Sodium Channel Blockers for the Treatment of Neuropathic Pain

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Summary: Drugs that block voltage-gated sodium channels are efficacious in the management of neuropathic pain. Accordingly, this class of ion channels has been a major focus of analgesic research both in academia and in the pharmaceutical/biotechnology industry. In this article, we review the history of the use of sodium channel blockers, describe

the current status of sodium channel drug discovery, highlight the challenges and hurdles to attain sodium channel subtype selectivity, and review the potential usefulness of selective sodium channel blockers in neuropathic pain. **Key Words:** Sodium channel, subtype, selectivity, neuropathic pain, drug discovery.

HISTORY OF THE USE OF SYSTEMIC SODIUM CHANNEL BLOCKERS FOR PAIN

The current appreciation of the use of sodium channel blockers in the treatment of neuropathic pain represents the convergence of a number of separate advances in scientific understanding. Pharmacological distinctions between acute and chronic pain could not be made until drugs with relevant yet pharmacologically different actions were created. Trigeminal neuralgia was described as early as the first century AD, but the consequences of injuries to other peripheral nerves were not formally recognized until the American Civil War,¹ and a general concept of neuropathic pain did not emerge until more than a century later. Improvements in electrophysiological recording techniques led to the ability to study the role of sodium channel blockers in the treatment of electrophysiological disorders with manifestations as different as cardiac arrhythmias, epilepsy, and neuropathic pain. Confirming neuropathic pain as an electrophysiological disorder required experimental observations from patients and adequate preclinical experimental models.

The history of the use of sodium channel blockers as analgesics considerably predates any modern understanding of the role of ion channels in pain. Use of the coca plant for its invigorating powers was known at least 3,000 years ago, based on radiocarbon dating of Andean mummies containing traces of a stable cocaine metabolite.² Systemic use of coca was likely based primarily on its stimulatory, dopamine transporter-blocking properties, rather than its local anesthetic, sodium channel blocking properties, but topical use is presumed as well.³ Widespread European use of cocaine was first enabled by the extraction of pure cocaine from the perishable coca leaves by Gaedcke⁴ in 1855, whereupon its uptake into medicinal and other forms of use was rapid. Both Sigmund Freud and Carl Koller have been credited with recognizing the usefulness of cocaine as a topical anesthetic for surgical use in 1884.⁵ The first recorded treatment of neuropathic pain with a sodium channel blocker is probably Freud's treatment of Ernst von Fleischl, who suffered from trigeminal neuralgia, with cocaine injections.⁶ The evident toxic liabilities of cocaine soon led to medicinal chemistry efforts to find a safer compound with similar local anesthetic properties.⁷ To this end, Albert Einhorn synthesized procaine in 1904, leading the way for additional ester local anesthetics. Local anesthetics addressed an enormous unmet medical need for alternatives to early general anesthesia techniques, and these anesthetics were readily adopted for use in topical

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and spinal anesthesia, as well as regional nerve blockade and local infiltration.

Systemic infusion of local anesthetics for general anesthesia was also quite popular for many decades; procaine or lidocaine (synthesized by Nils Lofgren in 1943) was used alone or in combination with nitrous oxide.^{8,9} Although systemically administered local anesthetics were extremely useful in the surgical setting, studies revealed that they held less practical use as analgesics outside the operating room. In 1944, Bigelow and Harrison¹⁰ specifically explored procaine's analgesic dose-response by administering it subcutaneously to five conscious, un-anesthetized subjects. They recorded the resulting suppression of noxious radiant heat sensation, which they described as transient, and accompanied by sedation.

The treatment of trigeminal neuralgia with the anti-convulsant phenytoin (diphenylhydantoin, hydantoin, Dilantin [Parke-Davis]) was advocated in published literature as early as the 1950s.¹¹ Of note, Kugelberg and Lindblom¹² performed an unblinded study of the effects of intravenous lidocaine and phenytoin on trigeminal neuralgia attacks in 1959. Both agents showed efficacy, albeit short-lived. In 1962, efficacy of the new anticonvulsant carbamazepine (Tegretol [Novartis]) in trigeminal neuralgia patients was reported in the journal *Lancet*.¹³ These reports represented significant advances in the pharmacological management of trigeminal neuralgia for which primarily surgical or ablative options were previously available. Controlled studies of the use of sodium channel blocking anticonvulsants in neuropathic pain are listed in [Table 1](#).

Clinical recognition of a common mechanism of action of phenytoin, carbamazepine, and lidocaine came from a separate therapeutic context. In 1975, Vaughn Williams¹⁴ published a classification of the mechanisms of action of cardiac anti-arrhythmics into four groups, based on their electrophysiological effects. In this classification, lidocaine, which had gained currency by then as a treatment for cardiac ventricular dysrhythmias, was grouped with the anticonvulsants phenytoin and carbamazepine.^{15,16} These agents were assigned to Vaughn Williams class Ib, characterized by: "interfering specifically with the process by which depolarizing charge is transferred across the membrane (i.e., by fast inward current carried by sodium ions)."¹⁷ Thus, these three agents were all recognized as sodium channel blockers, all were known as anti-arrhythmics, and all had demonstrated efficacy in the suppression of the pain of trigeminal neuralgia.

Early studies characterizing abnormal electrical activity in pathways related to chronic pain states provided important support for a pharmacological approach explicitly aimed at suppressing these foci. Examples included a series of intraoperative extracellular recordings by Loeser¹⁸ from the spinal cord dorsal horn of an individ-

ual with spinal cord injury resulting in chronic spontaneous neuropathic pain. Burst firing and spontaneous high-frequency firing, similar to patterns seen in cortical epileptic foci, were recorded from dorsal horn neurons. Burchiel and Wyler¹⁹ recorded abnormal discharges from experimentally compressed feline trigeminal ganglia, which were suppressed by phenytoin. These and other similar studies helped to frame the treatment of abnormal pain states in the context of abnormal electrical activity.

