

Voltage Gated Sodium Channel Blockers: Potential Treatment for Neuropathic Pain

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Voltage-gated sodium channels (VGSCs) in sensory neurons play a crucial role in neuropathic pain. Following nerve injury, alterations in the expression, distribution, kinetics and voltage-dependence of these sodium channels in sensory neurons can lead to alteration in initiation and propagation of electrical impulses in a way that contributes to enhance pain perception. Electrophysiological and pharmacological studies have revealed that specific sodium channel subtypes particularly Nav1.3, Nav1.7, Nav1.8 and Nav1.9 are predominantly expressed and involved in the peripheral nociceptive neurons associated pain signalling. Moreover, a human studies have shown that gain of function mutations in Nav1.7 lead to enhanced pain while loss of function mutations lead to complete insensitivity to pain. The clinical usefulness are limited by their off-target adverse effects. Development of subtype selective VGSCs blockers might be an effective approach for the treatment of neuropathic pain. This review will enlighten the role of sodium channels in neuropathic pain and development of newer subtype selective sodium channel blockers for neuropathic pain.

Introduction

Neuropathic pain is a chronic, debilitating condition that arise from injury or damage in the nervous system. International Association for the Study of Pain (IASP) defines neuropathic pain as "pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral or central nervous system (CNS)"¹. Most prominent causes are trauma, diabetic neuropathy, viral infection (post-herpetic neuralgia, AIDS) or chemotherapeutic agents. Although the exact mechanism of neuropathic pain is still unclear, there are strong evidences suggesting that hyperexcitability in damaged sensory neurons play important role in neuropathic pain². Hyperexcitability can give rise to ectopic firing, which is characterised by hyperalgesia, allodynia and persistent pain syndrome. Electrophysiological studies revealed that alteration in gating kinetics and voltage dependent properties of specific subtypes of VGSCs can lead to repetitive firing³. Moreover, recent scientific approaches by several molecular genetic studies like transgenic animals, knockdown studies and siRNA have confirmed that subtype VGSCs like Nav1.3, Nav1.7, Nav1.8 and Nav1.9 are appeared to be involved in different pain condition⁴. Sodium channel blockers like carbamazepine, lidocaine and amitriptyline are proved to be effective in treatment of neuropathic pain. However, these drugs are not developed as an analgesic agent. Therefore, these agents are lacking the specificity for blocking the particular sodium channel subtypes. This kind of pharmacotherapy often produces CNS and cardiovascular

side effects, which limit their wide clinical use. Recently, the development of subtype selective sodium channel blockers have not shown only better therapeutic index, but also exhibit greater efficacy in specific pain syndromes.

Voltage Gated Sodium Channel

VGSCs are heterotrimeric protein complexes comprised of one large pore-forming α subunit (260 kDa) and two auxiliary β subunits (33-45 kDa). The VGSCs α subunit consist of transmembrane helices arranged in four homologous domains, which is mainly responsible for function of sodium channel. To date, nine subtypes of α subunits (Nav1.1-Nav1.9) and their distribution in the central and peripheral nervous systems have been identified in mammals. However, β subunits (β_1 - β_4) are composed of single transmembrane segment and a larger extra cellular immunoglobulin like domain, which is important for surface expression and modulation of α subunit gating property⁵. Functionally, sodium channels are responsible for the generation and propagation of action potential in excitable cells. Sodium channels exist in three distinct states: open, closed and inactivated. In response to membrane depolarization, activation of sodium channels allow the rapid influx of Na^+ ions leading to upstroke of action potential. During depolarization, sodium channels rapidly get inactivated within few millisecond and Na^+ influx declines. When membrane potential is repolarized to resting membrane potential, recovery of sodium channels from inactivated state to closed state occurs, and again available to open in response to membrane depolarization⁶. The VGSCs family can be classified into two main groups based on its sensitivity to

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Table 1: Classification of VGSCs

