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Regulatory role of voltage-gated Na^+ channel β subunits in sensory neurons

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Voltage-gated sodium Na^+ channels are membrane-bound proteins incorporating aqueous conduction pores that are highly selective for sodium Na^+ ions. The opening of these channels results in the rapid influx of Na^+ ions that depolarize the cell and drive the rapid upstroke of nerve and muscle action potentials. While the concept of a Na^+-selective ion channel had been formulated in the 1940s, it was not until the 1980s that the biochemical properties of the 260-kDa and 36-kDa auxiliary β subunits (β_1, β_2) were first described. Subsequent cloning and heterologous expression studies revealed that the α subunit forms the core of the channel and is responsible for both voltage-dependent gating and ionic selectivity. To date, 10 isoforms of the Na^+ channel α subunit have been identified that vary in their primary structures, tissue distribution, biophysical properties, and sensitivity to neurotoxins. Four β subunits (β_1–β_4) and two splice variants (β_{1A}, β_{1B}) have been identified that modulate the subcellular distribution, cell surface expression, and functional properties of the α subunits. The purpose of this review is to provide a broad overview of β subunit expression and function in peripheral sensory neurons and examine their contributions to neuropathic pain.

Keywords: voltage-gated sodium channel, pain, β subunit, peripheral nervous system

INTRODUCTION

Ten isoforms of voltage-gated Na^+ channels have been identified that vary in tissue distribution, structure, biophysical properties, and sensitivity to neurotoxins (**Table 1**; Chahine et al., 2005). In standardized nomenclature, the nine confirmed members with >50% common amino acid identity in the transmembrane and extracellular loop regions have been designated as $Na_v1.1$ through $Na_v1.9$. The prefix Na_v indicates the chemical symbol of the principal permeating ion (Na) with the principal physiological regulator (voltage; Catterall et al., 2003). The tenth isoform has not yet been fully identified because it has not been functionally expressed. However, this isoform plays an important role in the detection of body fluid Na^+ levels and the regulation of salt intake (Watanabe et al., 2000, 2003). At least eight of the mammalian α subunits are expressed in the nervous system: $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, and $Na_v1.6$ are widely expressed in the central nervous system (CNS) while $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are preferentially expressed in the peripheral nervous system (PNS; Black et al., 1996).

Primary sensory neurons in the dorsal root ganglia (DRG) give rise to afferent nerve fibers that convey information about thermal, mechanical, and chemical stimulations from peripheral tissues to the CNS. These neurons express a unique combination of tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) Na^+ currents that produce the rapid rising phase of action potentials. Much of what is currently known about the Na^+ channels expressed in sensory neurons is derived from electrophysiological studies of cultured DRG neurons (Cummins et al., 2007; Rush et al., 2007). Small-diameter DRG neurons (<25 μm) are the cell bodies of unmyelinated C-fiber nociceptors that preferentially express TTX-R Na^+ currents. This contrasts with the myelinated large-diameter (>30 μm) neurons typically associated with low-threshold A-fibers that predominately express TTX-S Na^+ currents. Primary sensory neurons express a variety of Na^+ channel isoforms that display properties similar to the endogenous TTX-S ($Na_v1.1$, $Na_v1.2$, $Na_v1.6$, $Na_v1.7$) and TTX-R ($Na_v1.8$, $Na_v1.9$) Na^+ currents observed in these neurons (Black et al., 1996; Dib-Hajj et al., 1998; Amaya et al., 2000; Ho and O'Leary, 2011).

In vivo, most Na^+ channel α subunits are associated with one or more auxiliary β subunits (Isom, 2002). Four distinct isoforms (β_1, β_4) and two splice variants (β_{1A}, β_{1B}) have been identified (**Table 2**). They share a common structure (Chahine et al., 2005) consisting of a single membrane spanning domain, a small intracellular C-terminal domain, and a large extracellular N-terminal domain incorporating an immunoglobulin-like fold similar to that of cell adhesion molecules (**Figure 1**; Isom, 2001; Yu et al., 2003). The β_{1A} and β_{1B} subunits are splice variants of β_1. They share an identical N-terminal domain but have a novel C-terminal domain resulting from intron retention (Kazen-Gillespie et al., 2000; Qin et al., 2003). Na^+ channel β subunits can be broadly classified based on sequence homology and molecular interactions with α subunits. The β_1, $\beta_{1A–B}$, and β_3 subunits have similar amino acid sequences and form non-covalent interactions with α subunits (Isom et al., 1992; Morgan et al., 2000). This contrasts with the β_2 and β_4 subunits, which are best characterized as closely related (sharing 35% amino acid sequence), and which are covalently linked to α subunits via a disulfide bridge (Yu et al., 2003).