Beginning in the early 1980s, a series of studies using lidocaine and related local anesthetics brought both the problem of neuropathic pain and the therapeutic potential of sodium channel blockers into greater focus. In 1982, Boas et al.²⁰ published an unblinded study of the analgesic effect of intravenous lidocaine in severe, chronic pain of neurological origin. A stated rationale for the study was the known use of lidocaine in reducing bursting electrical activity in brain and cardiac foci, along with the spinal cord and trigeminal recordings previously described. The five patients studied suffered from thalamic pain, trigeminal neuralgia, phantom pain, arachnoiditis, and post-rhizotomy pain. This study broke significant ground in proposing a common mechanistic basis for these disparate forms of refractory pain, and in proposing treatment of neuropathic pain explicitly based on suppression of an abnormally active electrophysiological focus. During the lidocaine infusion, four patients experienced profound reductions in pain scores. Importantly, the magnitude of the effect of lidocaine in these neuropathic pain states far exceeded previous results using lidocaine in acute or experimental pain states. This study inspired controlled studies of intravenous lidocaine in patients with a variety of neuropathic pain disorders and painful diabetic neuropathy. Following up on a small case series using lidocaine to treat the pain of Dercums' disease,²¹ Kastrup et al.²² performed a controlled study in 1987 in patients suffering from painful diabetic neuropathy. Of note, in addition to significant differences between placebo and lidocaine treatment, the duration of relief from lidocaine infusion in this study ranged from 3 to 21 days, presumably outlasting the complete elimination of lidocaine. A host of subsequent studies with lidocaine or its analogs (see [Table 1](#)) have supported these positive findings. Confirmation of the efficacy of lidocaine in well-controlled trials brought attention to the mechanistic relevance of sodium channel blockade and also provided a meaningful therapeutic intervention for many patients.

The lack of oral bioavailability and low safety margin of lidocaine have remained constraints on its use, although it remains among the most consistently efficacious treatments for neuropathic pain. In 1987, Lindstrom and Lindblom²³ conducted a double-blind crossover trial of the anti-arrhythmic tocainide (an orally bioavailable analog

Table 1. *Controlled Clinical Trials of Sodium Channel Blockers for Neuropathic Pain*

Agent	Condition	Result	Year	Ref. No.
4030W92	Peripheral	NS	2002	42
Amitriptyline	PHN	Pos	1982	31
Amitriptyline/ Carbamazepine	Central poststroke	Pos		
Amitriptyline		Pos	1989	32
Amitriptyline	Postmastectomy	Pos	1996	166
Amitriptyline	Chemotherapy-induced	NS	2008	167
Carbamazepine	Trigeminal neuralgia	Pos	1966	168
Carbamazepine	Multiple	Mixed	1968	169
Carbamazepine	PDN	Pos	1969	170
Carbamazepine	CRPS	Pos	2001	171
Desipramine	PHN	Pos	1990	172
Desipramine	PDN	Pos	1991	173
Duloxetine	PDN	Pos	2005	174
Duloxetine	PDN	Pos	2005	175
Duloxetine	PDN	Pos	2006	176
Lacosamide	PDN	Pos	2007	177
Lacosamide	PDN	Pos	2009	178
Lacosamide	PDN	Pos	2009	179
Lamotrigine	Trigeminal neuralgia	Pos	1997	180
Lamotrigine	Various	NS	1999	181
Lamotrigine	PDN	Pos	2001	182
Lamotrigine	Central poststroke	Mixed	2001	183
Lamotrigine	Spinal cord injury	Mixed	2002	184
Lamotrigine	HIV-ART neuropathy	Pos	2003	185
Lamotrigine	Chemotherapy-induced	NS	2008	186
Lidocaine	PDN	Pos	1989	187
Lidocaine	Cancer/treatment	NS	1989	188
Lidocaine	PHN	Pos	1991	189
Lidocaine	Malignant plexopathy	NS	1992	190
Lidocaine	Sciatica	Pos	1999	191
Lidocaine	CRPS I and II	Pos	2000	192
Lidocaine	Central neuropathic	Pos	2000	193
Lidocaine	Spinal cord injury	Pos	2005	194
Lidocaine	Peripheral	Pos	2006	195
Lidocaine	Central poststroke	Pos	1992	196
Lidocaine	PHN, nerve trauma	Pos	2004	197
Lidocaine/ Mexiletine	Multiple sclerosis	Pos		
Mexiletine		Pos	1999	198
Mexiletine	PDN	Pos	1988	24
Mexiletine	Nerve injury	Pos	1989	199
Mexiletine	Neuropathy	Pos	1992	200
Mexiletine	PDN	NS	1992	201
Mexiletine	Spinal cord injury	NS	1996	202
Mexiletine	PDN	Pos	1997	203
Mexiletine	PDN	NS	1997	204
Mexiletine	Unspecified	NS	2000	205
Oxcarbazepine	PDN	Pos	2005	39
Oxcarbazepine	PDN	Pos	2006	40
Phenytoin	PDN	NS	1977	206
Phenytoin	PDN	Pos	1978	207
Ralfinamide	Various	Pos	2008	*
Riluzole	Peripheral	NS	2000	208
Tetrodotoxin	Cancer	Pos	2008	43

ART = antiretroviral therapy; CRPS = complex regional pain syndrome; NS = not significant; PDN = painful diabetic neuropathy; PHN = postherpetic neuralgia; Pos = positive.

Compilation of randomized, controlled trials of known sodium channel blocking agents in neuropathic pain states. This table is limited to studies whose methodology could be confirmed; access to some early literature was not possible. Inclusion of tricyclic antidepressants is limited to those demonstrated to have significant sodium channel blocking properties.