Name	TTX sensitivity	Distribution	Involvement in neuropathic pain
Nav1.1	Yes	CNS, Dorsal root ganglia (DRG)	Not involved
Nav1.2	Yes	CNS	Not involved
Nav1.3	Yes	Embryonic CNS, Injured DRG	Involved
Nav1.4	Yes	Skeletal muscle	Not involved
Nav1.5	Moderate	Heart, Embryonic CNS	Not involved
Nav1.6	Yes	DRG, Motor neurons	Not involved
Nav1.7	Yes	DRG, Sympathetic ganglia	Involved
Nav1.8	No	DRG	Involved
Nav1.9	No	DRG, Low level in CNS	Involved

tetradotoxin (TTX). TTX-sensitive includes (Nav1.1-Nav1.4, Nav1.6, Nav1.7) and TTX-resistant includes (Nav1.5, Nav1.8, Nav1.9) ^{7, 8}. The TTX sensitivity, distribution and involvement in neuropathic pain of VGSCs are summarized in table 1.

Sodium Channels in Neuropathic Pain

Evidences indicate that abnormal excitability of sensory neurons after axonal injury is associated with an increase in density of sodium channels⁹. By studying mRNAs encoding and using RT-PCR, in situ hybridization studies, it has been estimated that at least six mRNAs encoding different sodium channels are expressed in sensory neurons, which include Nav1.1, Nav1.3, Nav1.6–Nav1.9¹⁰. Nav1.1 and Nav1.6 are also expressed at high levels by other neurons within CNS, while distribution of Nav1.3, Nav1.7, Nav1.8, and Nav1.9 are limited to peripheral nociceptive neurons⁶. The following section deals with the nociception associated TTX-sensitive (Nav1.3, Nav1.7) and TTX-resistant (Nav1.8, Nav1.9) sodium channels, which contributes to pain signalling.

Nav1.3

Nav1.3 is a TTX-sensitive channel expressed in embryonic neurons, but significantly upregulated in axotomized sensory neurons^{11, 12}. Nav1.3 channel exhibits fast activation and inactivation kinetics and rapid recovery from inactivation. TTX-sensitive sodium currents in axotomized sensory neurons recover from inactivation four times faster than control TTX-sensitive currents¹³. Nav1.3 channels have been localized within distal axon tips in experimental neuromas in rats¹⁴ and in human neuromas¹⁵. Therefore ectopic firing observed within neuromas is because of up-regulation of Nav1.3 expression in large diameter A β and A δ fibres of axotomized sensory neurons³. Antisense knockdown of Nav1.3 failed to attenuate the pain-related behaviour in spinal cord injury and chronic constriction injury model¹⁶. It could be difficult to determine the precise role of Nav1.3 channels in acute, inflammatory and neuropathic pain conditions without a specific blocker.

Nav1.7

Nav1.7 is a TTX-sensitive channel highly expressed in

sensory neurons as well as in sympathetic ganglia. Nav1.7 channel exhibits fast activation and inactivation kinetics, but in contrast to other TTX-sensitive current, it substantially slower recovery from fast-inactivation⁶. Slow closed-state inactivation of Nav1.7 yields a substantial ramp current in response to small ramp depolarization^{17, 18}. These biophysical properties are thought be important in setting the threshold for the generation of action potential in small diameter sensory neurons. It was reported that spinal nerve ligation (SNL) model of neuropathic pain is associated with down regulation of mRNA expression and protein level of Nav1.7 channel¹². In addition similarly proportion of TTX-S current is also attenuated in small sensory neurons after axotomy¹³. By contrast in a rat model of diabetic neuropathy, expression of mRNA and protein level of Nav1.7 is significantly up-regulated and sensory neurons exhibit larger TTX-S currents and larger ramp current densities¹⁹. These studies indicate that alteration in expression of Nav1.7 contributes to different neuropathic conditions.

The most exciting finding in human studies has advanced our understanding the contribution of sodium channels to pain. Gain-of-function mutations of SCN9A, the gene which encodes sodium channel Nav1.7 have been identified in patients with two severe pain syndromes, inherited erythromelalgia (IE) and paroxysmal extreme pain disorder (PEPD), while loss-of-function mutations of SCN9A have been identified in patients with congenital insensitivity to pain and an impaired sense of smell^{20, 21}. IE is characterized by burning pain and hot skin flashes²², which causes significant hyperpolarizing shifts in the voltage dependence of activation^{23, 24}. PEPD is characterized by severe burning rectal, ocular and submandibular pain sensation²⁵, which causes depolarizing shifts in voltage dependence of steady-state inactivation and causes incomplete inactivation in Nav1.7, leading to prolonged persistent currents. The alteration in the biophysical property of the IE and PEPD mutation suggest that Nav1.7 channel is involved in severe chronic pain in humans.

