

Review

# The role of sodium channels in neuropathic pain

Marc Rogers<sup>a</sup>, Lam Tang<sup>a</sup>, David J. Madge<sup>a</sup>, Edward B. Stevens<sup>b,\*</sup>

<sup>a</sup> Xention Ltd., Iconix Park, Pampisford, Cambridge CB2 4EF, United Kingdom

<sup>b</sup> NeuroSolutions Ltd., Department of Biological Sciences, University of Warwick, Gibbet Hill Rd, Coventry CV4 7AL, United Kingdom

Available online 28 October 2006

## Abstract

Our knowledge of the ion channels, receptors and signalling mechanisms involved in pain pathophysiology, and which specific channels play a role in subtypes of pain such as neuropathic and inflammatory pain, has expanded considerably in recent years. It is now clear that in the neuropathic state the expression of certain channels is modified, and that these changes underlie the plasticity of responses that occur to generate inappropriate pain signals from normally trivial inputs. Pain is modulated by a subset of the voltage-gated sodium channels, including Nav1.3, Nav1.7, Nav1.8 and Nav1.9. These isoforms display unique expression patterns within specific tissues, and are either up- or down-regulated upon injury to the nervous system. Here we describe our current understanding of the roles of sodium channels in pain and nociceptive information processing, with a particular emphasis on neuropathic pain and drugs useful for the treatment of neuropathic pain that act through mechanisms involving block of sodium channels. One of the future challenges in the development of novel sodium channel blockers is to design and synthesise isoform-selective channel inhibitors. This should provide substantial benefits over existing pain treatments.

© 2006 Elsevier Ltd. All rights reserved.

**Keywords:** Sodium channels; Pain; Neuropathic; Review

## Contents

1. Introduction .....	571
2. Molecular biology of voltage-gated sodium channels .....	572
3. Sensory physiology .....	573
4. Role of sodium channel subunits in neuropathic pain .....	573
4.1. Nav1.3 .....	573
4.2. Nav1.7 .....	574
4.3. Nav1.8 .....	574
4.4. Nav1.9 .....	575
4.5. Accessory $\beta$ subunits .....	575
4.6. Central mechanisms of pain .....	576
5. Current treatment of pain with sodium channel blockers .....	576
5.1. Anticonvulsants .....	577
5.2. Tricyclic antidepressants .....	577
5.3. Topical local anesthetics .....	577
6. Summary .....	578
References .....	578

## 1. Introduction

The role of sodium channels in the transmission of nociceptive and neuropathic pain messages is well-established. It is now clear that in the neuropathic state the expression of certain channels is modified, and that these changes underlie the plasticity

\* Corresponding author.

E-mail address: estevens@neurosolutionsltd.com (E.B. Stevens).

in responses that occur to generate inappropriate pain signals from normally trivial inputs. It is also increasingly clear that a number of drugs of previously unknown mechanism of action, often developed for diseases not related to pain, have usefulness in the treatment of neuropathic pain through a mechanism that involves block of sodium channels. Our knowledge of which channels are involved in pain pathophysiology, and indeed which specific channels play a role in subtypes of pain such as neuropathic and inflammatory pain, has expanded considerably in recent years. The availability of cloned channel subtypes and the means to assess the activity of small molecules as modulators of these channels has allowed us to reach the point where we can establish more focussed drug discovery projects to address pain subtypes.

## 2. Molecular biology of voltage-gated sodium channels

The voltage-gated sodium (Nav) channel  $\alpha$  subunit is a highly processed complex of transmembrane (TM) helices surrounding a central ion-conducting pore, usually capable of producing functional channels in a heterologous expression system. Approximately 2000 amino acid residues are arranged in 4 homologous domains, each consisting of 6 TM segments, and a hairpin loop that lines the pore and includes the selectivity filter. The voltage sensor is represented by a string of charged residues in TM segment S4 of each domain [1]. The large intracellular loop between domains III and IV is implicated in channel inactivation, as well as the binding site of many drugs, including those that stabilize the inactivated state of the Nav and show efficacy in treating neuropathic pain [2]. An additional family of accessory  $\beta$  subunits also exists, split into 2 groups discriminated by their

mechanism of interaction with the  $\alpha$  subunit: disulphide-linked  $\beta 2$  and  $\beta 4$ ; and non-covalently associated  $\beta 1$  (including splicing variant) and  $\beta 3$  [1]. The extracellular immunoglobulin-like domain of the  $\beta$  subunit is important for surface expression and modulation of  $\alpha$  subunit gating, while the TM domain influences Nav voltage-dependence [1].

The Nav family (Fig. 1) can be broadly categorized into three main groupings, based on sequence as well as function. The four neuronal sodium channels sensitive to nanomolar concentrations of tetrodotoxin (TTX) fall into the first group, and consist of CNS-located Nav1.1 and Nav1.2, as well as the more widely distributed Nav1.3 and peripheral Nav1.7. TTX-resistant (TTX-R) sodium channels are more diverse, including the closely related Nav1.5 in cardiac muscle and Nav1.8 in nociceptive neurons, as well as more distantly related Nav1.9, also expressed in nociceptive neurons. TTX-R channels are characterized by a single amino acid substitution in the pore-lining loop of domain I, as well as slower inactivation kinetics than TTX-sensitive (TTX-S) sodium channels. An intermediate group includes the TTX-S channels Nav1.4 in skeletal muscle, and Nav1.6, which is primarily expressed in central and peripheral axons [1].

Alternative splicing of Nav gene transcripts can produce biochemically, pharmacologically, and functionally distinct sodium channel isoforms, sometimes with a tissue-specific distribution. For example, Nav1.8 alternative splice variants have been identified in DRG, with single amino acid changes in the cytoplasmic loop between domains II and III, as well as exon repeats. A transcript with a repeat of exon 3 is profoundly up-regulated by nerve growth factor (NGF), raising the possibility of functional differences in Nav1.8 channels expressed in inflammatory and neuropathic pain [3].

Classification of Sodium Channel $\alpha$ -Subunits						
Name	Further Names	Gene	TTX Sensitive?	Localisation	Inactivation Rate	Disease link
Nav1.1	Type 1	SCN1A	Yes	CNS, DRG	Fast	Epilepsy
Nav1.2	Type 2	SCN2A2	Yes	CNS	Fast	Epilepsy
Nav1.3	Type 3	SCN3A	Yes	Embryonic CNS, injured DRG	Fast	Ectopic discharge in neuropathic pain
Nav1.4	Skm1	SCN4A	Yes	Skeletal muscle	Fast	Contractility problems
Nav1.5	H1, Skm2	SCN5A	Moderate	Heart, embryonic CNS	Slow	Cardiac arrhythmias
Nav1.6	PN4, CerIII	SCN8A	Yes	DRG, motor neurons	Fast	Neurological dysfunction
Nav1.7	PN1, hNe, NaS	SCN9A	Yes	DRG, low levels in CNS	Fast	Peripheral transmission
Nav1.8	PN3, SNS	SCN10A	No	DRG	Slow	Sensory hypersensitivity
Nav1.9	PN5, NaN, SNS-2	SCN11A	No	DRG, low levels in hippocampus	Slow	Modulates resting potential in DRG, linked to hyperalgesia

Fig. 1. Classification of sodium channel  $\alpha$ -subunits.

### 3. Sensory physiology

Sensory neurons have been classified into A $\beta$ , A $\delta$  and C fibres according to activation threshold, conduction velocity and physiological function, where A $\beta$  fibres are high conductance, low threshold mechanoreceptive fibres, A $\delta$  are polymodal intermediate conductance fibres, and C fibres are slow conductance high threshold nociceptive fibres [4]. However, such a rigid classification can be misleading as a proportion of A $\beta$  fibres are nociceptive, while a substantial subpopulation of C fibres are low threshold mechanoreceptive [5].

Both TTX-S and TTX-R currents have been identified in dorsal root ganglion neurons (DRGs). TTX-S currents have low activation threshold and display rapid inactivation. TTX-S currents represent multiple subtypes of sodium channel reflected by the diversity of  $\alpha$  subunits [6,7] and the range of inactivation kinetics in different fibre types [8]. TTX-R currents have been detected in small, where they are most prominent, medium and large diameter DRGs [9–11], and associated with nociceptive fibres [12,13]. Four types of TTX-R currents have been identified in isolated adult rat small diameter DRGs with a range of activation thresholds: two high threshold slowly inactivating currents, TTX-R1 (encoded by Nav1.8) [9,14] and TTX-R2 [9], which is possibly a different gating mode of Nav1.8 [15]; a rarely observed low threshold rapidly inactivating current, TTX-R3 encoded by Nav1.5 [9,16], and a low threshold persistent current encoded by Nav1.9 [17]. TTX-R1 and persistent currents have been confirmed in human small diameter DRGs [18].

