signaling axis have been shown to contribute to the establishment and maintenance of pain states (Waxman & Hains 2006; Dib-Hajj et al. 2007, 2009a). This pivotal role of sodium channels in pain has been empirically confirmed by symptomatic relief in patients treated with sodium channel blockers (Rice & Hill 2006, Dworkin et al. 2007), but the nonspecific nature and side effects of existing blockers (Sindrup & Jensen 2007, Gerner & Strichartz 2008) have limited their clinical utility, providing an impetus for the search for isoform-specific sodium channel blockers.

Central sensitization: enhanced excitability of CNS neurons typically triggered by hyperexcitable peripheral nociceptors leading to an exaggerated response to a normal stimulus

SODIUM CHANNEL DYSREGULATION IN EXPERIMENTAL MODELS OF PAIN

Several animal models of nerve injury and inflammation have shown transcriptional regulation of sodium channel genes in DRG neurons, with transcription of some channels "turned off" and others "turned on" (Waxman 2001). For example, $Na_v1.3$ channel expression, which is undetected in adult rat DRG neurons, is upregulated in axotomized neurons (Waxman et al. 1994, Dib-Hajj et al. 1996, Black et al. 1999), whereas $Na_v1.8$ and $Na_v1.9$, which are abundant in small rat DRG neurons, are downregulated in axotomized neurons (Dib-Hajj

et al. 1998b, Sleeper et al. 2000, Decosterd et al. 2002). Importantly, two studies have reported a reduction of $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ within injured human DRG neurons (Coward et al. 2000, 2001), but other studies have shown that $Na_v1.7$ and $Na_v1.8$ can accumulate within injured axons in painful human neuromas (Kretschmer et al. 2002, Bird et al. 2007, Black et al. 2008). The dysregulated expression of sodium channels is not a generalized injury-induced nonspecific response or a recapitulation of a developmental expression program, since transection of the centrally projecting axons of DRG neurons by dorsal rhizotomy does not alter $Na_v1.3$, $Na_v1.8$, or $Na_v1.9$ expression (Black et al. 1999, Sleeper et al. 2000) and severing peripheral axons does not lead to an upregulation of $Na_v1.2$, which is normally expressed during embryogenesis within DRG neurons (Waxman et al. 1994).

CONTRIBUTION OF INDIVIDUAL SODIUM CHANNELS TO ACQUIRED PAIN

$Na_v1.3$

Peripheral nerve injury triggers upregulated $Na_v1.3$ expression in DRG (Waxman et al. 1994, Dib-Hajj et al. 1996, Black et al. 1999, Kim et al. 2001, Lindia et al. 2005), dorsal horn (Hains et al. 2004), and thalamic (Zhao et al. 2006) neurons. Similarly, spinal cord injury (SCI) leads to $Na_v1.3$ expression within dorsal horn and thalamic neurons (Hains et al. 2003, 2005; Lampert et al. 2006b). Injury-induced $Na_v1.3$ upregulation within DRG neurons is reversed by administration of neurotrophic growth factor (NGF) and glial-derived neurotrophic factor (GDNF) (Boucher et al. 2000, Leffler et al. 2002), suggesting that loss of target-derived neurotrophic factors derepresses transcriptional silencing of $Na_v1.3$. The trigger for injury-induced $Na_v1.3$ upregulation within second- and third-order neurons is not yet understood, but may also involve changes regulated by alterations in neurotrophic factor levels.

$Na_v1.3$ channel activation produces a fast-inactivating, rapid-repriming (recovery from inactivation) TTX-S current, with slow closed-state inactivation that yields a substantial ramp current in response to small, slow depolarizations, and these properties are modulated in a cell type–dependent manner (Cummins et al. 2001). Contactin/F3, a cell-adhesion molecule that translocates to the cell surface in an activity-dependent manner (Pierre et al. 2001), interacts with $Na_v1.3$ and increases its current density (Shah et al. 2004). Similarities in the biophysical properties of $Na_v1.3$ and the TTX-S current within injured DRG neurons (Cummins & Waxman 1997) implicate $Na_v1.3$ in injury-induced neuron hyperexcitability. $Na_v1.3$ has also been linked to an increase in persistent current within dorsal horn neurons following SCI (Lampert et al. 2006b).

Ectopic firing within neuromas is now well established (Devor 2006). $Na_v1.3$ channels have been localized within distal axon tips in experimental neuromas in rats (Black et al. 1999) and in human neuromas (Black et al. 2008). Contactin, which is upregulated following axotomy, coaccumulates with $Na_v1.3$ in experimental neuromas (Shah et al. 2004), suggesting a positive feedback loop in which ectopic activity enhances trafficking of contactin to the plasma membrane, leading to increased $Na_v1.3$ expression at the axonal tips, and exacerbation of neuropathic pain (Shah et al. 2004). The attenuation of ectopic firing (Liu et al. 2001) and amelioration of pain behavior (Lyu et al. 2000) by 20nM TTX is consistent with a contribution of $Na_v1.3$ channels and other TTX-S channels to ectopic discharges within neuromas.

In support of a link between upregulated expression of $Na_v1.3$ and hyperexcitability of primary afferants and central neurons in the ascending pain pathway, enlargement of their peripheral receptive fields, and neuropathic pain, Hains et al. (2003, 2004) observed that intrathecal treatment with antisense oligonucleotide (ODN) targeting $Na_v1.3$ reduces levels of $Na_v1.3$ within dorsal horn neurons and ameliorates pain after sciatic nerve and spinal cord injury (**Table 2**). However, Lindia et al.