Table 1 | Gene location and distribution of Na channels α subunits in subpopulations of DRG sensory neurons.

Channel	Gene	Human chromosome location	TTX sensitivity	Expression in DRG subpopulations*	Expression levels
$Na_v1.1$	*SCN1A*	2q2a	Sensitive	Large myelinated	++
$Na_v1.2$	*SCN2A*	2q23–24	Sensitive	Large myelinated/small unmyelinated	+
$Na_v1.3$	*SCN3A*	2q24	Sensitive	Not present	Increased after nerve injury
$Na_v1.4$	*SCN4A*	17q23–25	Sensitive	Not present	–
$Na_v1.5$	*SCN5A*	3p21	Resistant	Not present	–
$Na_v1.6$	*SCN8A*	12q13	Sensitive	Large myelinated	+++
$Na_v1.7$	*SCN9A*	2q24	Sensitive	Large myelinated/small unmyelinated	+++
$Na_v1.8$	*SCN10A*	3p22–24	Resistant	Small unmyelinated/some large	+++
$Na_v1.9$	*SCN11A*	3p21–24	Resistant	Small unmyelinated	+++

**Small- (<25 μm) and Large-diameter (>30 μm) DRG neurons. State of myelination determined by overlapping expression of peripherin, NF200 and Necl-1. +,++,+++: different levels of expression.*

Table 2 | Tissue distribution of auxiliary β subunits.

Subunit	Apparent M_r (kDa)	Tissue expression	Expression in DRG sensory neurons
β_1	36	Heart, skeletal muscle, CNS, glial cells, PNS	Large, intermediate diameter, and low levels in small-diameter
β_{1A}	45	Heart, skeletal muscle, adrenal gland, PNS	Large, intermediate, and small
β_{1B}	30.4	Human brain, spinal cord, DRG, cortical neurons, and skeletal muscle	Large, intermediate, and small
β_2	33	CNS, PNS, heart	Large, intermediate, and small
β_3	–	CNS, adrenal gland, kidney, PNS	Predominately in small-diameter
β_4	38	Heart, skeletal muscle, CNS, PNS	Large-diameter very low levels in intermediate and small

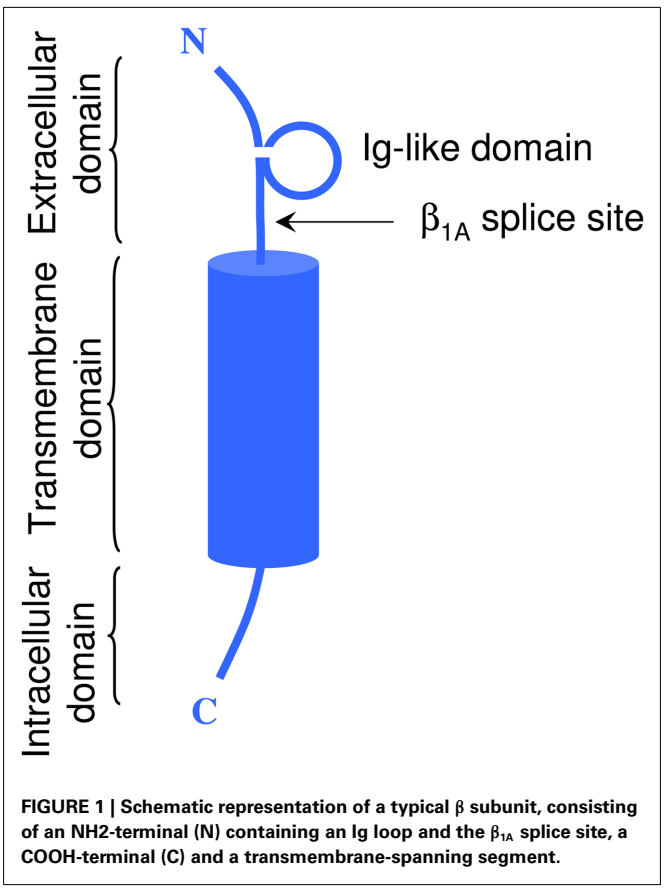

FIGURE 1 | Schematic representation of a typical β subunit, consisting of an NH2-terminal (N) containing an Ig loop and the β_{1A} splice site, a COOH-terminal (C) and a transmembrane-spanning segment.