The majority of C fibres are associated with a broad somatic action potential and an inflection on the repolarizing phase [19,20]. Isolated small DRGs also display the broad action potential ‘hump’ on the falling phase [21]. Both TTX-S and TTX-R channels are important in determining the shape of the action potential, TTX-S channels underlying the initial depolarization and TTX-R channels contributing the majority of the upstroke as well as to the inflection of the repolarizing phase [21]. The importance of TTX-R1 channels to action potential generation is highlighted in Nav1.8 knockout mice, where small DRGs are less likely to fire action potentials. During high frequency firing at depolarized potentials TTX-S channels are inactivated, but the high threshold, rapidly repriming TTX-R1 channels can sustain action potentials, indicated by the absence of repetitive firing in small DRGs from Nav1.8 knockout mice [22]. The persistent current, Nav1.9, is thought to be important in setting resting membrane potential [23]. TTX-R currents contribute to action potential initiation in the terminals of slow conducting (C- and A $\delta$ ) sensory neurons in intracranial dura [24] and nociceptive fibres in cornea [25], while TTX-S channels underlie action potential initiation in terminals of fast conducting A $\delta$  fibres [24].

Spontaneous activity of sensory neurons is thought to underlie neuropathic pain by causing central sensitization [26], and much debate surrounds the source of this activity. Ectopic firing following axotomy has been shown to be generated by neuromas developing at the site of injury [4]. Following L5 spinal nerve lesion, ectopic activity has been shown to be limited to A fibres [27], while in a diabetic neuropathy model depletion

of capsaicin-sensitive C fibres did not affect the development of allodynia [28]. On the other hand, uninjured C fibres in L4 spinal nerves, proximal to L5 spinal nerve lesion, develop spontaneous activity [29], and spontaneous pain in rat models of inflammation and neuropathic pain is related to rapid firing frequency of intact C fibres [30].

Following neuropathy, spontaneous activity of sensory neurons is increased through a reduction in the firing threshold, influenced by remodelling of sodium channel conductances, and an increase in spontaneous membrane potential oscillations [31]. Conductances are modified by changes in sodium channel gene expression, alterations in sodium channel trafficking, or phosphorylation of sodium channel proteins. For example, TTX-S and TTX-R currents recorded in DRGs from rats with diabetic neuropathy have increased amplitudes and hyperpolarized conductance-voltage and steady-state inactivation properties compared with normal DRGs. The leftward shift in voltage-gating properties of TTX-S and TTX-R currents is associated with phosphorylation of Nav1.6, Nav1.7 and Nav1.8 channel proteins, while changes in current amplitude are associated with increased expression of Nav1.3 and Nav1.7 and reduced expression of Nav1.6 and Nav1.8 [32].

### 4. Role of sodium channel subunits in neuropathic pain

Amongst the family of voltage-gated sodium channels there are several channels that have been linked to neuropathic pain, namely Nav1.3, Nav1.7, Nav1.8 and Nav1.9. Alterations in the expression, distribution, kinetics, and voltage-dependence of these sodium currents have been well-documented and recently reviewed [15,33] and a brief outline is given below.

#### 4.1. Nav1.3

The Nav1.3 channel mediates a TTX-sensitive current with fast activation and inactivation kinetics, and rapid recovery from inactivation [34,35]. Although traditionally thought of as an embryonic Nav [36], mRNA and protein for the Nav1.3 channel is present at quite high levels in the CNS of adult rats [37], primates [38] and humans [34,39]. Most importantly for studies of neuropathic pain, there is notable expression of Nav1.3 protein in sensory nerve tracts and in spinal cord white matter, dorsal roots, and deep laminae of the dorsal and ventral horn, but protein immunoreactivity is only just above background levels in the adult rat DRG [37,40]. However, there is significant (2–30-fold) up-regulation of Nav1.3 expression in the adult DRG, as measured at the mRNA and protein level, in a range of neuropathic pain models and conditions including DRG axotomy [41–43], spinal nerve ligation (SNL) [27,40], chronic constriction injury (CCI) [44,45], spared nerve injury (SNI) [46], diabetic neuropathy [32], and post-herpetic neuralgia [47].

This increase in Nav1.3 expression has been correlated with the appearance of a novel TTX-S current in injured DRG neurons, characterized by a more rapid recovery from inactivation (repriming) than that seen in the normal DRG. Again, this plasticity in Nav1.3 activity has been observed in several neuropathic models [35,44,48,49]. The phenotypic change in Nav1.3

expression and repriming kinetics is reversed by intrathecal delivery of glial cell derived neurotrophic factor (GDNF) and/or neurotrophic growth factor (NGF) [50], which also abolishes the hyperalgesia and allodynia produced in the SNL model of neuropathic pain [51]. Coupled with evidence for profound decreases in Nav1.1, Nav1.2, and Nav1.7 expression in axotomised DRG neurons [38,40,52], it would appear that Nav1.3 becomes the predominant TTX-S channel in injured DRG neurons. Significantly, the ectopic discharges and mechanical allodynia associated with the SNL model of neuropathic pain are both blocked by low doses of TTX [53,54], indicating the primary role of TTX-S currents in generating functional aspects of neuropathic pain. It is thought that the fast activation and inactivation kinetics of Nav1.3, together with its rapid repriming kinetics and persistent current component, contributes to the development of spontaneous ectopic discharges and sustained rates of firing characteristics of injured sensory nerves [49].

It should be mentioned that most, if not all, studies of Nav1.3 channel activity in DRG are from small diameter (C fibre) neurons, whereas most neuropathic ectopic firing is observed in large diameter A $\beta$  and A $\delta$  fibres [27,53]. However, up-regulation of Nav1.3 mRNA and protein also occurs in medium and large diameter neurons in several models of neuropathic pain [40,42,46].

This data strongly suggests that activity of Nav1.3 channels is correlated with the expression of ectopic firing and development of neuropathic pain. A more direct test of this hypothesis is provided by selective inhibition of Nav1.3 function by gene ablation and antisense knockdown, as no selective pharmacological blockers have been described. Surprisingly, a recent paper published while this manuscript was in press showed that ectopic firing and neuropathic pain (as well as acute and inflammatory pain) develops normally in global Nav1.3 knockout mice [139]. However, there is evidence for compensatory increases in TTX-S and TTX-R currents in DRG neurons from these mice, and the embryonic splice variant of Nav1.3 is still expressed (at 20% of total mRNA levels), suggesting that these sodium channels may contribute to pain signalling in the global Nav1.3 knockout. More difficult to reconcile with previous molecular and pharmacological data implicating Nav1.3 in neuropathic pain is the fact that mechanical allodynia (produced by the Chung model of spinal nerve ligation) developed normally in two Cre-Lox conditional knockouts where Nav1.3 expression was deleted from all nociceptors from embryonic day 14, and from all central and peripheral neurons postnatally. No data was presented concerning compensatory changes in sodium channels in these conditional knockouts. The evidence from antisense (AS) studies is equivocal. Lindia et al. [46] failed to see any effect of Nav1.3 AS on the level of allodynia produced by the SNI model of neuropathy, although the oligonucleotides did permeate the DRG and reduced Nav1.3 expression by 50%. Waxman and coworkers, on the other hand, used a similar approach and showed greater reductions in Nav1.3 expression, as well as decreased ectopic firing in the spinal cord dorsal horn and significant reductions in both allodynia and hyperalgesia associated with spinal cord injury (SCI) and CCI models of neuropathic pain [45,55]. In these studies there was no penetration of fluo-

rescent oligonucleotides into the DRG after 5 h, however, and no change in the CCI-induced up-regulation of Nav1.3 mRNA and protein in the DRG after 4 days of AS treatment. These results may be explained by the requirement for secondary and tertiary levels of synaptic activity in the spinal cord and thalamus to induce and maintain neuropathic pain, sites where Nav1.3 up-regulation and activity were blocked by their intrathecal AS delivery. The normal appearance of allodynia in Lindia's study [46] could be explained by the weaker knockdown of Nav1.3 expression in the DRG, leaving sufficient channel activity to drive the development of this facet of neuropathic pain.