Neuromas: a collection of de- and dysmyelinated axon sprouts and connective tissue that results from abortive regeneration of transected axons

SCI: spinal cord injury

NGF: neurotrophic growth factor

GDNF: glial-derived neurotrophic factor

Neuropathic pain: pain resulting from lesions or diseases of the somatosensory system

Table 2 Results of knock-down and knock-out studies

Channel	Knock-down	Knock-out
$Na_v1.3$	Attenuation of pain with antisense ODN after SCI and CCI in rat (Hains et al. 2003, 2004) No effect on pain behavior with antisense ODN in rat (Lindia et al. 2005)	Normal neuropathic pain behavior (Nassar et al. 2005)
$Na_v1.7$	Attenuation of pain with HSV-delivered antisense construct in mice (Yeomans et al. 2005)	Abrogated inflammatory response and thermal hyperalgesia (Nassar et al. 2004) Normal neuropathic pain behavior (Nassar et al. 2006)
$Na_v1.8$	Attenuation of pain with antisense ODN after CCI in rat (Lai et al. 2002, Porreca et al. 1999, Joshi et al. 2006, Gold et al. 2003, Yoshimura et al. 2001) Attenuation of pain following lentivirus-delivered siRNA (Dong et al. 2007)	Impaired thermal hyperalgesia and inflammatory (Akopian et al. 1999, Laird et al. 2002) and cold pain (Zimmermann et al. 2007)
$Na_v1.9$	No ODN effect on neuropathic pain in rat (Porreca et al. 1999)	Impaired inflammatory pain (Priest et al. 2005, Amaya et al. 2006), but see (Hillsley et al. 2006)

(2005) did not observe amelioration of neuropathic pain after peripheral nerve injury following knock-down of $Na_v1.3$ by different ODNs (**Table 2**). Additionally, global or DRG-specific knock-out of $Na_v1.3$ does not impair pain behavior after nerve injury (Nassar et al. 2006), a result suggesting that either this channel does not contribute to injured neuron hyperexcitability, that its function is redundant, or that compensatory changes obscure the effect of losing this channel. Despite clear upregulation of $Na_v1.3$ expression in DRG, dorsal horn, and thalamic neurons after axonal injury, sodium channels other than $Na_v1.3$ may mediate injury-induced hyperexcitability.

Generator potentials: passively transmitted, typically small stimulus-evoked currents that depolarize cell membrane and, once it reaches a threshold, trigger an all-or-none action potential at the first trigger zone of the neuron

MAPK: mitogen-activated protein kinase

$Na_v1.7$

$Na_v1.7$ is preferentially expressed in DRG and sympathetic ganglion neurons (Sangameswaran et al. 1997, Toledo-Aral et al. 1997, Djouhri et al. 2003b). $Na_v1.7$ produces a fast-activating and -inactivating, slow-repriming, TTX-S current (Klugbauer et al. 1995). Slow closed-state inactivation of $Na_v1.7$ yields a substantial ramp current in response to small, slow depolarizations (Cummins et al. 1998, Herzog et al. 2003). Based on its biophysical properties, $Na_v1.7$ is poised to amplify generator potentials in neurons expressing it, including nociceptors, and to act as a threshold channel for firing action potentials (Rush et al. 2007), thereby setting the gain in pain-signaling neurons (Waxman 2006, Dib-Hajj et al. 2007). The switch from slow-repriming to rapid-repriming TTX-S currents in injured DRG neurons (Cummins & Waxman 1997) is consistent with reduced $Na_v1.7$ mRNA levels following axotomy (Kim et al. 2002). However, the incomplete loss of $Na_v1.7$ channels in injured DRG neurons suggests that other factors influence repriming of residual TTX-S channels in these neurons, including modulation of $Na_v1.6$, the other TTX-S channel within small DRG neurons (Black et al. 2002).

In agreement with animal studies, reduced levels of $Na_v1.7$ in DRG neurons have been reported following peripheral nerve injury in humans (Coward et al. 2000, 2001). However, recent studies have demonstrated accumulation of $Na_v1.7$ within axons in painful human neuromas, including those in amputees with phantom limb pain (Kretschmer et al. 2002, Bird et al. 2007, Black et al. 2008). Activated p38 and ERK1/2 MAPK (mitogen-activated protein kinase) also accumulate within axons in human neuromas (Black et al. 2008) raising the possibility that modulation of $Na_v1.7$ by activated MAPKs (Stamboulian et al. 2010) may contribute to ectopic firing at neuromas.

Inflammation causes an upregulation of $Na_v1.7$ and TTX-S current in DRG neurons

that project to the inflamed area (Black et al. 2004, Gould et al. 2004, Strickland et al. 2008). Inflammatory mediators, e.g., NGF, upregulate $Na_v1.7$ expression (Toledo-Aral et al. 1997, Gould et al. 2000), and increased levels of $Na_v1.7$ transcripts and phosphorylated $Na_v1.7$ protein have been reported in a rat model of painful diabetic neuropathy (Hong et al. 2004, Chattopadhyay et al. 2008). Activated p38 MAPK and PKC, which are signal transducers of inflammatory mediators, have been reported to regulate the expression of $Na_v1.7$ in diabetic neuropathy (Chattopadhyay et al. 2008). Peptide toxins that preferentially block $Na_v1.7$ have been identified (Middleton et al. 2002, Xiao et al. 2008); however, they do not ameliorate pain in nerve-injury animal models, perhaps owing to impaired accessibility (Schmalhofer et al. 2008). In contrast, an important role for $Na_v1.7$ in inflammatory pain is supported by the observations that $Na_v1.7$ knock-down in primary afferents ameliorates thermal hyperalgesia in mice following complete Freund's adjuvant injection into the paw (Yeomans et al. 2005).

A role for $Na_v1.7$ in inflammatory pain is confirmed in knock-out studies. Global knock-out of $Na_v1.7$ was neonatal lethal, but a conditional $Na_v1.7$ knock-out in $Na_v1.8$-expressing mouse DRG neurons abrogates inflammation-induced pain (Nassar et al. 2004). The loss of $Na_v1.7$ in $Na_v1.8$-expressing DRG neurons did not impair neuropathic pain. The presence of $Na_v1.7$ in $Na_v1.8$-negative DRG neurons may perhaps contribute to neuropathic pain-signaling, although this is a very limited population of cells (J.A. Black and S.G. Waxman, unpublished observations). Alternatively, $Na_v1.7$ may be dispensable for neuropathic pain signaling in animal models, or the animal models are not suitable to uncover the role of this channel (see discussion below on the limitations of animal models in pain testing).