*<http://www.newron.com/uploads/posterA3nocrop.pdf>.

of lidocaine developed as an anti-arrhythmic) and carbamazepine. They concluded that tocainide was highly effective in trigeminal neuralgia, and speculated that its mechanism was similar to carbamazepine. Due to safety concerns, however, there was little uptake of tocainide for use in pain treatment. In 1988, the publication of a positive study of mexiletine (another orally bioavailable analog of lidocaine) in diabetic neuropathy by Dejdard and colleagues²⁴ created a furor of interest, and inspired numerous additional studies, because it offered the hope of an oral agent suitable for clinical use with efficacy similar to lidocaine. Studies have shown that sodium channel blockade contributes to the efficacy of another important category of drugs used to treat pain. Amitriptyline and other similar tricyclic antidepressants are among the more efficacious drugs in a variety of neuropathic pain states such as postherpetic neuralgia and central poststroke pain.²⁵⁻²⁷ Although the primary pharmacology of amitriptyline and other tricyclic antidepressants is monoamine reuptake inhibition, a clinically validated mechanism of action in neuropathic pain management in its own right, many tricyclics are also sodium channel blockers. *In vitro*, amitriptyline competes with lidocaine for a binding site on cardiac sodium channels and blocks brain sodium channels; *in vivo*, blockade of cardiac sodium channels contributes to its cardiotoxicity in overdose.^{28,29} Additional tricyclic antidepressants with efficacy in neuropathic pain exhibit similar secondary pharmacology (Table 1).³⁰

Over the past two or three decades, the creation of preclinical models of nerve injury has provided an experimental basis for the study of neuropathic pain mechanisms. Early studies in axotomy models revealed that spontaneous firing developed after nerve injury.³¹ Major nerve injury models were subsequently developed in which motor function of the affected limb was spared, permitting the study of pain behavior as well as neuronal activity. These models, commonly known as the chronic constriction injury (or Bennett) model,³² the partial sciatic ligation (or Seltzer) model,³³ and the L5/6 spinal nerve ligation (or Chung) model,³⁴ enabled systematic laboratory investigations of neuropathic pain mechanisms and continue to be fundamentally important research tools. In 1988, Kajander et al.³⁵ described the origin of abnormal neuronal discharges from the dorsal root ganglion (DRG) as well as the injury site of the chronically constricted rat sciatic nerve. In 1992, using the Seltzer model, Devor et al.³⁶ reported that intravenous administration of lidocaine temporarily suppressed ectopic discharges from the DRG of the partially ligated rat sciatic nerve. The ability to correlate neuropathic pain states in these anatomically reproducible models with electrophysiological, histological, and molecular changes, has led to great progress in pain research.

CLINICAL EXPERIENCE WITH NEWER SODIUM CHANNEL BLOCKERS IN NEUROPATHIC PAIN

There continues to be a need for new, safer, more tolerable, and more efficacious neuropathic pain treatments. At this time, all currently available drugs with sodium channel blocking properties have tolerability limitations. Regardless of off-target adverse effects, the therapeutic margin for nonselective sodium channel blockade is narrow, and optimization of efficacy in pain may be at the expense of central nervous system liabilities, including seizures (due to blockade of inhibitory pathways), ataxia, confusion, and sedation. To maintain plasma concentrations within a therapeutic window, often drug level monitoring is necessary, necessitating medical follow-up and titration. Off-target adverse effects of these generally low potency drugs may be problematic as well. Phenytoin is associated with numerous adverse effects, including rash, gingival hypertrophy, horizontal nystagmus, and teratogenicity. Carbamazepine may be associated with bone marrow suppression. Tocainide was associated with bone marrow suppression and pulmonary fibrosis, and is no longer marketed in the United States. Mexiletine is often poorly tolerated due to gastrointestinal upset. Although studied tricyclic antidepressants have a comparatively high likelihood of efficacy, the magnitude of their efficacy may be somewhat limited, and their sedative and anticholinergic side effects can limit tolerability.

Newer drugs have been developed, or are in development, with better safety/tolerability profiles. Some of these have been launched as anticonvulsants, and are currently still in clinical trials for neuropathic pain. For example, oxcarbazepine, a carbamazepine derivative, is also a sodium channel blocker, and it was developed to retain the anticonvulsant efficacy of carbamazepine while avoiding the hepatic enzyme induction believed to be associated with an epoxide metabolite.^{37,38} Oxcarbazepine has given positive results in two controlled, painful diabetic neuropathy trials, as well as a number of open label studies.^{39,40} Similarly, lamotrigine, whose pharmacology includes NMDA receptor antagonism, as well as sodium channel blockade, has been efficacious in painful diabetic neuropathy, central poststroke pain, HIV-related painful neuropathy, and in spinal cord injury patients with incomplete (but not complete) transections. A tolerability consideration with lamotrigine therapy is the 8% to 9% incidence of rash. Lacosamide, another new anticonvulsant, has been proposed to bind to a novel site that enhances slow inactivation, thus increasing a physiological mechanism of channel inhibition.⁴¹ Lacosamide has shown positive results in painful diabetic peripheral neuropathy in phase II and III clinical trials. Successful registration of these agents for use in neuro-

Of note, with the sole exception of tetrodotoxin, all the agents previously described are distributed into the central nervous system as well as the peripheral compartment. However, the anatomical location of critical sodium channel blockade is difficult to localize. Studies have pointed to a spinal site of action of lidocaine, but this question is difficult to conclusively resolve.⁴⁴ Effi-