#### 4.2. *Nav1.7*

The Nav1.7 channel is almost exclusively expressed in DRG, concentrated in small C fibre nociceptors and to a lesser extent in medium-sized A $\delta$  and large A $\beta$  cells [6,56]. Biophysically, the Nav1.7 channel underlies a fast TTX-sensitive current with slow repriming kinetics, where the slow inactivation kinetics allows Nav1.7 channels to be activated by small depolarizing ramps, such as those produced by sensory generator potentials [57]. Significantly, the Nav1.7 channel has been localized to sensory endings, such that both its distribution and physiology may predispose it to a major role in transmitting painful stimuli.

Expression of Nav1.7 is reduced by over half at the mRNA level, including all four splice variants, in rat SNL models of neuropathic pain [38,52]. Similarly, the proportion of a TTX-S current with features consistent with the biophysics of Nav1.7 is reduced in small DRG neurons after axotomy [35]. Conversely, protein levels of Nav1.7 are increased in a model of diabetic neuropathy [32], correlating with an increase in TTX-S currents and, in particular, the appearance of currents activated by voltage ramps, a characteristic of Nav1.7 channels.

However, it was recently shown that mechanical allodynia associated with neuropathic pain develops normally in mice where Nav1.7 [58] or Nav1.7 and Nav1.8 [59] were selectively ablated from DRG nociceptors by gene knockout. It would appear, however, that Nav1.7 plays a major role in inflammatory pain. A recent development in this story was the first demonstration of a pain channelopathy involving Nav, specifically the role of Nav1.7 mutations in erythromelalgia, a rare autosomal dominant disease characterized by burning pain and hot skin flashes in the extremities (see [60] for review). The identified mutations alter the kinetics of activation and deactivation, lowering the threshold for spike initiation and producing hyperexcitability characterized by high frequency discharges in nociceptive DRG neurons.

#### 4.3. *Nav1.8*

Paradoxically, the high expression of Nav1.8 in nociceptors is profoundly reduced at both the mRNA and protein level in most, but not all, in vivo models of neuropathic pain [27,61,62], as well as in human patients [63]. Decreases in Nav1.8 expression can be reversed by NGF and GDNF, trophic factors secreted from targets in the peripheral field of DRG neurons [27,64–66]. An important question to answer is how can such a reduction in

a rapidly repriming sodium channel, suited to generating high frequency discharges, explain the increase in ectopic firing that characterizes neuropathic pain? Ectopic firing is not seen in small diameter C fibres, where Nav1.8 expression and TTX-R currents are profoundly decreased [35,42,64,67–69]. Rather, most ectopic firing occurs in medium and large diameter fibres, where Nav1.8 expression does not change appreciably in most neuropathic pain models [42,67,69]. Spontaneous firing appears in uninjured neurons and axons in several models of neuropathy, and this has been associated with a significant redistribution of Nav1.8 immunoreactivity [67,70] but little alteration in overall Nav1.8 expression [68,62,69,71]. As spontaneous firing in uninjured C fibres has been suggested to underlie ongoing pain [29], it has been claimed that Nav1.8 channels in uninjured fibres contribute to neuropathic pain. This is supported by antisense knockdown experiments, where Nav1.8 AS reduces the development of mechanical allodynia and thermal hyperalgesia in the SNL and CCI models of neuropathic pain [71–73], but not in the vincristine model of chemotherapy-induced neuropathic pain [73].

The conflicting results from these genetic ablation experiments can be explained by two mechanisms; compensatory increases in TTX-S channels in the knockout animals could support the normal development of neuropathic pain (i.e. Nav1.3), while antisense knocks down enough Nav1.8 in injured and uninjured neurons and axons to affect firing.

Overall, these experiments suggest that the primary afferent nerves containing Nav1.8 contribute to the abnormal conduction of sensory input following neuropathy, facilitating repetitive firing in the DRG upon sensory stimulation [74]. However, the relative involvement of Nav1.8 may be dependent on the model of neuropathic pain employed. In contrast to the robust and almost universal up-regulation of Nav1.3 in various neuropathy models, changes in Nav1.8 expression are more variable; axotomy and SNL reduce Nav1.8 expression by around 50%, but streptozotocin-induced diabetic neuropathy only produces a 25% reduction [32,75], and CCI elicits little change in mRNA [67], while Nav1.8 expression increases in a model of post-herpetic neuralgia [47].

#### 4.4. Nav1.9

Nav1.9 is found mainly in the DRG, expressed solely in nociceptive neurons and fibres, mainly in small diameter C fibres and medium-sized A $\delta$  cells, and a few large diameter A $\beta$  fibres. It is relatively resistant to TTX, but has kinetic properties distinct from the similarly TTX-resistant Nav1.8, producing a persistent current with an activation potential of  $-70$  mV, close to the resting membrane potential, where it may set the threshold for activation [76].

As with Nav1.8, expression of Nav1.9 in sensory pathways is drastically reduced in various models of neuropathic pain. mRNA levels are reduced in DRG after neuropathic injury [27,61,77] and in a trigeminal ganglia model of neuropathic pain [78], as well as in several models and human cases of radicular pain [79,63]. Protein expression and persistent TTX-R currents are reduced in DRG after axotomy, SNL or CCI [44,62,66,68].

These effects can be reversed by GDNF, a trophic factor presumably delivered to DRG neurons from their peripheral targets [65]. The attractiveness of this channel as a target for neuropathic pain is limited for several reasons. Under conditions of persistent excitability, as found in neuropathic pain, the majority of these channels will be in the inactivated state and therefore not available for conduction of painful stimuli. Secondly, knockdown of Nav1.9 function by antisense oligonucleotides or genetic ablation has little or no effect on thermal hyperalgesia or mechanical hypersensitivity in the neuropathic rat [71,80].

#### 4.5. Accessory $\beta$ subunits

The role of accessory  $\beta$  subunits in modulating Nav function has attracted considerable attention, due to their selective expression in sensory pathways of the DRG and spinal cord, and facilitatory effects upon  $\alpha$  subunit activity in *Xenopus* oocytes and mammalian cells [81]. However, it may be that  $\beta$  subunits merely increase the efficiency of sodium channel expression and normalize the kinetics and voltage-dependent gating of  $\alpha$  subunits studied in non-mammalian cells [82], while having only minor effects on the peak current and voltage-dependent gating of neuronal Navs expressed in physiological conditions. Hence, their attractiveness as therapeutic targets is questionable.

The  $\beta 1$  subunit is primarily expressed in medium and large diameter (A $\beta$  fibres) neurons of the DRG and throughout the laminae of the dorsal and ventral horns of the spinal cord, as well as in the CNS postnatally [81]. There is no change in  $\beta 1$  mRNA levels in the DRG after axotomy or in streptozocin-induced diabetic neuropathy, and protein levels decrease in human sensory ganglia in patients suffering from spinal cord injury [83,85]. In the spinal cord,  $\beta 1$  subunit mRNA expression is transiently increased after DRG axotomy and CCI, but not in a model of diabetic neuropathy [84].

The  $\beta 2$  subunit is expressed at low levels in sensory neurons, including all diameter neurons in the DRG, but is widespread in the grey matter of the spinal cord and throughout the CNS. There is conflicting data concerning changes in the expression of  $\beta 2$  subunit mRNA in DRG neurons and fibres after injury, with two groups seeing no change after axotomy, SNI or SNL [85,86] and one documenting a progressive increase [43].  $\beta 2$  mRNA expression decreases slightly in the spinal cord after CCI [84]. Protein levels of  $\beta 2$  are decreased in human sensory ganglia after SCI [83], but increase in injured rat DRG nerves after SNI and SNL, in contrast to the lack of any change in mRNA [86]. This latter study is a good warning about over-interpreting changes in mRNA, which may not correlate with alterations in the functional expression or activity of cell surface sodium channels. Nevertheless, a modulatory role of the  $\beta 2$  accessory subunit in neuropathic pain is suggested from knockout mice, where there is a small attenuation in mechanical allodynia after SNI [86].

The  $\beta 3$  subunit exhibits a complimentary pattern of expression to the  $\beta 1$  subunit, being localized to small diameter neurons (C fibres) in the DRG and outer laminae of the spinal cord, and only expressed in the embryonic CNS [87]. In contrast to the conflicting results found for changes in the expression of  $\beta 1$

and  $\beta 2$  subunits in various models of neuropathic pain, the  $\beta 3$  subunit is universally up-regulated, at both mRNA and protein levels, in rat and human sensory ganglia [88,89]. In spinal cord  $\beta 3$  mRNA levels remain unchanged after CCI injury, while an increase in  $\beta 3$  mRNA expression has been reported in a model of diabetic neuropathy [85].