In the aggregate, the preferential expression of $Na_v1.7$ in nociceptors, the functional role of $Na_v1.7$ in regulating neuronal excitability, and the results of knock-down studies support a critical role for $Na_v1.7$ in pain signaling, which is further supported by identification of $Na_v1.7$ mutations in human hereditary pain disorders (see below).

$Na_v1.8$

$Na_v1.8$ is a sensory neuron-specific channel that is preferentially expressed in DRG and trigeminal ganglia (Akopian et al. 1996, Sangameswaran et al. 1996), most of which are nociceptive (Djouhri et al. 2003a), and is also present along peripheral axons shafts (Rush et al. 2005) and free nerve terminals in skin (Zhao et al. 2008) and cornea (Black & Waxman 2002). $Na_v1.8$ produces a slow-inactivating, rapid-repriming TTX-R current with depolarized activation and inactivation voltage-dependency (Akopian et al. 1996, 1999). Activation and inactivation properties of the slow-inactivating TTX-R current are conserved in human DRG neurons (Dib-Hajj et al. 1999). $Na_v1.8$ trafficking to the cell membrane is enhanced by annexin II light-chain (Okuse et al. 2002), and by contactin in $IB4^+$ but not in $IB4^-$ DRG neurons (Rush et al. 2005). In contrast, SCLT1 (Sodium-Channel-CLaThrin-linker 1; previously known as CAP1A) internalizes $Na_v1.8$ in a clathrin-dependent manner (Liu et al. 2005), and Nedd4-2 ubiquitin ligase, but not Nedd4, induces a reduction in $Na_v1.8$ current density (Fotia et al. 2004).

$Na_v1.8$ contributes most of the sodium current underlying the action potential upstroke in neurons that expresses it (Renganathan et al. 2001, Blair & Bean 2002). Depolarized inactivation and rapid repriming may explain why $Na_v1.8$ accounts for most of the current in later spikes in a train (Blair & Bean 2003). $Na_v1.8$ slow-inactivation is differentially modulated in peptidergic ($IB4^-$) and nonpeptidergic ($IB4^+$) nociceptors (Choi et al. 2007), possibly contributing to different degrees of adaptation of action potential firing in response to sustained stimulation (Blair & Bean 2003, Tripathi et al. 2006, Choi et al. 2007).

The biophysical properties of $Na_v1.8$, its critical role in repetitive firing, and its presence

in free nerve endings, where pain-signaling is initiated, suggest that $Na_v1.8$ can significantly influence nociceptor excitability, thus contributing to pain. The role of $Na_v1.8$ in neuropathic pain is, however, not well understood. Axonal transection in the sciatic nerve causes a downregulation of $Na_v1.8$ mRNA, protein and current in injured neurons (Dib-Hajj et al. 1996, Cummins & Waxman 1997, Sleeper et al. 2000, Decosterd et al. 2002). However, increased $Na_v1.8$ levels have been reported in spared axons and neuronal cell bodies in neuropathic pain models (Gold et al. 2003, Zhang et al. 2004), possibly in response to inflammatory cytokines produced during Wallerian degeneration. $Na_v1.8$-mediated hyperexcitability of uninjured neurons provides a plausible explanation for a contribution of $Na_v1.8$ to neuropathic pain in animal models. Human patients with chronic neuropathic pain show increased $Na_v1.8$ channel expression proximal to injury sites (Coward et al. 2000, Yiangou et al. 2000, Black et al. 2008). A role for $Na_v1.8$ in neuropathic pain is also suggested by studies of knockdown (Lai et al. 2002, Joshi et al. 2006, Dong et al. 2007), toxin-inhibition (Bulaj et al. 2006, Ekberg et al. 2006), and the small molecule inhibitor, A-803467 (Jarvis et al. 2007) (**Table 2**).

The contribution of $Na_v1.8$ in inflammatory pain is well documented in animal studies. $Na_v1.8$ levels in DRG neurons are increased following carrageenan injection into rat hindpaw (Tanaka et al. 1998, Black et al. 2004), and following treatment of cultured DRG neurons with inflammatory mediators (Gold et al. 1996, Jin & Gereau 2006, Binshtok et al. 2008). Injection of complete Freund's adjuvant into rat hindpaw does not increase $Na_v1.8$ levels in DRG neurons (Okuse et al. 1997), but does increase $Na_v1.8$ translocation to myelinated and unmyelinated axons in the sciatic nerve (Coggeshall et al. 2004). Increased $Na_v1.8$ current density was also reported in an animal model of colitis (Beyak et al. 2004). Further evidence for an important role of $Na_v1.8$ in inflammatory pain is provided by knock-down studies (Joshi et al. 2006) and inhibition by A-803467 (Jarvis et al. 2007).

Pro-inflammatory mediators, released by damaged tissue and infiltrating immune cells (Scholz & Woolf 2007), have been shown to modulate sodium currents through activation of protein kinases (Jin & Gereau 2006, Hucho & Levine 2007, Binshtok et al. 2008). NGF, an inflammatory cytokine, upregulates $Na_v1.8$ within DRG neurons in vivo (Dib-Hajj et al. 1998a, Leffler et al. 2002) and in vitro (Fjell et al. 1999b, Cummins et al. 2000); ceramide, a second messenger for NGF, increases $Na_v1.8$ current density (Zhang et al. 2002). PGE2 and other inflammatory mediators act through PKA and PKC kinases (England et al. 1996; Gold et al. 1998, 2002; Zhou et al. 2002; Hucho & Levine 2007) to increase $Na_v1.8$ current density and produce a hyperpolarizing shift in activation voltage-dependency, possibly via PKA/PKC phosphorylation of serine residues within L1 (Fitzgerald et al. 1999, Vijayaragavan et al. 2004). Patch-clamp studies of DRG neurons from diabetic rats show increased slow-inactivating TTX-R current amplitude and hyperpolarizing shifts of activation and steady-state inactivation, consistent with increased serine/threonine phosphorylation of $Na_v1.8$ (Hong et al. 2004).