Nav1.8

Nav1.8 is another sodium channel preferentially expressed

in small diameter sensory neurons and trigeminal ganglion neurons^{26, 27}, but unlike Nav1.3 and Nav1.7 is TTX-R. Nav1.8 channel exhibits slower rate of depolarized activation and steady state voltage dependence of inactivation kinetics with rapid recovery from inactivation²⁷. However, studies on sensory neurons from Nav1.8-null mice indicate that 80-90% of the inward current responsible for action potential upstroke is mainly due to depolarized activation of Nav1.8²⁸. In addition, voltage dependence of slow inactivation rates allow Nav1.8 channels to remain open following action potential upstroke, which is responsible for shaping the action potential waveform in nociceptive neurons²⁹. Recently, it has been found that Nav1.8 is not inactivated by cold perception like other TTX-S channel. These findings suggest that Nav1.8 is essential for the perception of cold pain³⁰. Several studies have shown that the expression of Nav1.8 mRNA and protein are substantially down-regulated in axotomized sensory neurons³¹, but there is a significant increase in Nav1.8 immuno-reactivity in uninjured axons³². This has been shown to be the result of a redistribution of Nav1.8 channels, which can lead to spontaneous firing in uninjured neurons. In addition, the ectopic firing in uninjured neurons are more resistant to TTX than control neurons, which suggests that the primary afferent sensory neurons containing Nav1.8 contributes to hyperactivity of uninjured neurons in neuropathic pain³³. Recently, it has been shown that patients with chronic neuropathic pain show increase Nav1.8 channel expression proximal to peripheral injury site¹⁵. Several antisense experimental studies have manifested that Nav1.8 antisense could attenuates the pain in several models of neuropathic pain³⁴, while siRNA selective knockdown of Nav1.8 could reverse mechanical allodynia caused by chronic constrictive injury in rats, suggesting that Nav1.8 is essential for the development of hyperexcitability following nerve injury³⁵. By contrast, other studies on Nav1.8-null mice failed to attenuate neuropathic pain response to injury, which might be due to up-regulation of expression of TTX-S channel for compensatory loss of Nav1.8 channel^{36, 37}.

Nav1.9

Nav1.9 is TTX-resistant channel prominently expressed in small diameter sensory neurons³⁸. Nav1.9 channel exhibits voltage dependent activation close to resting membrane potential (-70 mV) and show steady state inactivation at relatively positive potential (-45 mV). These kinetic properties suggest that activation of Nav1.9 may prolong the response to subthreshold depolarization and generate a persistent current³⁹. Further, electrophysiological studies on sensory neurons of Nav1.9 null mice have shown that it lowers the threshold for action potential electrogenesis and produces persistent current leading to hyperexcitability²³. Although inflammation induces up regulation of Nav1.9 gene,

expression of Nav1.9 mRNA and protein are substantially down-regulated in axotomized sensory neurons as well as in several animal models of neuropathic pain^{40, 41}. However, several results from anti-sense as well as knockout experiments failed to demonstrate role of Nav1.9 in neuropathic pain signalling^{42, 43}. These data indicate that though Nav1.9 is involved in inflammatory pain, its involvement in neuropathic pain is still unclear. The expression, biophysical property and activity of sodium channel subtypes in neuropathic pain are briefly summarized in table 2.

Sodium Channel Blockers

VGSC blockers are proved to be effective in treatment of neuropathic pain. Currently used drugs are acting by either 'use-dependent' (i.e. affinity is increase with respect to repetitive firing) or 'state-dependent' (i.e. drug molecule have the affinity towards specific conformation, which can be resting, activated or inactivated) inhibition. Blockade of VGSCs results in decreasing ectopic discharge and allowing normal impulse generation³³.