It is difficult to make any clear predictions about the potential role of  $\beta$  subunits in neuropathic pain, apart from the small decrease in mechanical allodynia seen in  $\beta 2$  knockout mice, which suggests a minor modulatory role. However, the consistent indication for co-expression, and up-regulation, of Nav1.3 and  $\beta 3$  subunits in injured neurons and sensory fibres in various neuropathic pain models [85] suggests that a functional coupling between these subunits may represent a neuropathic-specific Nav channel heteromer.

#### 4.6. Central mechanisms of pain

Neuropathic pain is generated in the periphery and sensed and maintained in the central nervous system. Lidocaine has proven most effective in reversing many of the symptoms of neuropathic pain, but the site of action of systemically administered compound is unclear. Significantly, systemic delivery of QX compounds, quaternary analogues of lidocaine that do not cross the blood–brain barrier, fails to reverse tactile hypersensitivity after SNL, while systemic lidocaine and its QX analogues reduce thermal hyperalgesia [90]. These and other results indicate that there is a significant contribution of sodium channels in the CNS to the development of certain aspects of neuropathic pain (reviewed in Amir et al. [33]). It is not possible to implicate specific sodium channels in these processes as local anesthetics do not discriminate well between Nav subtypes. However, two studies in spinal cord dorsal horn neurons have indicted a role for Nav1.3 and Nav1.8 channels in the central manifestation of neuropathic pain resulting from peripheral injury. Hains et al. [45] showed increased mRNA and protein levels of Nav1.3 produced by chronic constrictive injuries (CCI) correlated with increased spontaneous and evoked firing in second order dorsal horn neurons. The allodynia and hyperalgesia produced by this model of peripheral injury was attenuated by intrathecal delivery of Nav1.3 antisense oligonucleotides, as was the up-regulation in Nav1.3 expression and firing hyperresponsiveness [45]. Matthews et al. [90] followed up on results implicating Nav1.8 in neuropathic pain to show that this channel plays a role in transmitting mechanical, but not thermal, stimuli from the periphery to the CNS. Encoding of noxious and non-noxious mechanical stimuli, measured as evoked and spontaneous firing rates from dorsal horn neurons in vivo, was markedly reduced in Nav1.8 knockout mice [90].

Interest has also focused on the rostral ventromedial medulla in the brainstem, responsible for descending modulation of pain pathways. Selective cell ablation or microinjection of lidocaine or its QX analogues selectively blocks both mechanical and thermal hypersensitivity induced by SNL [91–93], without changes in baseline responses to nociceptor input in healthy animals. These effects develop with some delay after peripheral nerve

injury, suggesting central sensitization is initiated by peripheral activity and then maintains the neuropathic pain state after recovery of nociceptor function.

Damage to the CNS, notably spinal cord injury, produces classic neuropathic pain symptoms such as pricking, burning or aching pain and phantom phenomena. As well as complex effects upon cortical organization and various neurotransmitter systems, such damage has recently been associated with changes in the electrophysiology and Nav expression along the central pain processing pathways, including second order dorsal horn neurons in the spinal cord and third order neurons in the thalamus (reviewed in [94]). In a striking similarity to the pattern described in DRG nociceptors after peripheral injury, SCI induces up-regulation of Nav1.3 channels at the mRNA and protein level in dorsal horn and thalamic neurons [55,95]. This correlates with increased action potential firing at both levels in the pain pathway, at rest and in response to a range of innocuous and noxious mechanical and thermal stimuli. Antisense Nav1.3 delivered intrathecally reverses increased Nav1.3 expression and neuronal hyperexcitability in dorsal horn and thalamic neurons, and reduces the mechanical allodynia and thermal hyperalgesia in this model of central neuropathic pain. Neuronal hyperexcitability is thought to be an important contributor to neuropathic pain in both the periphery and CNS. Most significantly, thalamic firing becomes independent of ongoing activity in the periphery [95]. Thus, it would appear that up-regulation of Nav1.3 contributes to the initial amplification of peripheral pain transmission, as well as the subsequent formation of a central pain generator.

#### 5. Current treatment of pain with sodium channel blockers

The clinical diagnosis and treatment of pain has proven to be a difficult challenge because of the variety of mechanisms that underlie the condition, and the fact that different patient groups show diverse responses to the same therapy. Despite the wide-spread use of sodium channel blockers in the treatment of pain, their mode of action and sodium channel specificity have not been fully elucidated. It has also been found that some sodium channel blockers affect calcium-signalling, GPCRs and modulate neutrophil immune responses [33]. The three main categories of drugs currently prescribed for the treatment of neuropathic pain are anticonvulsants, tricyclic antidepressants and local anaesthetics, all of which appear to exert their therapeutic effects by modulating voltage-gated sodium channels. Current neuropathic pain treatments, however, still have significant drawbacks in terms of their propensity to cause adverse side-effects and interactions with other medications, reflecting their prior development for alternative indications.

One of the current challenges in the development of novel sodium channel blockers is to design and synthesise isoform-selective channel inhibitors. This should provide substantial benefits over existing pain treatments, since recent studies have revealed that pain is modulated by a subset of the voltage-gated sodium channels (Nav1.3, Nav1.7, Nav1.8 and Nav1.9), that these isoforms have unique expression patterns within specific

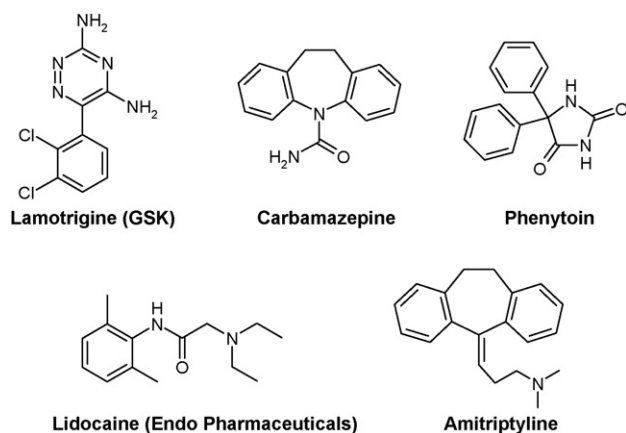


Fig. 2. Sodium channel inhibitors used in treatment of neuropathic pain.

tissues, and are either down- or up-regulated upon injury to the nervous system [96].

### 5.1. Anticonvulsants

Anticonvulsants have been utilized for treating neuropathic pain based on their mode of action in controlling epileptic seizures, reducing the synchronous firing of neurons that is also characteristic of neuropathic conditions. It has been suggested that abnormal sodium channels expressed following neuropathy are likely to be the target of several anti-convulsant drugs (Fig. 2) [97,98], ‘excitability blockers’, which include carbamazepine, phenytoin, Lamotrigine and topiramate, all well-known use-dependent sodium channel blockers. It has also been established that sensitized neurons which fire repetitive action potentials or are partially depolarized are more responsive to frequency-dependent inhibition of sodium channels [99].

Carbamazepine is currently used as a first-line treatment for trigeminal neuralgia, a paroxysmal form of facial pain [100]. Its metabolite carbamazepine-10, 11-epoxide also exhibits anti-neuralgic efficacy comparable to the parent compound [101]. Randomized clinical trials have also found Carbamazepine to be effective against painful diabetic neuropathy [102] and Guillain-Barré syndrome [103].

Evidence for phenytoin’s utility in treating neuropathic pain comes from clinical trials for diabetic neuropathy [104] and acute exacerbation of neuropathic pain [105], although there is still a lack of information in relation to its utility in the clinic.

Lamotrigine (LTG/Lamictal, GSK) has a more ambiguous profile in relation to its efficacy against neuropathic pain. Whereas no therapeutic effect was observed by McClean [106] in various neuropathic conditions, other researchers reported LTG to be effective against painful HIV-associated neuropathy [107], central post-stroke pain [108], diabetic neuropathy [109], and as an add-on medication in refractory trigeminal neuralgia [110, see 111 for review]. LTG is a voltage-dependent inhibitor of TTX-R sodium channels in peripheral sensory neurons, attenuating high frequency firing [112]. Studies in various animal models of neuropathic pain have provided supporting evidence for LTG’s utility. However, the anti-nociceptive actions

of sodium channel blockers on neuropathic pain behaviour is sensitive to the animal model being studied [113]. Furthermore, the clinical experience is that different drugs, even with the same mechanism of action, will be more suited to different disease populations.

Preliminary results from clinical trials of the anticonvulsant topiramate have indicated a role in relieving neuropathic pain where other anti-epileptics fail [114]. However, the potential use of topiramate is limited by its actions at multiple molecular targets [115] which likely underlies the large number of adverse effects reported [116].