In contrast, treatment of DRG neurons with proinflammatory cytokines TNF-α (Jin & Gereau 2006) and IL-1β (Binshtok et al. 2008) increases $Na_v1.8$ current density without altering its gating properties, via a p38 MAPK-mediated mechanism. The p38-mediated increase in $Na_v1.8$ current density results from phosphorylation of two serine residues within $Na_v1.8$-L1 that are distinct from the PKA/PKC phosphorylation sites (Hudmon et al. 2008). Similarly, inflammation of visceral organs causes an increase in $Na_v1.8$ current density without a hyperpolarizing shift in activation voltage-dependency (Yoshimura et al. 2001, Bielefeldt et al. 2002). Thus, multiple inflammatory modalities may differentially regulate the $Na_v1.8$ current.

Studies in $Na_v1.8$ knock-out mice have confirmed a role of $Na_v1.8$ in somatic inflammatory (Akopian et al. 1999, Kerr et al. 2001) and cold (Zimmermann et al. 2007) pain. $Na_v1.8$ is

expressed in all DRG neurons that innervate the colon (Gold et al. 2002), and $Na_v1.8$ knock-out mice show deficits in visceral inflammatory pain (Laird et al. 2002, Hillsley et al. 2006). However, a role for $Na_v1.8$ in neuropathic pain was not observed in the $Na_v1.8$ knock-out mouse (Akopian et al. 1999) despite a report of 20-fold reduction of ectopic discharges in neuromas in these mice (Roza et al. 2003). Additionally, the double $Na_v1.7$/$Na_v1.8$ deletion did not attenuate neuropathic pain response in mice (Nassar et al. 2005). Increased $Na_v1.7$ expression in DRG from $Na_v1.8$ knock-out mice (Akopian et al. 1999) may contribute to, but does not totally explain, their normal neuropathic pain behavior, especially because the absence of $Na_v1.8$ has been shown to attenuate the excitability of neurons expressing a gain-of-function $Na_v1.7$ mutation (Rush et al. 2006).

$Na_v1.9$

$Na_v1.9$ is preferentially expressed in small-diameter, nonpeptidergic DRG neurons (Dib-Hajj et al. 1998b, 2002), which are largely nociceptors (Fang et al. 2002, 2006), and in trigeminal ganglion and myenteric neurons (Dib-Hajj et al. 2002, Rugiero et al. 2003), and has been found within free nerve terminals in skin and cornea (Black & Waxman 2002, Dib-Hajj et al. 2002). $Na_v1.9$ expression is regulated by the trophic factor GDNF but not NGF (Fjell et al. 1999a, Leffler et al. 2002). $Na_v1.9$ current density is significantly reduced in $IB4^+$ neurons from contactin-null mice, suggesting a role for contactin in $Na_v1.9$ trafficking (Rush et al. 2005). Thus, the expression of $Na_v1.9$ appears to be tightly regulated within DRG neurons, and may contribute to the functional specialization (Stucky & Lewin 1999, Braz et al. 2005) of $IB4^+$ and $IB4^-$ neurons.

$Na_v1.9$ current is TTX-R, with a hyperpolarized voltage-dependency of activation close to the resting membrane potential of neurons (−60 to −70 mV) and an ultraslow inactivation leading to a persistent current (Cummins et al. 1999). Glycosylation of $Na_v1.9$ is developmentally regulated and hyperpolarizes inactivation voltage-dependency (Tyrrell et al. 2001). Recombinant $Na_v1.9$ produces a small current with similar properties in HEK 293 cell line (Dib-Hajj et al. 2002). The persistent TTX-R current is missing from DRG neurons of $Na_v1.9$ knock-out mice (Priest et al. 2005, Amaya et al. 2006, Ostman et al. 2007), and can be restored by expression of recombinant $Na_v1.9$ channels (Ostman et al. 2007), unequivocally confirming the identity of the current. Importantly, native human $Na_v1.9$ current activates at ∼−80 mV, 10–20 mV more negative than $Na_v1.9$ current in rodent DRG neurons, likely owing to species-specific differences in primary protein sequence (Dib-Hajj et al. 1999). The ultraslow kinetics of $Na_v1.9$ suggest that it does not contribute to the action potential upstroke, but that it may enhance and prolong the response to subthreshold depolarizations (Cummins et al. 1999, Herzog et al. 2001), and lower the threshold for single action potentials and repetitive firing (Baker et al. 2003). Based on computer simulations (Herzog et al. 2001) and empirical evidence (Baker et al. 2003, Ostman et al. 2007, Copel et al. 2009), $Na_v1.9$ appears to act as a threshold channel.

$Na_v1.9$ is sensitive to intracellular fluoride (Coste et al. 2004), suggesting modulation by kinases/phosphatases. Additionally, direct activation of G proteins in DRG neurons increases $Na_v1.9$ current with a subsequent reduction in action potential threshold and an increase in spontaneous firing (Baker et al. 2003, Ostman et al. 2007). Recently, $Na_v1.9$ current density has been shown to increase because of a rapid, transient hyperpolarizing shift of activation and inactivation following neurokinin 3 receptor activation in enteric neurons (which is also mimicked by activation of PKC), reducing the threshold for action potential generation of these neurons (Copel et al. 2009).