In vivo Na^+ channel α subunits are believed to form heteromultimeric complexes consisting of one non-covalently associated (β_1, β_3) and one covalently (β_2, β_4) linked β subunit (Catterall et al., 2005). Depending on the composition of the α–β subunit, these interactions have been shown to modulate the gating kinetics, voltage-dependence, and cell surface expression of the associated α subunits (Catterall, 2000). β subunits also function as adhesion molecules that interact with cytoskeleton proteins, the extracellular matrix, and other molecules that regulate cell migration and aggregation (Yu and Catterall, 2003; Brackenbury et al., 2008).

Voltage-gated Na^+ channels are important determinants of sensory neuron excitability, and changes in the expression and gating properties of these channels have been implicated in the development of neuropathic pain (Cummins et al., 2007; Chahine et al., 2008). Immunohistochemistry and *in situ* hybridization studies have shown that all four isoforms of β subunits and both slice variants are present in DRGs (Kazen-Gillespie et al., 2000; Morgan et al., 2000; Coward et al., 2001; Qin et al., 2003). Given the close physical and functional interactions between α and β subunits, it is not surprising that these auxiliary subunits are also important contributors to pain sensation (Isom, 2001). However, the precise role of these subunits in nociception and neuropathic pain has not been fully elucidated.

THE β_1 SUBUNIT AND ITS SPLICE VARIANTS

It has been convincingly demonstrated that the β_1 subunit regulates the expression and gating properties of Na^+ channels and thereby modulates the electrical excitability of both nerves

and muscles (Chahine et al., 2008). Immunohistochemistry and transcript analyses have shown that the β_1 subunit is differentially expressed in subpopulations of primary sensory neurons (Oh et al., 1995; Black et al., 1996; Takahashi et al., 2003; Zhao et al., 2011). β_1 is abundantly expressed in intermediate- and large-diameter (>30 μm) DRG neurons but is present at comparatively low levels in small-diameter (<25 μm) neurons. The preferential expression of β_1 subunits in medium and large neurons suggests that these subunits may contribute significantly to the excitability of low-threshold A-fibers but play a reduced role in small-diameter nociceptors. This is consistent with rodent models of nerve injury where β_1 expression is not significantly altered, suggesting that these subunits do not contribute significantly to the development of neuropathic pain (Shah et al., 2001; Takahashi et al., 2003).

The co-expression of β_1 subunits with sensory neuron $Na_v1.7$ and $Na_v1.8$ Na^+ channels in *Xenopus* oocytes accelerates current kinetics and produces a hyperpolarizing shift in steady-state inactivation (Vijayaragavan et al., 2001). In addition, β_1 selectively increases $Na_v1.8$ current density but has no effect on $Na_v1.7$ expression. These findings indicate that β_1 subunits regulate both the gating and cell surface expression of sensory neuron Na^+ channels in an isoform-specific manner. More recent work using mammalian cell lines revealed a twofold increase in $Na_v1.8$–β_1 peak current density and hyperpolarizing shifts in both activation and inactivation (Zhao et al., 2011). Studies on β subunit chimeras showed that the intracellular C-terminus, but not the membrane spanning or extracellular domains of β_1, was critical for retaining the functional regulation of $Na_v1.8$ gating (Zhao et al., 2011).

The role of β_1 subunits in sensory neuron excitability has been addressed using *SCN1b* null mice (Lopez-Santiago et al., 2007). The β_1 knockouts exhibit numerous neuronal deficits, including symptoms of epilepsy and ataxia consistent with a broad distribution of this subunit in the CNS (Chen et al., 2004; Lopez-Santiago et al., 2007; Patino et al., 2009). In DRG neurons, the β_1 knockout produces a slight reduction in persistent Na^+ current associated with small changes in the amplitudes and gating properties of the predominant TTX-S and TTX-R Na^+ currents (Lopez-Santiago et al., 2011). Overall, the subtle β_1 regulation of DRG Na^+ channels coupled with the low level expression in small-diameter neurons and the absence of change in models of nerve injury are inconsistent with the idea that β_1 subunits contribute significantly to the development of neuropathic pain.

