Regulatory role of voltage-gated Na\(^{+}\) channel β subunits in sensory neurons

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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\(^{+}\)\(_{1,1}\) through Na\(^{+}\)\(_{1,9}\). The prefix Na\(^{+}\) 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\(^{+}\)\(_{1,1}\), Na\(^{+}\)\(_{1,2}\), Na\(^{+}\)\(_{1,3}\), and Na\(^{+}\)\(_{1,6}\) are widely expressed in the central nervous system (CNS) while Na\(^{+}\)\(_{1,7}\), Na\(^{+}\)\(_{1,8}\), and Na\(^{+}\)\(_{1,9}\) 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\(^{+}\)\(_{1,1}\), Na\(^{+}\)\(_{1,2}\), Na\(^{+}\)\(_{1,6}\), Na\(^{+}\)\(_{1,7}\), Na\(^{+}\)\(_{1,8}\), Na\(^{+}\)\(_{1,9}\) 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\(_{2}\)) 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\(_{1}\), β\(_{1A-B}\), 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\textsubscript{v,1} | SCN1A | 2q22 | Sensitive | Large myelinated | ++ |
| Na\textsubscript{v,2} | SCN2A | 2q23–24 | Sensitive | Large myelinated/small unmyelinated | + |
| Na\textsubscript{v,3} | SCN3A | 2q24 | Sensitive | Not present | − |
| Na\textsubscript{v,4} | SCN4A | 2q24 | Sensitive | Increased after nerve injury | |
| Na\textsubscript{v,5} | SCN5A | 2q24 | Sensitive | Large myelinated | +++ |
| Na\textsubscript{v,6} | SCN6A | 2q24 | Sensitive | Large myelinated/small unmyelinated | +++ |
| Na\textsubscript{v,7} | SCN7A | 2q24 | Sensitive | Increased after nerve injury | |
| Na\textsubscript{v,8} | SCN8A | 2q24 | Sensitive | Small unmyelinated/some large | +++ |
| Na\textsubscript{v,9} | SCN9A | 2q24 | Sensitive | 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<sub>kDa</sub> | Tissue expression | Expression in DRG sensory neurons |
|---------|----------------|----------------|----------------------------------|
| β<sub>1</sub> | 36 | Heart, skeletal muscle, CNS, glial cells, PNS | Large, intermediate diameter, and low levels in small-diameter |
| β<sub>1A</sub> | 45 | Heart, skeletal muscle, adrenal gland, PNS | Large, intermediate, and small |
| β<sub>1B</sub> | 30.4 | Human brain, spinal cord, DRG, cortical neurons, and skeletal muscle | Large, intermediate, and small |
| β<sub>2</sub> | 33 | CNS, PNS, heart | Large, intermediate, and small |
| β<sub>3</sub> | – | CNS, adrenal gland, kidney, PNS | Predominately in small-diameter |
| β<sub>4</sub> | 38 | Heart, skeletal muscle, CNS, PNS | Large-diameter very low levels in intermediate and small |

In vivo Na\textsuperscript{+} channel α subunits are believed to form heteromultimeric complexes consisting of one non-covalently associated (β<sub>1</sub>, β<sub>3</sub>) and one covalently (β<sub>2</sub>, β<sub>4</sub>) 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\textsuperscript{+} 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<sub>1</sub> SUBUNIT AND ITS SPLICE VARIANTS**

It has been convincingly demonstrated that the β<sub>1</sub> subunit regulates the expression and gating properties of Na\textsuperscript{+} channels and thereby modulates the electrical excitability of both nerves.
and muscles (Chahine et al., 2008). Immunohistochemistry and transcript analyses have shown that the β1 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). β1 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 β1 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 β1 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 β1 subunits with sensory neuron Nav1.7 and Nav1.8 Na+ channels in Xenopus oocytes accelerates current kinetics and produces a hyperpolarizing shift in steady-state inactivation (Vijayaragavan et al., 2001). In addition, β1 selectively increases Nav1.8 current density but has no effect on Nav1.7 expression. These findings indicate that β1 subunits regulate both the gating and cell surface expression of sensory neuron Nav+ channels in an isoform-specific manner. More recent work using mammalian cell lines revealed a twofold increase in Nav1.8–β1 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 β1, was critical for retaining the functional regulation of Nav1.8 gating (Zhao et al., 2011).

The role of β1 subunits in sensory neuron excitability has been addressed using SCN1b null mice (Lopez-Santiago et al., 2007). The β1 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 β1 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 β1 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 β1 subunits contribute significantly to the development of neuropathic pain.