Experimental evidence supports a role for $Na_v1.9$ in inflammatory and diabetic neuropathy pain. Expression of $Na_v1.9$ has been shown to increase in DRG neurons

Haploinsufficiency: when one functional copy of a gene is not enough to prevent deficit

IEM: inherited erythromelalgia, also known as primary erythermalgia (PE)

PEPD: paroxysmal extreme pain disorder, also known as familial rectal pain

CIP: congenital insensitivity to pain

innervating inflamed rat hindpaw (Tate et al. 1998). PGE2, acting via G protein–coupled receptors, increases $Na_v1.9$ current density in DRG neurons in vitro, accompanied by hyperpolarized shifts of activation and inactivation (Rush & Waxman 2004), while treatment with IL-1β increases persistent TTX-R in a p38 MAPK-dependent manner (Binshtok et al. 2008). Although expression levels of $Na_v1.9$ do not appear to be altered in small DRG neurons from diabetic rats, increased $Na_v1.9$ levels in large-diameter neurons suggest a contribution to painful diabetic neuropathy (Craner et al. 2002). In contrast, $Na_v1.9$ mRNA and protein levels and current density are downregulated in several animal models of neuropathic pain (Cummins & Waxman 1997, Dib-Hajj et al. 1998b, Cummins et al. 2000, Sleeper et al. 2000, Decosterd et al. 2002). An early study using $Na_v1.9$ antisense ODN treatment did not report amelioration of neuropathic pain (Porreca et al. 1999). However, activation of neurokinin 3 receptor causes potentiation of $Na_v1.9$ leading to increased excitability of enteric neurons (Copel et al. 2009), which suggests an effect on nociceptive DRG neurons that coexpress neurokinin 3 receptor and $Na_v1.9$.

$Na_v1.9$ knock-out mice show impaired somatic inflammatory pain behavior (Priest et al. 2005, Amaya et al. 2006), but normal neuropathic pain (Amaya et al. 2006). Mice that are heterozygous for the $Na_v1.9$ null-allele manifested impaired inflammatory response (Priest et al. 2005), suggesting haploinsufficiency; however, similar findings have not been reported in another study with a different $Na_v1.9$ knock-out mouse (Amaya et al. 2006). $Na_v1.9$ knock-out mice did not manifest gastrointestinal or apparent nutritional deficits (Priest et al. 2005, Amaya et al. 2006). Another independently produced $Na_v1.9$ knock-out mouse strain displayed no deficits in visceral inflammatory pain (Hillsley et al. 2006), suggesting a differential role of this channel in somatic versus visceral pain.

Altogether, convincing evidence indicates a role for $Na_v1.9$ in inflammatory and diabetic neuropathy pain, although a role in neuropathic pain is less clear.

SODIUM CHANNELS IN HEREDITARY HUMAN PAIN

A compelling case can be made for a direct involvement of a target by establishing a monogenic link of mutations to disease. The recent discovery of a genetic link of $Na_v1.7$ to pain disorders in humans solidified the status of $Na_v1.7$ as central to pain-signaling. Dominant gain-of-function mutations in *SCN9A*, the gene that encodes sodium channel $Na_v1.7$, have been linked to two severe pain syndromes, inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD), and recessive loss-of-function mutations have been linked to congenital insensitivity to pain (CIP) (Dib-Hajj et al. 2007, Drenth & Waxman 2007). Electrophysiological characterization of these mutations has elucidated the molecular basis for altered excitability of DRG neurons that express these mutant channels, establishing a mechanistic link to human pain.

Pain in IEM is localized to the distal extremities (feet and hands) and has been reported as early as 1-year-old (early onset), in the second decade (delayed-onset), and in adults (adult-onset) (Dib-Hajj et al. 2007, Drenth & Waxman 2007). Mutations in $Na_v1.7$ have been identified in patients with early- and delayed-onset IEM (**Table 3**), but the molecular basis of adult-onset IEM remains unknown. Treatment for IEM, even with sodium channel blockers, e.g., lidocaine or mexiletine, is largely ineffective (Dib-Hajj et al. 2007, Drenth & Waxman 2007), and in one case may be the result of reduced affinity of the mutant channel to these drugs (Sheets et al. 2007). Recently, however, two cases of IEM were reported with favorable pain management with sodium channel blockers: V872G, controlled by lidocaine/mexiletine (Choi et al. 2009), and V400M, controlled by carbamazepine (Fischer et al. 2009). The V872G mutation shows enhanced use-dependent block by lidocaine (Choi et al. 2009), whereas V400M displays a

Table 3 Effects of IEM and PEPD mutations on gating properties of $Na_V1.7$, compared to wild-type channels

Mutation	$\Delta V_{1/2}$ activation	$\Delta V_{1/2}$ inactivation	Slow inactivation	Deactivation	Ramp current	Repriming	Persistent current[a]	Reference
IEM mutations								
Q10R	−5.3 mV	0	Enhanced	Slower	Unchanged	Unchanged	0	Han et al. 2009
I136V	−5.7 mV	0	Enhanced	Slower	3.4X WT	Faster	0	Cheng et al. 2008
F216S	−11.8 mV	0	Enhanced	Slower	2X	Unchanged	0	Choi et al. 2006
S241T	−8.4 mV	0	Enhanced	Slower	5X	Unchanged	0	Lampert et al. 2006a
N395K	−7.7 mV	0	Impaired	Slower	ND	ND	0	Sheets et al. 2007
V400M	−6.5 mV	+7.3 mV	Unchanged	Slower	2X[b]	ND	0	Fischer et al. 2009
L823R	−14.6 mV	−9.8 mV	ND	Slower	ND	ND	0	Lampert et al. 2009
I848T	−13.8 mV	0	Impaired	Slower	3X	ND	0	Cummins et al. 2004
L858H	−13.3 mV	0	Enhanced	Slower	4.5X	ND	0	Cummins et al. 2004
L858F	−9.0 mV	+3.0 mV	Unchanged	Slower	4.5X	Faster	0	Han et al. 2006
A863P	−8 mV	+10 mV	Steep VD	Slower	10X	Faster	0	Harty et al. 2006
V872G	−9.3 mV	0	ND	Slower	2X	ND	0	Choi et al. 2009
F1449V	−7.6 mV	+4.3 mV	Unchanged	Unchanged	Unchanged	Faster	0	Dib-Hajj et al. 2005
PEPD mutations								
V1298F	+6.3 mV	+19.8 mV	Impaired	Unchanged	2X	Faster	6@8ms	Jarecki et al. 2008
V1299F	+4.5 mV	+21.0 mV	Impaired	Unchanged	5X	Faster	6@8ms	Jarecki et al. 2008
I1461T	+2.5 mV	+18.8 mV	Impaired	Unchanged	2X	Faster	6@8ms	Jarecki et al. 2008
I1461T	0	+29.3 mV	ND	ND	ND	ND	40@8ms	Fertleman et al. 2006
T1464I	+6.8 mV	+9.4 mV	ND	ND	ND	ND	30@8ms	Fertleman et al. 2006
M1627K	−2.9 mV	+19.3 mV	Unchanged	Unchanged	7X	Faster	0@8ms	Dib-Hajj et al. 2008
M1627K	0	+22.2 mV	ND	ND	ND	ND	7@8ms	Fertleman et al. 2006
Mixed phenotype mutations								
A1632E[c]	−7.0 mV	+17 mV	Impaired	ND	5X	Faster	4@8ms	Estacion et al. 2008