### 5.2. Tricyclic antidepressants

The tricyclic antidepressants (TCAs) are highly efficacious at treating neuropathic pain. For example, amitriptyline is the most effective drug based upon the NNT (number-needed-to-treat; Fig. 3) efficacy measure when compared with serotonin reuptake inhibitors (SSRIs), the anticonvulsant carbamazepine and local anesthetic mexiletine [117].

Similar to anticonvulsants, TCAs have several mechanisms of pharmacological action in addition to sodium channels [118–123] possibly explaining why TCAs, such as amitriptyline, are effective in treating both peripheral neuropathic and central pain [124], and for the associated treatment-limiting side effects [125].

Antidepressants inhibit batrachotoxin binding to neurotoxin receptor site-2 on the sodium channel through a negative allosteric interaction, indicating that TCAs may produce analgesia by blocking  $\text{Na}^+$  channels in a similar fashion to anticonvulsants and local anaesthetics [126]. However, another report shows no local anaesthetic effect of locally administered amitriptyline [127]. A further study revealed imipramine to differentially block voltage-gated sodium and potassium channels [128], reinforcing the view that TCAs act as use-dependent blockers of sodium channels, having greater affinity for the inactivated-state and shifting their voltage-dependence to hyperpolarized potentials.

### 5.3. Topical local anesthetics

Local anesthetics comprise the third major class of voltage-gated sodium blockers demonstrating consistent efficacy against neuropathic pain. One report suggests that local anaesthetics such as lidocaine, tocainide, and flecainide are more effective against peripheral neuropathic pain than central neuropathy [129]. In contrast, when lidocaine was applied intravenously in a trial of spinal cord injury pain, results suggested a central-acting effect on neuronal hyperexcitability [130]. Recently, the lidocaine patch has been approved as a topical treatment for post-herpetic neuralgia. Its mode of action appears to be attenuation of both peripheral nociceptor sensitization and CNS hyperexcitability by sodium channel blockade [131]. Lidocaine has been postulated to target sodium channels by stabilizing the open state [132], although lidocaine could also modify pain hypersensitivity through sodium channel-independent routes [133,134]. A more recent study of lidocaine, mexiletine, benzocaine and

Efficacy (NNT) and Side Effect (NNH) rates for common Neuropathic Pain Drugs (NNT/NNH)				
Drug	Painful/Diabetic Neuropathy	Post-Herpetic Neuralgia	Peripheral Nerve Injury	Trigeminal Neuralgia
Amitriptyline	2.4/4.9	2.3/6.0	2.5/ND	
Desimipramine	2.0/9.7	2.3/6.2	2.5/ND	
SSRI's (overall)	6.7/ND			
Paroxetine	2.9/ND			
Citalopram	7.7/ND			
Phenytoin	2.1/9.5			
Carbamazepine	3.3/1.9			
Lamotrigine				2.1/ND
Mexiletine	10.0/6.3			
Gabapentin	3.7/1.8	3.2/3.4		
Baclofen				1.4/ND
Tramadol	3.4/ND			
Oxycodone		2.5/ND		

Fig. 3. Efficacy of current neuropathic pain treatments.

ambroxol revealed these agents inhibit resting TTX-resistant sodium channels by shifting the steady-state inactivation curve to more negative potentials [135]. Both mexiletine [136], an oral congener of lidocaine, and ambroxol [137] have been reported to reduce symptoms of neuropathic pain and compared with other neuropathic pain agents, lidocaine and mexiletine show success rates similar to morphine, gabapentin, amitriptyline and amantadine [138].

Given the potentially lucrative market for novel pain therapeutics with limited adverse effects, it is not surprising to see great interest from drug discovery companies on the development of novel sodium channel blockers for pain. The design of novel sodium channel inhibitors which selectively target specific sodium channel isoforms implicated in physiological pain states is still in its infancy. It remains to be determined whether approaches focusing on use-dependence and/or preferential inactivated-state sodium channel blockade will provide a pathway to the next generation of pain therapeutics.

## 6. Summary

Recent years have seen a rapid expansion in our knowledge and understanding of the roles, modulation and regulation of sodium channels in nociceptive information processing. Currently there is a growing validation of sodium channels as targets for different pain states, and this trend is certainly set to continue as more compounds are validated in clinical models and advantages over current treatments start to appear.

## References

[1] Catterall WA, Goldin AL, Waxman SG. International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacol Rev* 2005;57:397–409.

[2] George AL. Inherited disorders of voltage-gated sodium channels. *J Clin Invest* 2005;115:1990–9.

[3] Akopian AN, Okuse K, Souslova V, England S, Ogata N, Wood JN. Trans-splicing of a voltage-gated sodium channel is regulated by nerve growth factor. *FEBS Lett* 1999;445:177–82.

[4] Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol* 1999;57:1–164.

[5] Lawson SN. Phenotype and function of somatic primary afferent nociceptive neurons with C-, A $\delta$ - or A $\alpha$ / $\beta$ -fibres. *Exp Physiol* 2002;87:239–44.

[6] Black JA, Dib-Hajj S, McNabola K, Jeste S, Rizzo MA, Kocsis JD, et al. Spinal sensory neurons express multiple sodium channel  $\alpha$  subunit mRNAs. *Brain Res Mol Brain Res* 1996;43:117–31.

[7] Black JA, Liu S, Tanaka M, Cummins TR, Waxman SG. Changes in the expression of tetrodotoxin-sensitive sodium channels within dorsal root ganglia neurons in inflammatory pain. *Pain* 2004;108:237–47.

[8] Caffrey JM, Eng DL, Black JA, Waxman SG, Kocsis JD. Three types of sodium channels in adult rat dorsal root ganglion neurons. *Brain Res* 1992;592:283–97.

[9] Rush AM, Bräu ME, Elliott AA, Elliott JR. Electrophysiological properties of sodium current subtypes in small cells from adult rat dorsal root ganglia. *J Physiol* 1998;511:771–89.

[10] Renganathan M, Cummins TR, Hormuzdiar WN, Waxman SG.  $\alpha$ -SNS produces the slow TTX-resistant sodium current in large cutaneous afferent DRG neurons. *J Neurophysiol* 2000;84:710–8.

[11] Hong S, Wiley JW. Altered expression and function of sodium channels in large DRG neurons and myelinated A-fibers in early diabetic neuropathy in the rat. *Biochem Biophys Res Commun* 2006;339:652–60.

[12] Djouhri L, Fang X, Okuse K, Wood JN, Berry CM, Lawson SN. The TTX-resistant sodium channel Nav1.8 (SNS/PN3): expression and correlation with membrane properties in rat nociceptive primary afferent neurons. *J Physiol* 2003;550:739–52.

[13] Fang X, Djouhri L, Black JA, Dib-Hajj SD, Waxman SG, Lawson SN. The presence and role of the tetrodotoxin-resistant sodium channel Na(v)1.9 (NaN) in nociceptive primary afferent neurons. *J Neurosci* 2002;22:7425–33.

[14] Akopian AN, Souslova V, England S, Okuse K, Ogata N, Ure J, et al. The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways. *Nat Neurosci* 1999;2:541–8.

[15] Baker MD, Wood JN. Involvement of Na<sup>+</sup> channels in pain pathways. *Trends Pharmacol Sci* 2001;22:27–31.