A generalization regarding the above trials is that agents that are both efficacious and well tolerated are use-dependent sodium channel blockers. Compounds exhibiting strong use-dependent effects are often referred to as local anesthetic-like. A diverse group of drugs have local anesthetic-like properties, including anesthetics, anti-convulsants, anti-arrhythmics, and other various miscellaneous drugs.^{45–49} Local anesthetic-like drugs bind at a site composed of residues in the inner pore region of the sodium channel, a motif that is highly conserved across all mammalian voltage-gated sodium channels. As a result of recognizing this conserved motif, they do not exhibit subtype selectivity (FIG. 1). Use-dependence (or frequency dependence) describes a phenomenon whereby compounds preferentially block sodium channels that are rapidly cycling between resting, open, and inactivated states of the channel (such as may occur in tissues firing action potentials at high frequency) compared to those that reside for prolonged periods in the closed state (such as may occur in tissues firing action potentials at low frequencies).^{50–52} At the molecular level, frequency/use-dependence is a reflection of the ability of drugs to bind in a state-dependent manner, binding with low affinity to closed channels and relatively high affinity to open and/or inactivated channels.

according to the classical “modulated receptor hypothesis”⁵³ (for review, see Hondeghem and Katzung⁵⁴). Once bound to the open/inactivated state, these local anesthetic-like drugs stabilize the inactivated conformation, preventing reactivation of the channel. The degree of use dependence exhibited by any given drug is a function of the on-rate and off-rate for the interaction between the drug and the open/inactivated states of the channel. Interestingly, most of the agents previously described exhibit low sodium channel potency (micromolar, and in some cases high micromolar, *in vitro* potencies at sodium channels) with relatively fast off-rates, and strong use-dependence. This strong use-dependence provides for a safety margin for efficacy without impairment of critical cardiac, neuromuscular, or ordinary sensory functions. Despite this, it is clear that not all patients benefit from these drugs, and these compounds often provoke dose-limiting side effects. There is clearly a need for second-generation sodium channel blockers with improved efficacy and/or fewer side effects. Because all clinically used sodium channel blockers lack sodium channel subtype selectivity (i.e., they block all voltage-gated sodium channels with similar potency), a generally held view is that improvements in subtype selectivity are required for advances over currently available drugs. The following sections will discuss the rationale for subtype-selective sodium channel blockers in the search for optimally efficacious, safe, and tolerable therapeutics.

VOLTAGE-GATED SODIUM CHANNELS

Voltage-gated sodium channels function as heteromultimeric proteins that consist of the pore forming α subunit in association with an auxiliary β ($\beta 1$ – $\beta 4$) subunit. The 260 kDa mammalian α subunit is encoded by nine distinct genes, giving rise to sodium channels Na_v1.1 through Na_v1.9 (for a complete description of nomenclature, see the 2003 International Union of Pharmacology Compendium of Voltage Gated Channels⁵⁵), and is composed of four homologous domains, with each domain spanning the membrane six times (S1–S6) consistent with the architecture of the classical voltage-gated ion channel superfamily.⁵⁶ The sodium channel α subunit determines the biophysical properties of the channel and contains the ion selectivity filter. Modification of the α subunit alters the properties of the channel, whether due to binding of exogenous ligands, such as small molecules or neurotoxins/peptides, modulation by endogenous intracellular signaling molecules, such as protein kinases A and C, or amino acid sequence alteration due to genetic manipulation or naturally occurring polymorphisms. Sodium channels are commonly annotated as either tetrodotoxin sensitive (Na_v1.1–Na_v1.4, Na_v1.6, Na_v1.7) or resistant (Na_v1.5, Na_v1.8, Na_v1.9). In addition to tetrodotoxin, a host of other peptide toxins isolated

from scorpions, spiders, sea anemones, and cone snails modulate channel function, and to date, six different neurotoxin binding sites have been defined on the α subunit of the sodium channel (see FIG. 2).^{57,58}

SODIUM CHANNELS AND PAIN

Eight of the nine sodium channel subtypes are expressed in the DRG; the exception is Na_v1.4, whose expression is confined to the skeletal muscle. Three of these eight, Na_v1.7, 1.8, and 1.9, are expressed exclusively in the peripheral nervous system; Na_v1.3 is ordinarily only expressed during embryonic development but is re-expressed by neurons after injury. Five subtypes are expressed in the brain: Na_v1.1–1.3, Na_v1.5, and Na_v1.6. Of interest, a recent report found splice variant differences between brain and cardiac Na_v1.5 in both rat and human, and suggested that the properties of the cardiac and brain versions of the channel may therefore differ.⁵⁹

Most interest in selective sodium channel drug discovery centers on Na_v1.3, Na_v1.7, Na_v1.8, and Na_v1.9, and the evidence that these channels contribute to neuropathic pain will be briefly reviewed. Recent clinical descriptions of Na_v1.7 gain and loss of function mutations in probands from affected families have brought a great deal of attention to the role of this channel in all forms of pain perception, as described in greater detail below.

Due to both anatomical distribution and to the substantial safety concerns inherent in targeting channels that are critical for normal brain or cardiac function, less attention has centered on the potential for selective blockade of Na_v1.1, 1.2, 1.4, 1.5, and 1.6 for the treatment of neuropathic pain. Both gain of function and loss of function mutations in Na_v1.1 lead to epilepsy.⁶⁰ One mutation has been associated with familial hemiplegic migraine.⁶¹ Various mutations that alter properties of Na_v1.2 result in epilepsy syndromes as well.^{62–71} Na_v1.4 is required for normal skeletal muscle function.^{72–74} Na_v1.5 is predominantly expressed on cardiac myocytes and is essential to cardiac action potential initiation and conduction.⁷⁵ Pharmacological inhibition or genetic mutations of Na_v1.5 interfere with channel function, resulting in disruption of cardiac excitability leading to arrhythmias.^{76,77} Humans and rodents with decreased function of Na_v1.6, predominantly located at nodes of Ranvier, exhibit neuropsychological abnormalities and motor impairment rather than sensory deficits.⁷⁸