[a]Persistent current is presented as percentage of peak current, measured at 8 ms after initiation of pulse to compare all published results.
[b]ND: Not done.
[c]A1632E patients presented with symptoms of both IEM and PEPD.

depolarizing shift of activation by carbamazepine, suggesting an allosteric effect of the drug on the mutant channel (Fischer et al. 2009).

A second set of mutations of $Na_v1.7$ (**Table 3**) underlies many of the PEPD cases reported thus far. Some cases of PEPD do not show this linkage to $Na_v1.7$, suggesting involvement of another target (Fertleman et al. 2006). Severe perirectal pain in PEPD along with skin flushing can start in infancy and possibly in utero, but with no reported involvement of feet and hands (Fertleman et al. 2007). Although seizures and cardiac symptoms may accompany PEPD, a link to the expression of the mutant $Na_v1.7$ channel in sympathetic neurons has not yet been established. As patients age, pain extends to ocular and maxillary/mandibular areas and is triggered by cold, eating, or emotional state (Fertleman et al. 2007). PEPD symptoms, in contrast to IEM, are well controlled by the anticonvulsant sodium channel blocker carbamazepine (Fertleman et al. 2006, Dib-Hajj et al. 2008, Estacion et al. 2008).

All IEM mutations in $Na_v1.7$ characterized thus far shift activation voltage-dependency in a hyperpolarized direction, increase ramp current and slow deactivation (**Table 3**; **Figure 2**). In contrast, PEPD mutations shift the voltage-dependency of steady-state fast-inactivation in a depolarizing direction and, depending upon the specific mutation, may make inactivation incomplete resulting in a persistent current (**Table 3**; **Figure 2**). The A1632E mutation displays changes both in hyperpolarizing activation and depolarizing steady-state inactivation, and there is a mixed phenotype including IEM and PEPD symptoms in this patient (Estacion et al. 2008). Thus, IEM and PEPD mutations can be considered part of a physiological continuum that can produce a continuum of clinical phenotypes including IEM, PEPD, and overlap disorders with a characteristic of both (**Figure 2**). At the cellular level, IEM mutant $Na_v1.7$ channels lower threshold for single action potentials and increase firing frequency in DRG neurons, with all but one (F1449V) causing a depolarizing shift in resting potential (**Figure 3**) (Dib-Hajj et al. 2005, Harty et al. 2006, Rush et al. 2006, Han et al. 2009). PEPD $Na_v1.7$ mutant channels lower threshold for single action potential and increase frequency of firing in DRG neurons, but without altering resting potential (Dib-Hajj et al. 2008, Estacion et al. 2008). Impaired inactivation of PEPD $Na_v1.7$ mutant channels could explain the favorable response of the patients to carbamazepine.

$Na_v1.7$-related CIP is caused by recessive loss-of-function mutations that truncate the channel protein or impair splicing signals to prevent the production of channel mRNA (Cox et al. 2006). Truncated $Na_v1.7$ mutant channels do not produce functional channels (Cox et al. 2006, Ahmad et al. 2007), or act as dominant negative proteins (Ahmad et al. 2007). Heterozygous parents are asymptomatic, indicating that loss of one *SCN9A* allele does not lead to haploinsufficiency, and the occurrence of $Na_v1.7$-related CIP in progeny of nonconsanguinous marriages (Goldberg et al. 2007, Nilsen et al. 2009) indicates a more common occurrence of carriers of nonfunctional *SCN9A* alleles than initially thought after the reporting of $Na_v1.7$-related CIP in consanguinous Pakistani families (Cox et al. 2006). Patients do not report any form of pain, but report intact sensory modalities except for impaired olfaction (Goldberg et al. 2007, Nilsen et al. 2009), and do not display motor, cognitive, sympathetic, or gastrointestinal deficits.

To study the effect of gain-of-function mutations of $Na_v1.7$ on sympathetic neurons, in which $Na_v1.7$ is normally expressed, Rush et al. (2006) expressed the L858H IEM $Na_v1.7$ channel mutant (Yang et al. 2004) in superior cervical ganglion (SCG) neurons. Current-clamp analysis showed that L858H mutant channels depolarize resting potential in both DRG and SCG neurons by 6 mV, but render DRG neurons hyperexcitable and SCG neurons hypoexcitable. Co-expression of $Na_v1.8$, which is normally present in DRG but not SCG, rescued electrogenesis in SCG