- [16] Renganathan M, Dib-Hajj S, Waxman SG. Nav1.5 underlies the 'third TTX-R sodium current' in rat small DRG neurons. *Brain Res Mol Brain Res* 2002;106:70–82.
- [17] Cummins TR, Dib-Hajj SD, Black JA, Akopian AN, Wood JN, Waxman SG. A novel persistent tetrodotoxin-resistant sodium current in SNS-null and wild-type small primary sensory neurons. *J Neurosci* 1999;19:RC43.
- [18] Dib-Hajj SD, Tyrrell L, Cummins TR, Black JA, Wood PM, Waxman SG. Two tetrodotoxin-resistant sodium channels in human dorsal root ganglion neurons. *FEBS Lett* 1999;462:117–20.
- [19] Harper AA, Lawson SN. Electrical properties of rat dorsal root ganglion neurons with different peripheral nerve conduction velocities. *J Physiol* 1985;359:47–63.
- [20] Zhang JM, Donnelly DF, LaMotte RH. Patch clamp recording from the intact dorsal root ganglion. *J Neurosci Methods* 1998;79:97–103.
- [21] Blair NT, Bean BP. Roles of tetrodotoxin (TTX)-sensitive  $\text{Na}^+$  current, TTX-resistant  $\text{Na}^+$  current, and  $\text{Ca}^{2+}$  current in the action potentials of nociceptive sensory neurons. *J Neurosci* 2002;22:10277–90.
- [22] Renganathan M, Cummins TR, Waxman SG. Contribution of Nav1.8 sodium channels to action potential electrogenesis in DRG neurons. *J Neurophysiol* 2001;86:629–40.
- [23] Herzog RI, Cummins TR, Waxman SG. Persistent TTX-resistant  $\text{Na}^+$  current affects resting potential and response to depolarization in simulated spinal sensory neurons. *J Neurophysiol* 2001;86:1351–2136.
- [24] Brock JA, McLachlan EM, Belmonte C. Tetrodotoxin-resistant impulses in single nociceptor nerve terminals in guinea-pig cornea. *J Physiol* 1998;512:211–7.
- [25] Strassman AM, Raymond SA. Electrophysiological evidence for tetrodotoxin-resistant sodium channels in slowly conducting dural sensory fibers. *J Neurophysiol* 1999;81:413–24.
- [26] Woolf CJ. Excitability changes in central neurons following peripheral damage. In: Willis Jr WD, editor. *Hyperalgesia and allodynia*. New York: Raven; 1992. p. 221–43.
- [27] Boucher TJ, Okuse K, Bennett DL, Munson JB, Wood JN, McMahon SB. Potent analgesic effects of GDNF in neuropathic pain states. *Science* 2000;290:124–7.
- [28] Khan GM, Chen SR, Pan HL. Role of primary afferent nerves in allodynia caused by diabetic neuropathy in rats. *Neuroscience* 2002;114:291–9.
- [29] Wu G, Ringkamp M, Hartke TV, Murinson BB, Campbell JN, Griffin JW, et al. Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers. *J Neurosci* 2001;21:RC140.
- [30] Djouhri L, Koutsikou S, Fang X, McMullan S, Lawson SN. Spontaneous pain, both neuropathic and inflammatory, is related to frequency of spontaneous firing in intact c-fiber nociceptors. *J Neurosci* 2006;26:1281–92.
- [31] Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci* 1999;19:8589–96.
- [32] Hong S, Morrow TJ, Paulson PE, Isom LL. Early painful diabetic neuropathy is associated with differential changes in tetrodotoxin-sensitive and -resistant sodium channels in dorsal root ganglion neurons in the rat. *J Biol Chem* 2004;279:29341–50.
- [33] Amir R, Argoff CE, Bennett GJ, Cummins TR, Durieux ME, Gerner P, et al. The role of sodium channels in chronic inflammatory and neuropathic pain. *J Pain* 2006;7:S1–S29.
- [34] Chen YH, Dale TJ, Romanos MA, Whitaker WR, Xie XM, Clare JJ. Cloning, distribution and functional analysis of the type III sodium channel from human brain. *Eur J Neurosci* 2000;12:4281–9.
- [35] Cummins TR, Waxman SG. Downregulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. *J Neurosci* 1997;17:3503–14.
- [36] Felts PA, Yokoyama S, Dib-Hajj S, Black JA, Waxman SG. Sodium channel alpha-subunit mRNAs I, II, III, NaG, Na6 and hNE (PN1): different expression patterns in developing rat nervous system. *Brain Res Mol Brain Res* 1997;45:71–82.
- [37] Lindia JA, Abbadie C. Distribution of the voltage-gated sodium channel Nav1.3-like immunoreactivity in the adult rat central nervous system. *Brain Res* 2003;960:132–41.
- [38] Raymond CK, Castle J, Garrett-Engle P, Armour CD, Kan Z, Tsinoremas N, et al. Expression of alternatively spliced sodium channel alpha-subunit genes. Unique splicing patterns are observed in dorsal root ganglia. *J Biol Chem* 2004;279:46234–41.
- [39] Whitaker WR, Faulk RL, Waldvogel HJ, Plumpton CJ, Emson PC, Clare JJ. Comparative distribution of voltage-gated sodium channel proteins in human brain. *Brain Res Mol Brain Res* 2001;88:37–53.
- [40] Kim CH, Oh Y, Chung JM, Chung K. The changes in expression of three subtypes of TTX sensitive sodium channels in sensory neurons after spinal nerve ligation. *Brain Res Mol Brain Res* 2001;95:153–61.
- [41] Waxman SG, Kocsis JD, Black JA. Type III sodium channel mRNA is expressed in embryonic but not adult spinal sensory neurons, and is reexpressed following axotomy. *J Neurophysiol* 1994;72:466–70.
- [42] Dib-Hajj S, Black JA, Felts P, Waxman SG. Down-regulation of transcripts for Na channel  $\alpha$ -SNS in spinal sensory neurons following axotomy. *Proc Natl Acad Sci USA* 1996;93:14950–4.
- [43] Xiao HS, Huang QH, Zhang FX, Bao L, Lu YJ, Guo C, et al. Identification of gene expression profile of dorsal root ganglion in the rat peripheral axotomy model of neuropathic pain. *Proc Natl Acad Sci USA* 2002;99:8360–5.
- [44] Dib-Hajj SD, Fjell J, Cummins TR, Zheng Z, Fried K, LaMotte R, et al. Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain. *Pain* 1999;83:591–600.
- [45] Hains BC, Saab CY, Klein JP, Craner MJ, Waxman SG. Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury. *J Neurosci* 2004;24:4832–9.
- [46] Lindia JA, Kohler MG, Martin WJ, Abbadie C. Relationship between sodium channel Nav1.3 expression and neuropathic pain behavior in rats. *Pain* 2005;117:145–53.
- [47] Garry EM, Delaney A, Anderson HA, Sirinathsinghi EC, Clapp RH, Martin WJ, et al. Varicella zoster virus induces neuropathic changes in rat dorsal root ganglia and behavioral reflex sensitization that is attenuated by gabapentin or sodium channel blocking drugs. *Pain* 2005;18:97–111.
- [48] Black JA, Cummins TR, Plumpton C, Chen YH, Hormuzdiar W, Clare JJ, et al. Upregulation of a silent sodium channel after peripheral, but not central, nerve injury in DRG neurons. *J Neurophysiol* 1999;82:2776–85.
- [49] Cummins TR, Aglieco F, Renganathan M, Herzog RI, Dib-Hajj SD, Waxman SG. Nav1.3 sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons. *J Neurosci* 2001;21:5952–61.
- [50] Leffler A, Cummins TR, Dib-Hajj SD, Hormuzdiar WN, Black JA, Waxman SG. GDNF and NGF reverse changes in repriming of TTX-sensitive  $\text{Na}^+$  currents following axotomy of dorsal root ganglion neurons. *J Neurophysiol* 2002;88:650–8.
- [51] Wang R, Guo W, Ossipov MH, Vanderah TW, Porreca F, Lai J. Glial cell line-derived neurotrophic factor normalizes neurochemical changes in injured dorsal root ganglion neurons and prevents the expression of experimental neuropathic pain. *Neuroscience* 2003;121:815–24.
- [52] Kim CH, Oh Y, Chung JM, Chung K. Changes in three subtypes of tetrodotoxin sensitive sodium channel expression in the axotomized dorsal root ganglion in the rat. *Neurosci Lett* 2002;323:125–8.
- [53] Liu X, Zhou JL, Chung K, Chung JM. Ion channels associated with the ectopic discharges generated after segmental spinal nerve injury in the rat. *Brain Res* 2001;900:119–27.
- [54] Lyu YS, Park SK, Chung K, Chung JM. Low dose of tetrodotoxin reduces neuropathic pain behaviors in an animal model. *Brain Res* 2000;871:98–103.
- [55] Hains BC, Klein JP, Saab CY, Craner MJ, Black JA, Waxman SG. Upregulation of sodium channel Nav1.3 and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury. *J Neurosci* 2003;23:8881–92.
- [56] Djouhri L, Newton R, Levinson SR, Berry CM, Carruthers B, Lawson SN. Sensory and electrophysiological properties of guinea-pig sensory neurons expressing Nav 1.7 (PN1)  $\text{Na}^+$  channel alpha subunit protein. *J Physiol* 2003;546:565–76.