THE β_{1A} AND β_{1B} SUBUNITS

There are two splice variants of the β_1 subunit, the β_{1A} subunit in the rat and β_{1B} subunit in humans (Kazen-Gillespie et al., 2000; Qin et al., 2003). These variants have N-terminal domains that are identical to that of the β_1 subunit, but have novel C-terminals resulting from intron retention. The retained β_{1B} intron codes for a novel membrane spanning and intracellular domain that shares little sequence homology with β_1 (17%) or β_{1A} (33%). When co-expressed in oocytes, the β_{1B} subunit increases peak $Na_v1.2$ currents twofold but does not alter the current kinetics or gating properties of the channels (Qin et al., 2003).

The β_{1A} subunit is highly expressed during embryonic development but decreases after birth (Kazen-Gillespie et al., 2000). Western blotting analyses have revealed that β_{1A} is expressed in the heart, brain, spinal cord, and DRGs. When co-expressed in Chinese hamster ovary (CHO) cells, the β_{1B} subunit produces a 2.5-fold increase in $Na_v1.2$ current density and a slight depolarizing shift in activation (<3 mV), but no change in steady-state inactivation or current kinetics. β_{1A} appears to preferentially increase the cell surface expression of $Na_v1.2$ channels, a feature it shares with the parent β_1 subunit. These findings suggest that β_{1B} regulation may involve the homologous N-terminal domain that is common to the β_1 and β_{1A} variants.

THE β_2 SUBUNIT

The β_2 subunit is widely expressed in DRG neurons of all sizes (Coward et al., 2001; Takahashi et al., 2003) and throughout the CNS, including the spinal cord, cerebral cortex, and cerebellum (Gastaldi et al., 1998). $Na_v1.2$ channels expressed in *Xenopus* oocytes result in currents that display abnormally slow activation and inactivation kinetics (Auld et al., 1988; Krafte et al., 1988). Co-expressing the β_2 subunit induces more rapid activation and inactivation, which is consistent with a shift of $Na_v1.2$ channels from a slow to a fast mode of gating (Isom et al., 1995). The slow gating observed in oocytes contrasts sharply with the properties of $Na_v1.2$ channels expressed in CHO (West et al., 1992) and tsA201(O'Leary, 1998; Qu et al., 2001) cell lines, where rapid kinetics similar to those of native tissues are typically observed. In addition to changes in current kinetics, co-expressing the β_2 subunit in oocytes results in a hyperpolarizing shift in $Na_v1.2$ inactivation (2 mV) and a twofold increase in peak current (Isom et al., 1995). Again, this contrasts with results from tsA201 cells, where the β_2 subunit produces small depolarizing shifts (3–4 mV) in $Na_v1.2$ activation and inactivation but no changes in current kinetics or recovery from inactivation (Qu et al., 2001). This suggests that β_2 regulation of $Na_v1.2$ depends on the host cells used for expression, which may be related to differences in cellular genetic background, post-translational protein modification, or regulation by endogenous signal transduction pathways (West et al., 1992; Qu et al., 2001).

Recent work has focused on β_2 subunit regulation of Na^+ channel isoforms that are preferentially expressed in sensory neurons. The co-expression of $Na_v1.8$ and β_2 subunits in *Xenopus* oocytes results in a relatively modest depolarizing shift in inactivation (4 mV) but no change in activation, current kinetics, or peak Na^+ current (Vijayaragavan et al., 2004). Subsequent studies of $Na_v1.8$–β_2, $Na_v1.6$–β_2, and $Na_v1.3$–β_2 channels expressed in mammalian cells largely confirmed these findings, demonstrating little or no effect of β_2 on voltage-dependence, kinetics, or current density (Cummins et al., 2001; Zhao et al., 2011). Similar results have been observed in preliminary studies of heterologously expressed $Na_v1.7$–β_2 channels (Ho et al., 2011). Overall, the β_2 subunit appears to weakly regulate many of the voltage-gated Na^+ channels expressed in sensory neurons.