DISTRIBUTION AND FUNCTION OF “PAINFUL” SODIUM CHANNELS

Studies of the anatomical distribution and regulation of sodium channel expression in experimental preclinical pain states have contributed somewhat to our current understanding of the role of the various subtypes in

Binding site	Neurotoxin	Effect	Small molecule
Site 1	Tetrodotoxin Saxitoxin μ -Conotoxin	Pore block Pore block Pore block	Not known
Site 2	Batrachotoxin Grayanotoxin	Pore block Activation gate modulation	Local anesthetics Antiarrhythmics Tricyclic antidepressants Veratridine
Site 3	α -Scorpion toxins Sea anemone toxins	Slow inactivation Slow inactivation	Not known
Site 4	β -Scorpion toxins Protoxin-I/II	Activation gate modulation Activation gate modulation	Not known
Site 5	Brevetoxin	Enhanced activation	Not known
Site 6	δ -Conotoxins	Inactivation gate modulation	Not known

FIG. 2. Diagram of toxin binding sites on the sodium channel α subunit. Table 1 lists toxins known to bind at identified sites (color-coded on diagram) and corresponding effects on channel function. (STX = saxitoxin; TTX = tetrodotoxin.) (Reprinted from Catterall WA, et al., 2007,⁵⁷ with permission from Elsevier, with modification.)

pathophysiology. In a few cases, human tissue samples from patients with clinically described pain states have been available as well. Techniques enabling selective manipulation of the expression of specific subtypes, using knockout or mRNA knockdown, have been used to study the relative contribution of different gene products as well. It is difficult to make robust interpretations of these data, because distribution evidence is descriptive and circumstantial rather than dispositive, and genetic studies in mice have been somewhat inconclusive. In the case of $\text{Na}_v1.7$, genetic studies in mice have been in less than complete agreement with human evidence. Nevertheless, these important studies continue to teach us about human pain mechanisms, reveal to us what there is still to learn, and document potential species differences that delineate gaps between rodent and human pathophysiology.

$\text{Na}_v1.3$

$\text{Na}_v1.3$ expression is developmentally regulated, with widespread expression observed in the developing nervous system and lower levels of expression in the adult. There appears to be significant differences between the adult levels of expression in the rat compared to the human; however, although $\text{Na}_v1.3$ is expressed only in restricted areas of the rat brain, messenger RNA is readily detected in almost all areas of the human brain.⁷⁹ Of note, upregulation of $\text{Na}_v1.3$ may be a response to neuronal injury, as increases in expression in primary sensory neurons have been repeatedly described after nerve transection and inflammation.^{80–83} In the naïve rat DRG, only 6.3% of neurons expressed $\text{Na}_v1.3$; after L5 axotomy, expression was seen in 40% of DRG neurons, in cells of all sizes, but predominantly in medium- and large-diameter neurons.⁸⁴ Upregulation in secondary neurons in the ventroposterolateral nucleus of the thalamus has been demonstrated after peripheral nerve injury as well.⁸⁵ Seizure activity also appears to induce increases in hippocampal channel expression, as described in rat models of spontaneous and kainate-induced epilepsy.^{86,87} The upregulation of $\text{Na}_v1.3$ channels, along with their fast recovery from inactivation is speculated to contribute a critical role in the hyperexcitability of damaged neurons. Curiously, the role of $\text{Na}_v1.3$ in initiation and maintenance of neuropathic pain is not supported by knockout studies, because constitutive null mutants develop similar neuropathic pain behavior and ectopic neuronal discharge to wild type controls.⁸⁸ Studies using antisense knockdown of $\text{Na}_v1.3$ have provided conflicting results, with knockdown after spinal cord injury reducing neuropathic signs, but knockdown after peripheral nerve injury producing no reduction in pain behaviors.^{85,89,90}

$\text{Na}_v1.7$

$\text{Na}_v1.7$ expression is restricted predominantly to the peripheral nervous system. It is abundantly expressed in the DRG, sympathetic ganglia, and in peripheral terminals of both high- and low-threshold sensory neurons.^{91,92} In the naïve DRG, $\text{Na}_v1.7$ is expressed by most neurons (83%–86.8%) across all size profiles. In a variant of the chronic constriction injury of the rat sciatic nerve, Nav1.7 mRNA expression was significantly decreased (54.1%) in the ipsilateral L4 and L5 DRG, but unchanged in the proximal sciatic nerve segment.⁹³ However, accumulation of $\text{Na}_v1.7$ has been described in human painful neuromata.⁹⁴ $\text{Na}_v1.7$ channels recover slowly from inactivation and display slow inactivation at voltages around the resting membrane potential, thereby contributing to the threshold setpoint for action potential generation.⁹⁵ $\text{Na}_v1.7$ global knockout mouse pups die shortly after birth, possibly due to anosmia leading to impaired feeding. This lethality was circumvented by engineering a “nociceptor-specific” knockout line in which null expression of $\text{Na}_v1.7$ was governed by the $\text{Na}_v1.8$ promoter.⁹⁶ The resulting mice displayed a marked deficit in noxious thermal and mechanical sensitivity, and loss of inflammatory thermal and mechanical hyperalgesia. Nevertheless, they developed mechanical allodynia after nerve injury that was indistinguishable from wild-type mice.⁹⁷ Although the authors interpreted these findings to mean that $\text{Na}_v1.7$ appears not to be involved in the development of neuropathic pain, a more cautious interpretation is that $\text{Na}_v1.7$ expression in neuronal subclasses expressing $\text{Na}_v1.8$ is not required for the development of neuropathic pain. Because $\text{Na}_v1.8$ is not expressed in the majority of $\text{A}\beta$ neurons, and because $\text{A}\beta$ neurons are strongly implicated in the development of neuropathic pain and allodynia, the pattern of $\text{Na}_v1.7$ knockout may have been too restricted in these constructs to fully assess its role.^{98,99} Of note, in this instance, the interpretation of mouse data has been upstaged by findings from human genetic studies. Two heritable pain disorders have been associated with mutations in the $\text{Na}_v1.7$ gene (SCN9A). Patients carrying one class of gain of function mutations in the SCN9A gene suffer from a pain syndrome known as paroxysmal extreme pain disorder, whereas those with another class of gain of functions suffer from a pain syndrome known as erythromelalgia or erythermalgia.^{100,101} Congenital indifference to pain, which is linked to truncation of the SCN9A gene resulting in loss of channel function, is an even more striking clinical phenotype.^{102–105} Although these subjects lack the ability to sense any form of pain, they retain otherwise normal mechanical and thermosensory function and normal autonomic physiology. Recent reports have pointed to anosmia as a possible additional feature of this phenotype.¹⁰⁴ Some of these mutations have been studied at the molecular level *in vitro* for their effects on gating proper-