- [57] Cummins TR, Howe JR, Waxman SG. Slow closed-state inactivation: a novel mechanism underlying ramp currents in cells expressing the hNE/PN1 sodium channel. *J Neurosci* 1998;18:9607–19.
- [58] Nassar MA, Stirling LC, Forlani G, Baker MD, Matthews EA, Dickenson AH, et al. Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. *Proc Natl Acad Sci USA* 2004;101:12706–11.
- [59] Nassar MA, Levato A, Stirling LC, Wood JN. Neuropathic pain develops normally in mice lacking both Nav1.7 and Nav1.8. *Mol Pain* 2005;1:24.
- [60] Waxman SG, Dib-Hajj S. Erythralgia: molecular basis for an inherited pain syndrome. *Trends Mol Med* 2005;11:555–62.
- [61] Wang H, Sun H, Della Penna K, Benz RJ, Xu J, Gerhold DL, et al. Chronic neuropathic pain is accompanied by global changes in gene expression and shares pathobiology with neurodegenerative diseases. *Neuroscience* 2002;114:529–46.
- [62] Decosterd I, Ji RR, Abdi S, Tate S, Woolf CJ. The pattern of expression of the voltage-gated sodium channels Na(v)1.8 and Na(v)1.9 does not change in uninjured primary sensory neurons in experimental neuropathic pain models. *Pain* 2002;96:269–77.
- [63] Coward K, Plumpton C, Facer P, Birch R, Carlstedt T, Tate S, et al. Immunolocalization of SNS/PN3 and NaN/SNS2 sodium channels in human pain states. *Pain* 2000;85:41–50.
- [64] Dib-Hajj SD, Black JA, Cummins TR, Kenney AM, Kocsis JD, Waxman SG. Rescue of alpha-SNS sodium channel expression in small dorsal root ganglion neurons after axotomy by nerve growth factor in vivo. *J Neurophysiol* 1998;79:2668–76.
- [65] Fjell J, Cummins TR, Dib-Hajj SD, Fried K, Black JA, Waxman SG. Differential role of GDNF and NGF in the maintenance of two TTX-resistant sodium channels in adult DRG neurons. *Brain Res Mol Brain Res* 1999;67:267–82.
- [66] Cummins TR, Black JA, Dib-Hajj SD, Waxman SG. Glial-derived neurotrophic factor upregulates expression of functional SNS and NaN sodium channels and their currents in axotomized dorsal root ganglion neurons. *J Neurosci* 2000;20:8754–61.
- [67] Novakovic SD, Tzoumaka E, McGivern JG, Haraguchi M, Sangameswaran L, Gogas KR, et al. Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. *J Neurosci* 1998;18:2174–87.
- [68] Sleeper AA, Cummins TR, Dib-Hajj SD, Hormuzdiar W, Tyrrell L, Waxman SG, et al. Changes in expression of two tetrodotoxin-resistant sodium channels and their currents in dorsal root ganglion neurons after sciatic nerve injury but not rhizotomy. *J Neurosci* 2000;20:7279–89.
- [69] Lai J, Hunter JC, Porreca F. The role of voltage-gated sodium channels in neuropathic pain. *Curr Opin Neurobiol* 2003;13:291–7.
- [70] Gold MS, Weinreich D, Kim CS, Wang R, Treanor J, Porreca F, et al. Redistribution of Na(V)1.8 in uninjured axons enables neuropathic pain. *J Neurosci* 2003;23:158–66.
- [71] Porreca F, Lai J, Bian D, Wegert S, Ossipov MH, Eglen RM, et al. A comparison of the potential role of the tetrodotoxin-insensitive sodium channels, PN3/SNS and NaN/SNS2, in rat models of chronic pain. *Proc Natl Acad Sci USA* 1999;96:7640–4.
- [72] Lai J, Gold MS, Kim CS, Bian D, Ossipov MH, Hunter JC, et al. Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, Nav1.8. *Pain* 2002;95:143–52.
- [73] Joshi SK, Mikusa JP, Hernandez G, Baker S, Shieh CC, Neelands T, et al. Involvement of the TTX-resistant sodium channel Nav 1.8 in inflammatory and neuropathic, but not post-operative, pain states. *Pain* 2006;123:75–82.
- [74] Roza C, Laird JM, Souslova V, Wood JN, Cervero F. The tetrodotoxin-resistant Na<sup>+</sup> channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J Physiol* 2003;550:921–6.
- [75] Okue K, Chaplan SR, McMahon SB, Luo ZD, Calcutt NA, Scott BP, et al. Regulation of expression of the sensory neuron-specific sodium channel SNS in inflammatory and neuropathic pain. *Mol Cell Neurosci* 1997;10:196–207.
- [76] Baker MD, Bostock H. Low-threshold, persistent sodium current in rat large dorsal root ganglion neurons in culture. *J Neurophysiol* 1997;77:1503–13.
- [77] Dib-Hajj SD, Tyrrell L, Black JA, Waxman SG. NaN, a novel voltage-gated Na channel, is expressed preferentially in peripheral sensory neurons and down-regulated after axotomy. *Proc Natl Acad Sci USA* 1998;95:8963–8.
- [78] Eriksson J, Jablonski A, Persson AK, Hao JX, Kouya PF, Wiesenfeld-Hallin Z, et al. Behavioral changes and trigeminal ganglion sodium channel regulation in an orofacial neuropathic pain model. *Pain* 2005;119:82–94.
- [79] Abe M, Kurihara T, Han W, Shinomiya K, Tanabe T. Changes in expression of voltage-dependent ion channel subunits in dorsal root ganglia of rats with radicular injury and pain. *Spine* 2002;27:1517–24.
- [80] Priest BT, Murphy BA, Lindia JA, Diaz C, Abbadie C, Ritter AM, et al. Contribution of the tetrodotoxin-resistant voltage-gated sodium channel Nav1.9 to sensory transmission and nociceptive behavior. *Proc Natl Acad Sci USA* 2005;102:9382–7.
- [81] Isom LL. Pathobiology of visceral pain: molecular mechanisms and therapeutic implications. I. cellular and molecular biology of sodium channel  $\beta$  subunits: therapeutic implications for pain? *Am J Physiol* 2000;278:G349–53.
- [82] Wood JN, Boorman J. Voltage-gated sodium channel blockers: target validation and therapeutic potential. *Curr Topics Medicinal Chem* 2005;5:529–37.
- [83] Coward K, Jowett A, Plumpton C, Powell A, Birch R, Tate S, et al. Sodium channel beta1 and beta2 subunits parallel SNS/PN3 alpha-subunit changes in injured human sensory neurons. *Neuroreport* 2001;12:483–8.
- [84] Blackburn-Munro G, Fleetwood-Walker SM. The sodium channel auxiliary subunits beta1 and beta2 are differentially expressed in the spinal cord of neuropathic rats. *Neuroscience* 1999;90:153–64.
- [85] Takahashi N, Kikuchi S, Dai Y, Kobayashi K, Fukuoka T, Noguchi K. Expression of auxiliary beta subunits of sodium channels in primary afferent neurons and the effect of nerve injury. *Neuroscience* 2003;121:441–50.
- [86] Pertin M, Ji RR, Berta T, Powell AJ, Karchewski L, Tate SN, et al. Upregulation of the voltage-gated sodium channel beta2 subunit in neuropathic pain models: characterization of expression in injured and non-injured primary sensory neurons. *J Neurosci* 2005;25:10970–80.
- [87] Shah BS, Stevens EB, Gonzalez MI, Bramwell S, Pinnock RD, Lee K, et al. Beta3, a novel auxiliary subunit for the voltage-gated sodium channel, is expressed preferentially in sensory neurons and is upregulated in the chronic constriction injury model of neuropathic pain. *Eur J Neurosci* 2000;12:3985–90.
- [88] Shah BS, Gonzalez MI, Bramwell S, Pinnock RD, Lee K, Dixon AK. Beta3, a novel auxiliary subunit for the voltage gated sodium channel is upregulated in sensory neurones following streptozocin induced diabetic neuropathy in rat. *Neurosci Lett* 2001;309:1–4.
- [89] Casula MA, Facer P, Powell AJ, Kinghorn IJ, Plumpton C, Tate SN, et al. Expression of the sodium channel beta3 subunit in injured human sensory neurons. *Neuroreport* 2004;15:1629–32.
- [90] Matthews EA, Wood JN, Dickenson AH. Nav1.8-null mice show stimulus-dependent deficits in spinal neuronal activity. *Mol Pain* 2006;2:5.
- [91] Porreca F, Burgess SE, Gardell LR, Vanderah TW, Malan Jr TP, Ossipov MH, et al. Inhibition of neuropathic pain by selective ablation of brainstem medullary cells expressing the mu-opioid receptor. *J Neurosci* 2001;21:5281–8.
- [92] Burgess SE, Gardell LR, Ossipov MH, Malan Jr TP, Vanderah TW, Lai J, et al. Time-dependent descending facilitation from the rostral ventromedial medulla maintains, but does not initiate, neuropathic pain. *J Neurosci* 2002;22:5129–36.
- [93] Chen Q, King T, Vanderah TW, Ossipov MH, Malan Jr TP, Lai J, et al. Differential blockade of nerve injury-induced thermal and tactile hypersensitivity by systemically administered brain-penetrating and peripherally restricted local anesthetics. *J Pain* 2004;5:281–9.
- [94] Waxman SG, Hains BC. Fire and phantoms after spinal cord injury: Na<sup>+</sup> channels and central pain. *Trends Neurosci* 2006;29:207–15.