This contrasts with studies of null mice, where the knockout of the β_2 subunit is associated with reductions in TTX-S Na^+ current amplitude, mRNA, and protein (Lopez-Santiago et al., 2006). This suggests that β_2 expression in DRG neurons increases TTX-S Na^+ current amplitude and accelerates current kinetics, effects that are not widely observed in α–β co-expression studies. The underlying cause of this discrepancy is not known. One possibility is that β_2

subunits in native DRG neurons interact with endogenous proteins or are the target of signal transduction processes that are not reconstituted in heterologous expression systems. This possibility has gained credence from studies showing that the expression of $Na_v1.3$ in DRG cells results in a depolarizing shift in activation and faster recovery from inactivation compared to $Na_v1.3$ channels expressed in HEK293 cells (Cummins et al., 2001). Interactions with endogenous β subunits or other cell-specific proteins could account for the observed differences in gating properties. Alternatively, the apparent differences in Na^+ channel function observed in knockout and heterologous expression studies may stem from the compensatory upregulation of related β subunits and Na^+ channel isoforms in null mice (Chen et al., 2004; Yu et al., 2006). Additional studies of the changes in α and β subunit expression that occur in β_2 null mice, or the development of conditional β_2 knockouts that reduce the opportunity for subunit compensation, may shed light on the apparent discrepancy between the *in vivo* and *in vitro* effects of β_2 subunit regulation.

Several studies have examined the contribution of β_2 subunits to the development of pain behaviors in rodent models of nerve injury. A study investigating β subunit expression using RT-PCR and *in situ* hybridization found that β_2 mRNA levels in DRG neurons are not significantly altered following peripheral nerve injury (Takahashi et al., 2003). However, subsequent studies of β_2 protein expression using immunohistochemistry and Western blotting revealed that the β_2 protein is upregulated following nerve injuries (Pertin et al., 2005). β_2 upregulation has been observed in both injured and uninjured sensory neurons, suggesting that the β_2 subunit contributes to the excitability of both these populations. This possibility is supported by studies showing that the β_2 knockout decreases the expression of TTX-S Na^+ channels in DRG neurons (Lopez-Santiago et al., 2006). Importantly, the mechanical allodynia associated with peripheral nerve injury is attenuated in β_2 null mice, which is consistent with a role for this subunit in the development of neuropathic pain (Pertin et al., 2005).

THE β_3 SUBUNIT

In situ hybridization has shown that β_3 subunit mRNA is highly expressed in small- (<25 μm) and medium-diameter (25–45 μm) DRG neurons and to a lesser extent in large-diameter (>45 μm) neurons (Shah et al., 2000, 2001). The cellular distribution of β_3 expression extensively overlaps that of TTX-R $Na_v1.8$ and $Na_v1.9$ channels, which are primarily expressed in nociceptors (Akopian et al., 1996; Sangameswaran et al., 1996). In rodent models of neuropathic pain, β_3 mRNA increases in C-fiber nociceptors following chronic constriction (Shah et al., 2000), spared nerve ligation, and sciatic nerve transection (Takahashi et al., 2003), and in medium-diameter Aδ fibers in the streptozocin rodent model of diabetes (Shah et al., 2001). The upregulation of β_3 observed in animal models of nerve injury is consistent with the increase in β_3 protein in human DRG neurons following avulsion injuries (Casula et al., 2004). The preferential expression of β_3 subunits in small DRG neurons and their upregulation in models of nerve injury support the idea that β_3 is an important contributor to both acute and chronic pain.

β_3 Subunits also appear to play a major role in the development of neuropathic pain. Chronic constriction injury and sciatic nerve axotomy have been shown to induce an increase in TTX-S Na^+ currents (Cummins and Waxman, 1997) that has been linked to the enhanced expression of $Na_v1.3$ channels in small- and medium-sized DRG neurons (Waxman et al., 1994; Dib-Hajj et al., 1996, 1999; Black et al., 1999; Kim et al., 2002; Takahashi et al., 2003). The injury-induced increase in $Na_v1.3$ expression is paralleled by a similar increase in β_3 mRNA and protein levels (Shah et al., 2000; Takahashi et al., 2003). Heterologous expression studies have shown that co-expressing the β_3 subunit produces depolarizing shifts in $Na_v1.3$ activation and inactivation, faster recovery from inactivation, and slower current kinetics (Cummins et al., 2001). One possibility is that the upregulation of $Na_v1.3$ channels and β_3 subunits may be an attempt by the neurons to compensate for the injury-induced decrease in the expression of $Na_v1.8$ and $Na_v1.9$ channels (Dib-Hajj et al., 1996, 1999; Sleeper et al., 2000). Replacing the slowly gating TTX-R $Na_v1.8$ current with the more rapid TTX-S current of $Na_v1.3$–β_3 channels is predicted to reduce the action potential threshold and promote high-frequency firing, thereby contributing to the hyperexcitability of injured DRG neurons (Cummins et al., 2001). However, immunohistochemical analysis suggests that $Na_v1.3$ channels are preferentially upregulated in medium to large size DRG neurons after nerve injury (Kim et al., 2001; Fukuoka et al., 2008) and therefore may not extensively overlap with $Na_v1.8$ channels primarily expressed in small-diameter nociceptors.