ties.¹⁰⁶ The erythromelalgia mutations (I136V, F216S, S241T, N395K, I848T, L858H, L858F, A863P, F1449V) shift the activation curve to hyperpolarized voltages, lowering the activation threshold and resulting in hyperexcitability.^{107–114} In contrast, the paroxysmal extreme pain disorder mutations (R996C, V1298F, V1298D, V1299F, I1461T, F1462V, T1464I, M1627K) shift the steady state inactivation to more depolarized potentials, resulting in greater channel availability.^{100,115,116}

Na_v1.8

Na_v1.8 channels are exclusively restricted to the periphery. The steady state inactivation of Na_v1.8 is relatively (compared with other sodium channels) right shifted, and consequently more channels are available for activation at physiological voltages. These channels may contribute to the longer action potential durations and action potential overshoots associated with nociceptive neurons, and the presence of Na_v1.8 is thus associated with a nociceptive role.⁹⁸ Unlike TTX-sensitive channels, the inactivation properties of Na_v1.8 are entirely cold-resistant, and as a result, Na_v1.8 is essential to the perception of cold pain.^{117,118} In naïve DRGs, Na_v1.8 is expressed in 66.5% to 68.9% of neurons overall, mostly those with small- and medium-sized profiles. After axotomy, expression in the affected DRG decreases dramatically, although redistribution to the axonal injury site has been reported.^{93,119–121} Although Na_v1.8 enjoys a comparatively undisputed role in inflammatory pain states, its role in neuropathic pain has been somewhat controversial, with temporal knockdown studies indicating a critical component of Na_v1.8 in neuropathic pain, electrophysiological studies showing a lack of ectopic neuronal discharges in nerve injured null mutant mice compared to the wild type, but normal development of neuropathic pain in constitutive knockout mice.^{97,118,122–125}

Na_v1.9

Na_v1.9 is still the least understood member of the sodium channel family, mostly because of the difficulty in expressing the protein in recombinant systems. This subtype is expressed in the sensory ganglia, mainly in small diameter C fibers (58.8%–61.5% of DRG neurons overall).^{84,126,127} The Na_v1.9 subtype is unique among sodium channels in that it displays slow activation and incomplete inactivation.¹²⁸ This channel was upregulated in innervating DRGs after hind paw inflammation, and was downregulated after axotomy.^{129,130} Using knockdown technology with antisense oligonucleotides, it was demonstrated that Na_v1.9 may not be involved in acute nociception or in producing thermal hyperalgesia or mechanical allodynia in spinal nerve ligated rats.¹³¹ Likewise, acute pain responses were unaltered in Na_v1.9 knockout animals and neuropathic pain behavior was observed for the entire duration of the study.¹³² In sharp contrast, Na_v1.9 in knockout mice failed to maintain

inflammation-induced thermal hyperalgesia with no effect on the mechanical endpoint, suggesting that Na_v1.9 may be important for aspects of persistent inflammatory pain.¹³³

THE SEARCH FOR SUBTYPE SELECTIVE SODIUM CHANNEL BLOCKERS

As previously noted, there exists a clear need for new sodium channel blockers with improved efficacy and/or fewer side effects. A popular view is that this could be achieved through improvements in subtype selectivity. Consequently, a great deal of effort has been expended in the pharmaceutical industry toward identifying selective inhibitors of one or more of the molecular sodium channel targets previously described. Unfortunately, progress in this endeavor has been slow. The vast majority of compounds identified to date, although often chemically novel (i.e., not related to first generation sodium channel blockers), do not appear to show improved subtype selectivity in comparison with existing drugs. Based on publicly disclosed information available at the time of writing, it would seem unlikely that any genuinely subtype selective sodium channel blockers are advancing through clinical trials. Only a few examples of subtype selective sodium channel blockers can be found in the scientific literature or in company press releases, and these examples are reviewed briefly below. Although these recent breakthroughs may provide evidence that subtype selectivity is indeed possible, it is clear that current screening paradigms are inefficient and novel approaches are needed. Some thoughts on future directions for sodium channel drug discovery are provided at the end of this section.