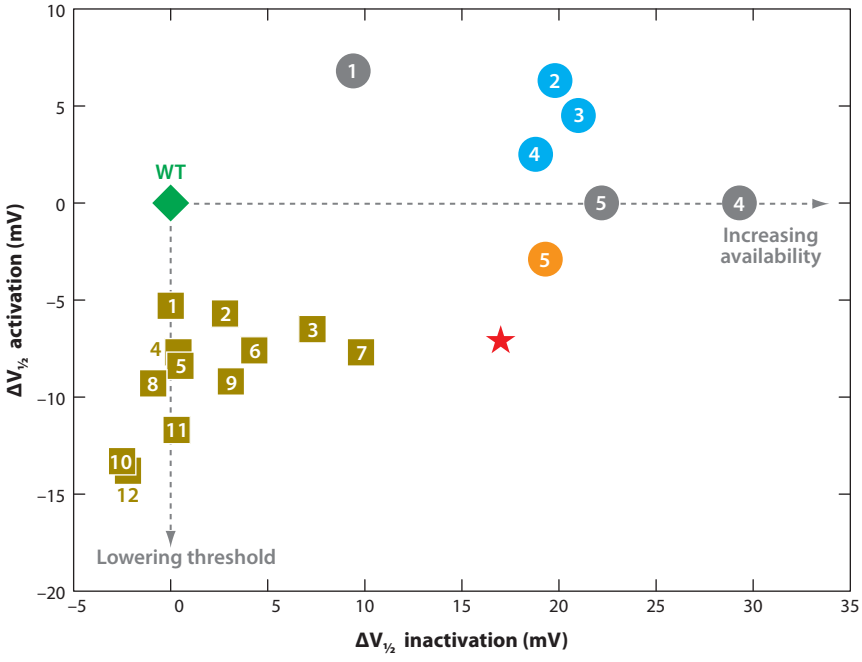

Figure 2

IEM and PEPD mutations are part of a physiological continuum linked to a continuum of clinical phenotypes. Shifts in the voltage-dependency of activation and fast-inactivation of each mutant compared to wild-type hNa$_V$1.7 are plotted for IEM mutants (*tan squares*) and PEPD mutants (*circles*) numbered to identify the specific mutation and reference from which the data were compiled. For PEPD mutations, same-colored symbols indicate mutations that were characterized electrophysiologically by the same group, while duplicate numbers indicate that the same mutation was profiled by different groups. The wild-type control is plotted as a green diamond at (0,0). The dotted lines through (0,0) demarcate between positive and negative shifts and indicate the outcome for the shifts. The A1632E mutation, from a patient with a mixed clinical phenotype, plotted with the red star symbol, shows shifts in activation and inactivation common to both IEM and PEPD mutants. The identities of the numbered IEM mutation are as follows (*shown as tan squares*): [1] Q10R (Han et al. 2009), [2] I136V (Cheng et al. 2008), [3] V400M (Fischer et al. 2009), [4] N395K (Sheets et al. 2007), [5] S241T (Lampert et al. 2006a), [6] F1449V (Dib-Hajj et al. 2005), [7] A863P (Harty et al. 2006), [8] V872G (Choi et al. 2009), [9] L858F (Han et al. 2006), [10] F216S (Choi et al. 2006), [11] L858H (Cummins et al. 2004), [12] I848T (Cummins et al. 2004). The identities of the numbered PEPD mutation are as follows (shown as colored circles): 1 (*gray*), T1464I (Fertleman et al. 2006); 2 (*blue*), V1298F (Jarecki et al. 2008); 3 (*blue*), V1299F (Jarecki et al. 2008); 4 (*gray*), I1461T (Fertleman et al. 2006); 4 (*blue*), I1461T (Jarecki et al. 2008); 5 (*gray*), M1627K (Fertleman et al. 2006); 5 (*orange*), M1627K (Dib-Hajj et al. 2008); red star, A1632E (Estacion et al. 2008). Adapted with permission from Estacion et al. (2008).

neurons that express the L858H mutant channels (Rush et al. 2006). Sympathetic neuron hypoexcitability may reduce tonic cutaneous vasoconstriction, thereby contributing to skin flushing in IEM. Why patients with gain-of-function mutations in Na$_v$1.7 do not suffer global sympathetic deficits, however, remains enigmatic.

LESSONS FROM DISCREPANCIES BETWEEN HUMAN AND ANIMAL STUDIES

Can we learn anything from the discrepancies (**Table 2**) between different knock-down and knock-out studies, and from the different phenotype in the murine global Na$_v$1.7 knock-out and Na$_v$1.7-related CIP in humans? Different