Early studies of $Na_v1.8$ channels expressed in *Xenopus* oocytes found that co-expressing β_3 increases Na^+ current density and produces a hyperpolarizing shift in activation (Shah et al., 2000). This contrasts with later studies showing that co-expressing β_3 in oocytes produces a depolarizing shift in $Na_v1.8$ inactivation but no change in current density (Vijayaragavan et al., 2004). Studies on $Na_v1.8$ expressed in mammalian cells revealed that β_3 causes a 31% decrease in peak current density but no change in activation or steady-state inactivation (Zhao et al., 2011). Collectively, these findings suggest that co-expressing the β_3 subunit either has no effect or reduces $Na_v1.8$ current density, without altering voltage-dependence or gating kinetics. Similar findings have been reported for the β_3 regulation of $Na_v1.6$, a rapidly gating TTX-S Na^+ channel that is preferentially expressed at the nodes of Ranvier of peripheral nerve fibers (Krzemien et al., 2000; Tzoumaka et al., 2000; Ulzheimer et al., 2004) and in large-diameter sensory neurons (Black et al., 1996; Fukuoka et al., 2008; Ho and O'Leary, 2011). Heterologous expression studies have indicated that co-expression with the β_3 subunit does not alter the peak current density, current kinetics, or voltage-dependence of $Na_v1.6$ channels (Zhao et al., 2011).

THE β_4 SUBUNIT

The mature β_4 subunit protein has a large extracellular Ig-like fold, a single membrane spanning segment, and a short cytoplasmic C-terminal domain that is structurally similar to those of the β_1–β_3 subunits. β_4 shares high amino acid identity (35%) with β_2 and includes an extracellular unpaired cysteine that enables β_4 to covalently associate with Na^+ channel α subunits via disulfide bonds (Yu et al., 2003). The β_4 subunit is highly expressed

in DRGs and at lower levels in the brain and spinal cord. At the cellular level, β_4 is abundantly expressed in large-diameter sensory neurons and at lower levels in intermediate and small neurons (Yu et al., 2003).

The co-expression of β_4 with the $Na_v1.2$ channel in tsA201 cells produces a hyperpolarizing shift in activation (−7 mV) but no change in steady-state inactivation (Yu et al., 2003). The effects of β_4 on the gating properties of the TTX-S $Na_v1.6$ and TTX-R $Na_v1.8$ channels have also been studied (Chen et al., 2008; Zhao et al., 2011). Co-expressing β_4 produces pronounced hyperpolarizing shifts in activation (−17 mV) and steady-state inactivation (−9 mV) of $Na_v1.8$, and a smaller hyperpolarizing shift (−8 mV) in $Na_v1.6$ activation (Zhao et al., 2011). β_4 subunits produce similar negative shifts in the activation of the neuronal $Na_v1.1$ and skeletal muscle $Na_v1.4$ channels (Yu et al., 2003; Aman et al., 2009). The consistent hyperpolarizing shift in activation produced by the β_4 subunit suggests that this subunit may modulate neuronal excitability by causing Na^+ channels to activate at more hyperpolarized voltages.

Resurgent currents were initially described in Purkinje neurons where they were found to promote the discharge of multiple action potentials in response to brief depolarizations (Raman and Bean, 1997, 1999). Subsequent work found that the open-channel block at depolarized voltages coupled with rapid unblocking and slow Na^+ channel deactivation at voltages near threshold produce an inward Na^+ current (resurgent current) that transiently depolarizes the neurons (Grieco et al., 2005). These resurgent currents increase excitability and are believed to underlie the high-frequency firing of Purkinje neurons (Raman and Bean, 2001). The cytoplasmic C-terminus of the β_4 subunit has emerged as a likely candidate for the endogenous blocking particle responsible for resurgent currents (Grieco et al., 2005; Bant and Raman, 2010). This possibility is supported by studies showing that siRNA targeting *SCN4b* abolishes resurgent currents in cultured cerebellar granule cells and that the exogenous application of synthetic β_4 C-terminal peptide ($\beta4_{154-167}$) blocks Na^+ currents and induces resurgent currents in inactivation-impaired Purkinje neurons. Resurgent currents are substantially reduced in Purkinje neurons isolated from $Na_v1.6$ null mice, indicating that these channels play an important role in the production of resurgent currents (Raman et al., 1997). However, persistent resurgent currents have been reported in the subthalamic nucleus and Purkinje neurons isolated from $Na_v1.6$ null mice, suggesting that other Na^+ channel isoforms may also produce these currents (Do and Bean, 2004; Grieco and Raman, 2004).