A-803467: a subtype selective blocker of Na_v1.8

The first genuinely subtype selective small molecule sodium channel blocker to be described in the scientific literature was A-803497 ([5-(4-chlorophenyl)-N-(3,5-dimethoxyphenyl)furan-2-carboxamide]).¹³⁴ A-803497 was discovered by a team of Abbott and Icagen scientists with an iterative screening strategy, using a Na_v1.8 isotopic flux assay, and whole cell voltage clamp to establish structure activity relationships for both potency and selectivity of Na_v1.8 block.^{134,135} A-803497 blocks hNa_v1.8 in a moderately state-dependent manner, with an IC₅₀ for block of the channel in the resting state (IC_{50 rest}) of 79 nM, and an IC₅₀ for block in the inactivated state (IC_{50 inact}) of 8 nM. Block also appeared dependent on species and cellular context, with lower potency against rat Na_v1.8 (IC_{50 inact} = 45 nM) and native TTX-resistant sodium current in rat DRG neurons (IC_{50 inact} = 140 nM). Interestingly, unlike most small molecule sodium channel blockers, inhibition of hNa_v1.8 by A-803497 was not frequency dependent, possibly indicating a dif-

ferent mode of interaction compared with classical local anesthetic-like sodium channel blockers.¹³⁴ In contrast to the impressive potency measured against hNa_v1.8, A-803497 appeared considerably less potent against other closely related voltage-gated sodium channels. Under comparable recording conditions (holding potential = V_{1/2} inactivated), the Na_v1.x: Na_v1.8 selectivity ratios were 923, 306, 918, and 843 for hNa_v1.2, hNa_v1.3, hNa_v1.5, and hNa_v1.7, respectively. In vivo, A-803497 significantly reduced spontaneous and evoked firing of spinal dorsal horn neurons in spinal nerve ligated rats.¹³⁶ In behavioral pain models, A-803497 attenuated mechanical allodynia in the L5/L6 spinal nerve ligation and chronic constriction injury models of neuropathic pain, reduced thermal hyperalgesia in the complete Freund's adjuvant (CFA) model of inflammatory pain and suppressed acute mechanical nociception. Cold allodynia was also reduced in the chronic constriction injury model. Free plasma concentrations at efficacious doses in the spinal nerve ligation model were in close agreement with *in vitro* estimates of potency against TTX-resistant currents in rat DRG. Given the high degree of selectivity of this compound, these data strongly support a role for Na_v1.8 in a variety of pain states. Furthermore, the finding that A-803497 did not significantly alter motor coordination at and above efficacious doses may provide the first direct experimental evidence to suggest that improvements in subtype selectivity will translate into improved safety/tolerability of sodium channel blockers.

Subtype selective sodium channel modulators from Vertex

In December 2005, GlaxoSmithKline and Vertex Pharmaceuticals announced that they had entered into an agreement to develop and commercialize VX-409, a novel, subtype selective sodium channel modulator for the treatment of pain (<http://investors.vrtx.com/releasedetail.cfm?ReleaseID=233027>). VX-409 was described as an orally bioavailable, highly active compound with a good safety profile in nonclinical models of both neuropathic and inflammatory pain. However, details of the structure of the compound or the target sodium channel were not disclosed. Phase I clinical development of VX-409 was expected to be initiated early in 2007. However, by 2007, GlaxoSmithKline had discontinued the preclinical development of VX-409 for the treatment of pain, although the reasons for discontinuation were not disclosed, and the agreement between the two companies was terminated by April 2008.

Novel Na_v1.7 blockers from Merck

Using a fluorescence resonance energy transfer (FRET) assay, scientists at Merck identified a series of benzazepinone sodium channel blockers.^{137–140} Compounds from this family potently inhibited veratridine-induced depolarization in HEK293 cells stably expressing

hNa_v1.7 channels. Interestingly, some members of this family displayed modest selectivity for Na_v1.7 in comparison with Na_v1.8 and the cardiac Na_v1.5 channel. For example, Compound 4¹⁴⁰ (also known as Compound 32¹³⁹) inhibited the Na_v1.7 FRET signal with an IC₅₀ value of 0.03 μM. In similar FRET-based assays, however, Compound 4 appeared less potent at blocking Na_v1.8 (IC₅₀ of 0.3 μM [i.e., 10× selective]) and Na_v1.5 (IC₅₀ of 0.18 μM [i.e., 6× selective]). Other compounds, such as Compound 7 and Compound 9, although less potent against Na_v1.7, appeared slightly more selective. The interaction of Compound 4 with Na_v1.7, Na_v1.8, and Na_v1.5 channels was further characterized in whole cell electrophysiology. Minimal block was observed when compound 4 was applied to hNa_v1.7 channels at –100 mV. In contrast, the IC₅₀ for block of Na_v1.7 at –65 mV was 0.55 μM, suggesting that compound 4 interacts selectively with channels in the inactivated state. Compound 4 was less potent at inhibiting hNa_v1.5 and hNa_v1.8 channels; IC₅₀ values for block of inactivated hNa_v1.5 and hNa_v1.8 were 4.3 μM and 5.5 μM, respectively. These findings were in close agreement with observations from the fluorescent assays and suggested that Compound 4 is a potent, state-dependent Na_v1.7 blocker that exhibits approximately 10-fold selectivity for Na_v1.7 in comparison with Na_v1.5 and Na_v1.8. Consistent with an important role for Na_v1.7 in pain transmission/sensation, Compound 4 (also known as Compound 32) proved to be highly efficacious in a rat spinal nerve ligation model of neuropathic pain. When dosed orally at 10 mg/kg, Compound 32 elicited significant reversal of allodynia at 2 h postdose (% reversal).¹³⁹ In 2008, Merck scientists described a related series of imidazopyridines.¹⁴¹ As for the parent benzazepinone series, several members of the imidazopyridine family exhibited modest selectivity for Na_v1.7 in comparison with Na_v1.8 (up to 7× [e.g., Compound 43]). The selectivity of these compounds for Na_v1.7 in comparison with other sodium channel subtypes has not been reported.