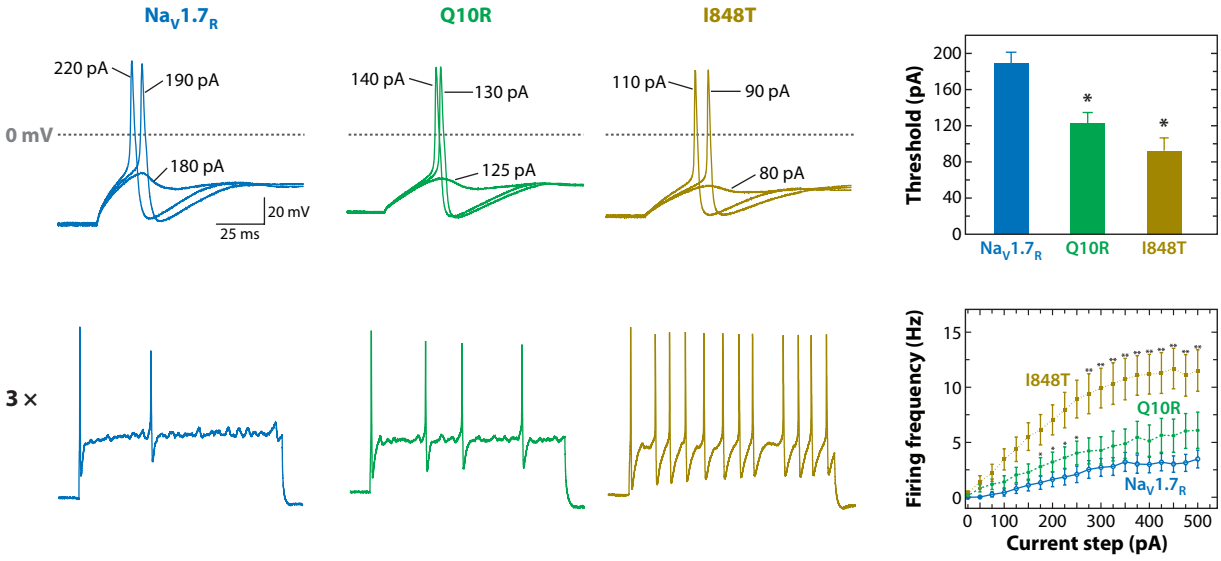

Figure 3

Both Q10R and I848T mutations decrease the action potential threshold in small DRG neurons, and increase firing frequency in small DRG neurons, but to different degrees. *Upper panels*: Representative traces from a cell expressing $Na_v1.7$ wild-type channels (*blue trace*), showing subthreshold response to 180 pA current injection and subsequent action potentials evoked by injections of 190 pA (current threshold for this neuron) and 220 pA. Representative traces from a cell expressing Q10R channels (*green trace*), showing a lower current threshold (130 pA for this cell) for action potential generation. Representative traces from a DRG neuron expressing I848T channels (*dark yellow trace*), showing a significantly lower current threshold (90 pA for this cell) for action potential generation. Histogram shows that threshold for action potential generation decreases significantly (*denotes $p < 0.05$) in those expressing Q10R channels and I848T channels. *Lower panels*: Response of cells expressing wild-type (*blue trace*), Q10R (*green traces*) and I848T (*dark yellow trace*) channels respectively to 1 s depolarizing current steps that are 3X the current threshold for action potential generation. Comparison of mean fire frequency among cells expressing wild-type, Q10R, and I848T channels across the range of current injections from 25 to 500 pA shows a quantitative difference between the effect on firing frequency of Q10R and I848T mutation, which is correlated with their hyperpolarized shifts of activation (*denotes $p < 0.05$, Q10R versus wild-type; **denotes $p < 0.05$, I848T versus Q10R). Adapted with permission from Han et al. (2009).

animal species, interstrain genetic differences, sex differences, and differences between responses to pain in rat (where most knock-down studies are performed) and mice (knock-out studies) may explain in part the apparently conflicting findings in different studies in experimental pain models (Mogil 2009). Additionally, multiple splice isoforms of $Na_v1.3$ (Thimmapaya et al. 2005) and $Na_v1.7$ (Raymond et al. 2004) exist, and it is possible that they may differentially contribute to hyperexcitability of neurons in which they are expressed. Compensatory changes during development may confound observations in channel-specific knock-out mice or after permanent ablation of a class of neurons (Abrahamsen et al. 2008), but they are less likely to occur in transient (knock-down) experiments, after acute block in adults or ablation of a specific cell type in adults. For instance, ablation of Mrpgrd$^+$ small DRG neurons in adult mouse produced more profound effects on mechanosensitivity to noxious stimuli compared to Mrpgrd knock-out mice (Cavanaugh et al. 2009). Mismatches between knock-out and knock-down studies may also result from off-target effects of antisense reagents. These factors may have contributed to the narrow conclusion from knock-out studies that $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are contributors to inflammatory but not neuropathic pain.

Humans tolerate total loss of $Na_v1.7$ with few physiological deficits other than

insensitivity to pain and blunted olfaction (Cox et al. 2006, Goldberg et al. 2007, Nilsen et al. 2009). Global $Na_v1.7$ knock-out is, however, lethal in mice (Nassar et al. 2004). Ahmad et al. (2007) reported the expression of $Na_v1.7$ in the hypothalamus and several brainstem nuclei of rodents but not humans and suggested this as a basis for the species-specific effect of global $Na_v1.7$ knock-out. Impaired olfaction in patients with global $Na_v1.7$ (Goldberg et al. 2007, Nilsen et al. 2009) suggests a more likely alternative explanation of blunted olfaction in $Na_v1.7$ knock-out mice, which would be consistent with the report of Nassar et al. (2004) that neonatal $Na_v1.7$ knock-out mice die because they apparently are unable to feed.

Additionally, methods of pain assessment may contribute to the incongruent manifestation of pain behavior in experimental pain models and human pain symptoms. For example, allodynia and mechanical hyperalgesia, which are typically inferred from reduction in latency for paw withdrawal threshold using von Frey filaments, do not describe the response to suprathreshold stimuli. Electrophysiological recordings in $Na_v1.8$ knock-out animals demonstrated marked reductions in responses to suprathreshold mechanical stimuli, compared to wild-type, although behavioral assessments could not be used in this range (Matthews et al. 2006). Interpretation of data supporting the role of individual sodium channels in pain necessitates careful consideration of the model itself and the methods for pain assessment.

PROSPECTS FOR NEW PAIN THERAPEUTICS

There is a large set of potential targets for development of pain therapeutics. Each of the channels discussed here—$Na_v1.3$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$—merits further study. The genetic linkage of $Na_v1.7$ to human pain disorders and the fact that total loss of this channel does not pose an immediate threat to life (no cardiac, cognitive, or motor deficit) have triggered substantial interest in $Na_v1.7$. Total loss of $Na_v1.7$ may predispose these patients to injuries and their complications. However, in a pharmacotherapeutic context, total block of this channel may not be needed. Indeed, characterization of Q10R, a delayed-onset IEM mutation that produces a small shift in $Na_v1.7$ activation, has demonstrated a quantitative difference in its effects on the gating properties of the channel and on its effects on DRG neuron excitability, compared to I848T, an early-onset IEM mutation that produced a larger shift in $Na_v1.7$ activation, providing evidence for a genotype-phenotype correlation (**Figure 3**) (Han et al. 2009). $Na_v1.7$ plays a definitive role in pain signaling, and current evidence suggests that it acts as a rheostat that sets the gain on pain. The physiological coupling of $Na_v1.7$ and $Na_v1.8$ (Rush et al. 2006) suggests that $Na_v1.8$, which is expressed exclusively in peripheral sensory neurons, may represent another especially opportune target.

Specific block of peripheral sodium channels may minimize risk of serious side effects. Robust $Na_v1.7$ expression within heterologous cells lends itself to high-throughput screening of small molecules and biological blockers. The discovery of a specific small molecule $Na_v1.8$ blocker (Jarvis et al. 2007) is encouraging and suggests that identification of isoform-specific, small molecule blockers is not unrealistic. Given the important role of the peripheral channels in pain states, and tolerance to loss of $Na_v1.7$ (humans, mice), $Na_v1.8$, and $Na_v1.9$ (mice), the pursuit of peripheral sodium channel blockers is an exciting prospect.

DISCLOSURE STATEMENT

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