**THE β1A AND β1B SUBUNITs**

There are two splice variants of the β1 subunit, the β1A subunit in the rat and β1B 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 β1 subunit, but have novel C-terminals resulting from intron retention. The retained β1B intron codes for a novel membrane spanning and intracellular domain that shares little sequence homology with β1 (17%) or β1A (33%). When co-expressed in oocytes, the β1B subunit increases peak Na+ currents twofold but does not alter the current kinetics or gating properties of the channels (Qin et al., 2003).

The β1A subunit is highly expressed during embryonic development but decreases after birth (Kazen-Gillespie et al., 2000). Western blotting analyses have revealed that β1A is expressed in the heart, brain, spinal cord, and DRGs. When co-expressed in Chinese hamster ovary (CHO) cells, the β1A subunit produces a 2.5-fold increase in Na+, current density and a slight depolarizing shift in activation (<3 mV), but no change in steady-state inactivation or current kinetics. β1A appears to preferentially increase the cell surface expression of Na+, channels, a feature it shares with the parent β1 subunit. These findings suggest that β1B regulation may involve the homologous N-terminal domain that is common to the β1 and β1A variants.

**THE β2 SUBUNIT**

The β2 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). Nav1.2 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 β2 subunit induces more rapid activation and inactivation, which is consistent with a shift of Nav1.2 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 Nav1.2 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 β2 subunit in oocytes results in a hyperpolarizing shift in Nav1.2 inactivation (2 mV) and a twofold increase in peak current (Isom et al., 1995). Again, this contrasts with results from tsA201 cells, where the β2 subunit produces small depolarizing shifts (3–4 mV) in Nav1.2 activation and inactivation but no changes in current kinetics or recovery from inactivation (Qu et al., 2001). This suggests that β2 regulation of Nav1.2 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 β2 subunit regulation of Na+ channel isoforms that are preferentially expressed in sensory neurons. The co-expression of Nav1.8 and β2 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 Nav1.8–β2, Nav1.6–β2, and Nav1.3–β2 channels expressed in mammalian cells largely confirmed these findings, demonstrating little or no effect of β2 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 Nav1.7–β2 channels (Ho et al., 2011). Overall, the β2 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 β2 subunit is associated with reductions in TTX-S Na+ current amplitude, mRNA, and protein (Lopez-Santiago et al., 2006). This suggests that β2 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 β2
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\textsubscript{v}1.3 in DRG cells results in a depolarizing shift in activation and faster recovery from inactivation compared to Na\textsubscript{v}1.3 channels expressed in HEK293 cells (Cummins et al., 2001). Interactions with endogenous \( \beta \) subunits or other cell-specific proteins could account for the observed differences in gating properties. Alternatively, the apparent differences in Na\textsuperscript{+} channel function observed in knockout and heterologous expression studies may stem from the compensatory upregulation of related \( \beta \) subunits and Na\textsuperscript{+} channel isoforms in null mice (Chen et al., 2004; Yu et al., 2006). Additional studies of the changes in \( \alpha \) and \( \beta \) subunit expression that occur in \( \beta \) null mice, or the development of conditional \( \beta \) knockout mice, may shed light on the apparent discrepancy between the \textit{in vivo} and \textit{in vitro} effects of \( \beta \) subunit regulation.

Several studies have examined the contribution of \( \beta \) subunits to the development of pain behaviors in rodent models of nerve injury. A study investigating \( \beta \) subunit expression using RT-PCR and \textit{in situ} hybridization found that \( \beta_{2} \) mRNA levels in DRG neurons are not significantly altered following peripheral nerve injury (Takahashi et al., 2003). However, subsequent studies of \( \beta_{2} \) protein expression using immunohistochemistry and Western blotting revealed that the \( \beta_{2} \) protein is upregulated following nerve injuries (Pertin et al., 2005). \( \beta_{2} \) upregulation has been observed in both injured and uninjured sensory nerves, suggesting that the \( \beta_{2} \) subunit contributes to the excitability of both these populations. This possibility is supported by studies showing that the \( \beta_{2} \) knockout decreases the expression of TTX-R Na\textsuperscript{+} channels in DRG neurons (Lopez-Santiago et al., 2006). Importantly, the mechanical allodynia associated with peripheral nerve injury is attenuated in \( \beta_{2} \) null mice, which is consistent with a role for this subunit in the development of neuropathic pain (Pertin et al., 2005).