FUTURE DIRECTIONS

As can be seen from the preceding section, very few examples of subtype selective sodium channel blockers exist in the scientific literature. Although there has been some progress, it is clear that current screening paradigms are less than adequate. Although the exact reason(s) are not clear, it seems highly likely that much of this inadequacy stems from limitations of currently available assays. Cell based, functional, fluorescence, or ion flux-based assays are typically the assays of choice for high throughput sodium channel screening.^{137,142–145} Although well suited to the screening of large compound collections, these assays have a number of significant limitations that may ultimately impact the probability of

identifying subtype selective sodium channel blockers. For example, although accurate for the most part, assays reliant on membrane potential dyes are prone to artifacts. Fluorescent compounds, compounds that quench the fluorescence of the reporter dye, compounds causing precipitation of the dye, toxic compounds, ionophores, and membrane permeabilizing agents will all result in erroneous activity in fluorescent assays. Time wasted following erroneous hits will ultimately reduce the chances of success. However, these limitations are not unique to sodium channel screening and are unlikely to be the major reason for the industry-wide inability to identify subtype selective sodium channel blockers. A more likely explanation is that the assays commonly used for sodium channel screening are inherently biased toward detection of nonselective “local anesthetic-like” compounds.

The observation that currently available assays are inherently biased toward detection of local anesthetics is not at all surprising. The resting membrane potential of sodium channel-expressing cell lines is typically around -40mV , which favors sodium channel inactivation and local anesthetic binding. Numerous studies have demonstrated the high sensitivity of commonly used cell-based functional assays to local anesthetics and related compounds.^{137,142–144} However, few studies have rigorously explored the sensitivity of commonly used assays for mechanistically novel sodium channel modulators, such as the gating modifier spider toxins protoxin I and protoxin II, for example (see below). Although activity of protoxin I and protoxin II has been demonstrated in a voltage ion-probe reader (VIPR) FRET-based assay, the potency of these peptides appeared highly dependent on the duration of the assay.^{146,147} It is therefore possible that, unless suitably optimized, high throughput fluorescent assays may not be able to reliably detect compounds with protoxin II-like activity. Of course, even if all commonly used high throughput sodium channel assays were capable of detecting compounds with novel mechanisms, the difficult task remains of separating the mechanistically novel compounds from the nonselective local anesthetic-like compounds. Given the high sensitivity of these assays for local anesthetic compounds, it seems that in all likelihood, nonselective local anesthetic-like compounds will far outnumber the potentially more interesting novel compounds. Finding the “needles” in this “haystack” of nonselective compounds will remain a major challenge.

In our opinion, the search for subtype selective sodium channel blockers would be greatly facilitated by the development of novel assays compatible with high throughput screening (HTS), with clearly demonstrated ability to detect mechanistically novel agents, and preferably with the ability to discriminate between mechanistically novel compounds and local anesthetics. Al-

though electrophysiological assays could be configured to identify compounds acting via any conceivable mechanism, even the highest throughput electrophysiology assays (e.g., Ionworks Quattro) are not truly HTS compatible.¹⁴⁸ A major stumbling block for development of novel assays to date has been a lack of suitable tools for assay validation. However, the spider toxins, protoxin I, protoxin II, and huwentoxin 4, have recently been identified as mechanistically novel $\text{Na}_v1.7$ blockers, and these peptides may therefore represent useful tools for development and validation of new assays.^{147,149–151}

These peptides inhibit sodium channel function by shifting the voltage-dependence of gating to more depolarized potentials (i.e., they are gating modifiers, not pore blockers, and they are mechanistically very different from local anesthetics). These spider toxins bind at a site close to the voltage sensor, in a region of the channel that is distinct from the local anesthetic binding site, which exhibits a relatively low level of conservation across the various sodium channel subtypes.^{151–153} This lack of conservation is reflected in the unique selectivity profile of protoxin II. According to recent publications, protoxin II is between 10-fold and greater than 100-fold selective for $\text{Na}_v1.7$ in comparison with all other voltage dependent subtypes.^{149,154} Thus, compounds binding at sites defined by gating modifier toxins such as protoxin II offer the potential for a degree of subtype selectivity far beyond that seen to date with local anesthetic-like compounds. Recently, scientists from Merck have described an ¹²⁵I-protoxin II binding assay.¹⁴⁹ In this assay, ¹²⁵I-protoxin II bound with high affinity to $\text{hNa}_v1.7$ and binding could be displaced with unlabeled protoxin I and protoxin II, with affinities of 680 and 389 pM, respectively. Interestingly, protoxin binding could not be displaced with tetrodotoxin, veratridine, α -scorpion toxins (Lqh α IT, Ltx-004), the sea anemone toxin anthopleurin B, β -scorpion toxins (C ssII , C ssIV), brevetoxin, deltamethrin, or the local anesthetics tetracaine or mexiletine.^{146,149} Furthermore, protoxin II binding could not be demonstrated on cells expressing $\text{Na}_v1.5$. Thus, this assay is sensitive to protoxins and insensitive to local anesthetic-like agents. These findings suggest that the protoxin II binding assay may be well suited for identification of mechanistically novel, subtype selective sodium channel blockers. However, whether it will be possible to identify small molecules that bind to the protoxin II site and modify channel function in a subtype selective manner remains to be determined.

CONCLUSIONS

Sodium channel blockers have proven useful in the treatment of neuropathic pain. However, the use of currently available drugs is often limited by incomplete

efficacy or poor tolerability. Due to the omnipresent role of sodium channels in vital physiological functions in addition to nociception, some form of selectivity of blockade is a safety requirement. To the extent that currently marketed sodium channel blockers are selective, it is on the basis of use-dependent inhibition of rapidly cycling channels. The degree of selectivity attainable with this strategy is limited because the channel motif targeted is common to all subtypes. An alternative approach, using different screening strategies to identify molecules that bind to distinctive channel subtype sequences in regions of structural divergence, is promising. Complicating this strategy, however, controversy exists regarding which channel subtypes are critical in the maintenance of neuropathic pain. This topic is of great ongoing interest in the field, and the reader is referred to additional recent reviews for further reading.¹⁵⁵⁻¹⁶⁴

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