- [95] Hains BC, Saab CY, Waxman SG. Changes in electrophysiological properties and sodium channel Nav1.3 expression in thalamic neurons after spinal cord injury. *Brain* 2005;128:2359–71.
- [96] Gribkoff VK, Winqvist RJ. Modulators of peripheral voltage-gated sodium channels for the treatment of neuropathic pain. *Expert Opin Ther Patents* 2005;15:1751–62.
- [97] Sindrup S, Jensen T. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;83:389–400.
- [98] Soderpalm B. Anticonvulsants: aspects of their mechanisms of action. *Eur J Pain* 2002;6(Suppl. A):3–9.
- [99] Tanelian DL, Brose WG. Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: Lidocaine, carbamazepine and mexilitine. *Anesthesiology* 1991;74:949–51.
- [100] Blom S. Trigeminal neuralgia; its treatment with a new anti-convulsant drug (G-32883). *Lancet* 1962;I:829–40.
- [101] Tomson T, Bertilsson L. Potent therapeutic effect of carbamazepine-10, 11-epoxide in trigeminal neuralgia. *Arch Neurol* 1984;41:588–601.
- [102] Rull JA, Quibrera R, Gonzalez-Millan H, Lozano CO. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine: double-blind crossover study. *Diabetologia* 1969;5:215–20.
- [103] Tripathi M, Kaushik S. Carbamazepine for pain management in Guillain-Barré syndrome patients in the intensive care unit. *Crit Care Med* 2000;28:655–8.
- [104] Chadda VS, Mathur MS. Double-blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy. *J Assoc Physicians India* 1978;26:403–6.
- [105] McCleane GJ. Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study. *Anesth Analg* 1999;89:985–8.
- [106] McCleane G. 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: a randomized, double-blind, placebo controlled trial. *Pain* 1999;83:105–7.
- [107] Simpson DM, Olney R, McArthur JC, Khan A, Godbold J, Ebel-Frommer K. A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. *Neurology* 2000;54:2115–9.
- [108] Vestergaard K, Andersen G, Gottrup H, Kristensen BT, Jensen TS. Lamotrigine for central post-stroke pain: a randomized controlled trial. *Neurology* 2001;56:184–90.
- [109] Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology* 2001;57:505–9.
- [110] Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain* 1997;73:223–30.
- [111] Blackburn-Munro G, Erichsen HL. Antiepileptics and the treatment of neuropathic pain: evidence from animal models. *Curr Pharm Design* 2005;11:2961–76.
- [112] Xie XM, John VH, Trezise DJ. Inhibitory effects of lamotrigine on action potential firing in rat sensory neurons *in vitro*. *Soc Neurosci Abstr* 1997;23:445–53.
- [113] Eisenberg E, Shifrin A, Krivoy N. Lamotrigine for neuropathic pain. *Exp Rev Neurotherapeutics* 2005;5:729–35.
- [114] Dib JG. Focus on topiramate in neuropathic pain. *Curr Med Res Opin* 2004;20:1857–61.
- [115] Chong MS, Libretto SE. The rationale and use of topiramate for treating neuropathic pain. *Clin J Pain* 2003;19:59–68.
- [116] Raskin P, Donofrio PD, Rosenthal NR, Hewitt DJ, Jordan DM, Xiang J, et al. Topiramate vs. placebo in painful diabetic neuropathy. *Neurology* 2004;63:865–73.
- [117] Sindrup SH, Jensen TS. Efficacy of pharmaceutical treatment of neuropathic pain: an update and effect related mechanism of drug action. *Pain* 1999;83:389–400.
- [118] Lavoie P-A, Beauchamp G, Elie R. Tricyclic antidepressants inhibit voltage-dependent calcium channels and Na<sup>+</sup>-Ca<sup>2+</sup> exchange in rat brain cortex synaptosomes. *Can J Physiol Pharmacol* 1990;68:1414–8.
- [119] Wang GK, Russell C, Wang SY. State-dependent block of voltage-gated Na<sup>+</sup> channels by amitriptyline via local anesthetic receptor and its implication for neuropathic pain. *Pain* 2004;110:166–74.
- [120] Sawynok J, Reid AR, Esser MJ. Peripheral antinociceptive action of amitriptyline in the rat formalin test: involvement of adenosine. *Pain* 1999;80:45–55.
- [121] Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol* 2005;96:399–409.
- [122] Valverde O, Mico JA, Maldonado R, Mellado M, Gibert-Rahola J. Participation of opioid and monoaminergic mechanisms on the antinociceptive effect induced by tricyclic antidepressants in two behavioural pain tests in mice. *Prog Neuropsychopharmacol Biol Psychiatry* 1994;18:1073–92.
- [123] Reynolds IJ, Miller RJ. Tricyclic antidepressants block N-methyl-D-aspartate receptors: similarities to the action of zinc. *Br J Pharmacol* 1998;95:95–102.
- [124] Sawynok J, Esser MJ, Reid AR. Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. *J Psychiatry Neurosci* 2001;26:21–9.
- [125] Rosenstein DL, Nelson JC, Jacobs SC. Seizures associated with antidepressants: a review. *J Clin Psychiatry* 1993;54:289–99.
- [126] Barber MJ, Starmer CF, Grant AO. Blockade of cardiac sodium channels by amitriptyline and diphenylhydantoin. Evidence for two use-dependent binding sites. *Circ Res* 1991;69:677–96.
- [127] Esser MJ, Sawynok J. Acute amitriptyline in a rat model of neuropathic pain: differential symptom and route effects. *Pain* 1999;80:643–53.
- [128] Nicholson GM, Blanche T, Mansfield K, Tran Y. Differential blockade of neuronal voltage-gated Na<sup>+</sup> and K<sup>+</sup> channels by antidepressant drugs. *Eur J Pharmacol* 2002;452:35–48.
- [129] Edmondson EA, Simpson Jr RK, Stubler DK, Beric A. Systemic lidocaine therapy for poststroke pain. *South Med J* 1993;86:1093–6.
- [130] Finnerup NB, Biering-Sorensen F, Johannesen IL, Terkelsen AJ, Juhl GI, Kristensen AD, et al. Intravenous lidocaine relieves spinal cord injury pain: a randomized, controlled trial. *Anesthesiology* 2005;102:1023–30.
- [131] Argoff CE. New analgesics for neuropathic pain: the lidocaine patch. *Clin J Pain* 2000;16(2 Suppl.):S62–6.
- [132] Castaneda-Castellanos DR, Nikonov I, Kallen RG, Recio-Pinto E. Lidocaine stabilizes the open state of CNS voltage-dependent sodium channels. *Brain Res Mol Brain Res* 2002;99:102–13.
- [133] Hollmann MW, Gross A, Jelacin N, Durieux ME. Local anesthetic effects on priming and activation of human neutrophils. *Anesthesiology* 2001;95:113–22.
- [134] Hollmann MW, Herroeder S, Kurz KS, Hoenemann CW, Struemper D, Hahnenkamp K, et al. Time-dependent inhibition of G-protein-coupled receptor signaling by local anesthetics. *Anesthesiology* 2004;100:852–60.
- [135] Weiser T. Comparison of the effects of four Na<sup>+</sup> channel analgesics on the TTX-resistant Na<sup>+</sup> currents in rat sensory neurons and recombinant Nav1.2 channels. *Neurosci Lett* 2006;395:179–84.
- [136] Jarvis B, Coukell AJ. Mexilitine, a review of its therapeutic use in painful diabetic neuropathy. *Drugs* 1998;56:691–707.
- [137] Gaida W, Klinder K, Arndt K, Weiser T. Ambroxol, a Nav1.8-preferring Na<sup>+</sup> channel blocker, effectively suppresses pain symptoms in animal models of chronic, neuropathic and inflammatory pain. *Neuropharmacology* 2005;49:1220–7.
- [138] Tremont-Lukats IW. Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. *Anesth Analg* 2005;101:1738–49.
- [139] Nassar MA, Baker MD, Levato A, Ingram R, Mallucci G, McMahon SB, Wood JN. Nerve injury induces robust allodynia and ectopic discharges in Nav1.3 null mutant mice. *Mol Pain* 2006;2:33–43.