**THE \( \beta_{3} \) SUBUNIT**

\textit{In situ} hybridization has shown that \( \beta_{3} \) subunit mRNA is highly expressed in small- (<25 \( \mu \)m) and medium-diameter (25–45 \( \mu \)m) DRG neurons and to a lesser extent in large-diameter (>45 \( \mu \)m) neurons (Shah et al., 2000, 2001). The cellular distribution of \( \beta_{3} \) expression extensively overlaps that of TTX-R Na\textsuperscript{+} channels in DRG neurons (Krzemien et al., 2000; Tzoumaka et al., 2000; Ulzheimer et al., 2000) and in large-diameter sensory neurons (Ranvier et al., 1994; Black et al., 1999; Kim et al., 2002; Takahashi et al., 2003). The injury-induced increase in Na\textsubscript{v}1.3 expression is paralleled by a similar increase in \( \beta_{3} \) mRNA and protein levels (Shah et al., 2000; Takahashi et al., 2003). Heterologous expression studies have shown that co-expressing the \( \beta_{3} \) subunit produces depolarizing shifts in Na\textsubscript{v}1.3 activation and inactivation, faster recovery from inactivation, and slower current kinetics (Cummins et al., 2001). One possibility is that the upregulation of Na\textsubscript{v}1.3 channels and \( \beta_{3} \) subunits may be an attempt by the neurons to compensate for the injury-induced decrease in the expression of Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9 channels (Dib-Hajji et al., 1996, 1999; Sleeper et al., 2000). Replacing the slowly gating TTX-R Na\textsubscript{v}1.8 current with the more rapid TTX-S current of Na\textsubscript{v}1.3–\( \beta_{3} \) 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\textsubscript{v}1.3 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\textsubscript{v}1.8 channels primarily expressed in small-diameter nociceptors.

Early studies of Na\textsubscript{v}1.8 channels expressed in \textit{Xenopus} oocytes found that co-expressing \( \beta_{3} \) increases Na\textsuperscript{+} current density and produces a hyperpolarizing shift in activation (Shah et al., 2000). This contrasts with later studies showing that co-expressing \( \beta_{3} \) in oocytes produces a depolarizing shift in Na\textsubscript{v}1.8 inactivation but no change in current density (Vijayaragavan et al., 2004). Studies on Na\textsubscript{v}1.8 expressed in mammalian cells revealed that \( \beta_{3} \) 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 \( \beta_{3} \) subunit either has no effect or reduces Na\textsubscript{v}1.8 current density, without altering voltage-dependence or gating kinetics. Similar findings have been reported for the \( \beta_{3} \) regulation of Na\textsubscript{v}1.6, a rapidly gating TTX-S Na\textsuperscript{+} 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 \( \beta_{3} \) subunit does not alter the peak current density, current kinetics, or voltage-dependence of Na\textsubscript{v}1.6 channels (Zhao et al., 2011).

**THE \( \beta_{4} \) SUBUNIT**

The mature \( \beta_{4} \) subunit protein has a large extracellular Ig-like domain, a single membrane spanning segment, and a short cytoplasmic C-terminal domain that is structurally similar to those of the \( \beta_{1}–\beta_{3} \) subunits. \( \beta_{4} \) shares high amino acid identity (35%) with \( \beta_{2} \) and includes an extracellular unpaired cysteine that enables \( \beta_{4} \) to covalently associate with Na\textsuperscript{+} channel \( \alpha \) subunits via disulfide bonds (Yu et al., 2003). The \( \beta_{4} \) subunit is highly expressed...
in DRGs and at lower levels in the brain and spinal cord. At the cellular level, β4 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 β4 with the Na1.2 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 β4 on the gating properties of the TTX-S Na1.6 and TTX-R Na1.8 channels have also been studied (Chen et al., 2008; Zhao et al., 2011). Co-expressing β4 produces pronounced hyperpolarizing shifts in activation (−17 mV) and steady-state inactivation (−9 mV) of Na1.8, and a smaller hyperpolarizing shift (−8 mV) in Na1.6 activation (Zhao et al., 2011). β4 subunits produce similar negative shifts in the activation of the neuronal Na1.1 and skeletal muscle Na1.4 channels (Yu et al., 2003; Aman et al., 2009). The consistent hyperpolarizing shift in activation produced by the β4 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 β4 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 β4 C-terminal peptide (β4154–167) blocks Na+ currents and induces resurgent currents in inactivation-impaired Purkinje neurons. Resurgent currents are substantially reduced in Purkinje neurons isolated from Na1.6 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 Na1.6 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 β4 subunit does not induce resurgent currents in heterologously expressed Na1.1 (Aman et al., 2009), Na1.6 (Zhao et al., 2011), or Na1.8 (Zhao et al., 2011) channels, indicating that the association with the intact β4 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, β4-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 Na1.6 null mice (Cummins et al., 2005). Large DRG neurons express both the Na1.6 (Black et al., 1996; Fukuoka et al., 2008; Ho and O’Leary, 2011) and β4 subunits (Yu et al., 2003), further supporting the idea that Na1.6–β4 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 Na1.6 (Black et al., 1996; Fukuoka et al., 2008; Ho and O’Leary, 2011) and β4 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 Na1.7 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 Na1.7–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 Na1.7 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 (β1–β4) and both splice variants (β1A, β1B) 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 (β1, β4) and small-diameter nociceptors (β3). 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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