The role of β subunits in the generation of resurgent currents has been further investigated *in vitro*. Co-expressing the β_4 subunit does not induce resurgent currents in heterologously expressed $Na_v1.1$ (Aman et al., 2009), $Na_v1.6$ (Zhao et al., 2011), or $Na_v1.8$ (Zhao et al., 2011) channels, indicating that the association with the intact β_4 subunit alone is insufficient to produce resurgent current. Additional proteins or post-translational modifications appear to be required to recapitulate the resurgent currents observed in native neurons (Grieco et al., 2002). These endogenous proteins and regulatory pathways may be highly specific to particular cell types and may thus be absent in the mammalian cells lines that are widely used for heterologous expression and cellular electrophysiology studies (Theile and Cummins, 2011). Alternatively, β_4-mediated resurgent currents may involve cell-specific enzymatic cleavage by proteases such as β-site amyloid precursor protein cleaving enzyme 1 (BACE1) or other proteases that are required to produce the functionally active blocking peptide (Huth et al., 2011).

Resurgent currents are observed in 40% of large-diameter (35–50 μm) DRG neurons and are substantially reduced in neurons from $Na_v1.6$ null mice (Cummins et al., 2005). Large DRG neurons express both the $Na_v1.6$ (Black et al., 1996; Fukuoka et al., 2008; Ho and O'Leary, 2011) and β_4 subunits (Yu et al., 2003), further supporting the idea that $Na_v1.6$–β_4 channels may play a role in these currents. This contrasts with small-diameter DRG neurons that do not routinely produce resurgent currents (Cummins et al., 2005) and that express low levels of $Na_v1.6$ (Black et al., 1996; Fukuoka et al., 2008; Ho and O'Leary, 2011) and β_4 subunits (Zhao et al., 2011).

Resurgent currents have recently been implicated in the neuronal hyperexcitability and pain associated with paroxysmal extreme pain disorder (PEPD; Jarecki et al., 2010; Theile and Cummins, 2011). In particular, the I1467T mutation in the interdomain III–IV linker of the $Na_v1.7$ channel reduces the rate of inactivation, increases the persistent Na^+ current, and induces a depolarizing shift in steady-state inactivation (Fertleman et al., 2006; Jarecki et al., 2008). These changes are consistent with impaired fast inactivation, which increases the probability of open-channel block, a suspected contributor to the generation of resurgent currents (Grieco and Raman, 2004). When heterologously expressed in cultured DRG neurons, the $Na_v1.7$–I1467T mutant channel increases both the percentage of neurons displaying resurgent currents and the peak current amplitude (Theile et al., 2011). Computer simulations further support the idea that PEPD mutations that alter $Na_v1.7$ inactivation induce resurgent currents in DRG neurons that contribute to aberrant action potential firing and increased cellular excitability. The evidence supporting a role for resurgent currents in the development of neuropathic pain is compelling and warrants further investigation.

SUMMARY

All four isoforms (β_1–β_4) and both splice variants (β_{1A}, β_{1B}) of β subunits are broadly expressed in the PNS. These subunits interact with many of the Na^+ channel isoforms in sensory neurons and alter the expression, voltage-dependence, and gating properties of these channels. β subunits are differentially expressed in large-diameter mechanoreceptors (β_1, β_4) and small-diameter nociceptors (β_3). This pattern of β subunit expression suggests that these auxiliary subunits may differentially regulate voltage-gated Na^+ currents and the excitability of these neuronal populations. Injury-induced changes in β subunit expression and the altered functional regulation of the Na^+ channels expressed in sensory neurons contribute to the hyperexcitability and ectopic firing of sensory neurons. Current evidence suggests that β subunits are important contributors to sensory physiology, nociception, and neuropathic pain.

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