Anticonvulsants

Carbamazepine was first approved for treatment of trigeminal neuralgia in the 1970s. It exerts membrane-stabilizing property by blocking inactivated state of sodium channels, reducing neuronal firing in sensitized C-fibres⁴⁴. Randomized clinical trial explained the effectiveness of carbamazepine against painful diabetic neuropathy and Guillain Barre Syndrome⁴⁵. Recently, it has been found that carbamazepine reduces the symptoms of PEPD, but not IE. This effect could be explained by its blocking inactivated state of sodium channel. However, carbamazepine treatment has several complications due to pharmacokinetic factors like induction of microsomal enzymes which may influence other drug metabolism. Its metabolite carbamazepine-10, 11-epoxide (Oxcarbazepine) also exhibits anti-neuralgic activity and avoiding the hepatic enzyme induction⁴⁶.

Phenytoin exerts membrane-stabilizing properties by blocking sodium channels similar to carbamazepine. It is useful in diabetic neuropathy and trigeminal neuralgia⁴⁷. However, it is associated with numerous adverse effects including rash, gingival hypertrophy, horizontal nystagmus and teratogenicity, which limit its use⁴⁸.

Lamotrigine, NMDA receptor antagonist, also has sodium channel blocking activity. It acts by stabilizing a slow inactivated conformation of sodium channels and suppressing the release of glutamate from presynaptic neurons⁴⁹. It is useful in painful diabetic neuropathy, central post-stroke pain, HIV-related painful neuropathy and in spinal cord injury⁴⁸.

Review Article

Table 2: Expression, biophysical property and activity of sodium channel subtypes in neuropathic pain

Type	Expression in sensory neurons	Biophysical property	Activity in neuropathic pain
Nav1.3	Large diameter A β -fibres and A δ -fibres	Rapid activation and inactivation, rapid recovery from inactivation	Reduce the threshold for action potential generation, increased firing frequencies
Nav1.7	C-fibres, A β -fibres and A δ -fibres	Rapid activation and inactivation, but slowly recovery from inactivation	Slow depolarizing property, acts as an amplifier of pain signalling
Nav1.8	C-fibres and A δ -fibres	Slower activation and faster inactivation, major contributors in upstroke of action potential	Facilitating repetitive firing in sensory neurons upon sensory stimulation
Nav1.9	C-fibres	Negative activation threshold and depolarized inactivation	Respond to sub-threshold stimuli and generates persistent current

Topiramate is a novel broad spectrum anticonvulsant drug useful in neuropathic pain. It shows multiple target mechanisms, which include use-dependent blockade of voltage activated sodium channels, blocking glutamate neurotransmission and enhancing GABAergic transmission at voltage gated calcium channel. In seltzer model of mononeuropathy in rats, topiramate shortens the period of allodynia. It also promotes nerve recovery in post-injury condition, which shows its neuroprotective effect and found to be effective in diabetic neuropathy⁵⁰.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are the drugs that act by multiple mechanisms. TCAs increase synaptic serotonin and norepineprine level by inhibiting the uptake and enhancing the descending analgesic pathway⁴⁶. The most recent study has shown that TCAs block batrachotoxin binding site (site-2) on sodium channel and produce analgesic action. TCAs also bind to the local anaesthetics receptor and cause blockade of the open and inactivated state of the sodium channel at therapeutic drug concentration⁵¹. TCAs (amitriptyline, duloxetine, imipramine, nortriptyline, doxepine) are effective against postherpetic neuralgia, painful diabetic neuropathy and central poststroke pain. TCAs are not effective in HIV-associated neuropathy. Recently, duloxetine is approved for the treatment of painful diabetic neuropathy. TCAs exert anti-cholinergic side effects like sedation, confusion, constipation, and serious cardiovascular effects such as conduction blocks, tachycardia, and ventricular arrhythmias^{48, 52}.

Local Anaesthetics

Lignocaine is use dependent sodium channel blocker. It exhibits both voltage dependent and state dependent blocking property and suppresses abnormal discharge generated at ectopic pacemaker site⁵³. Lignocaine have more affinity to inactivated state of sodium channel than resting state and proved to be effective in the treatment of postherpetic neuralgia and painful diabetic neuropathy. Because of its lipophilic in nature, i.v. infusion of lignocaine binds non-specifically to sodium channels in neural, gastrointestinal and cardiac tissues, which lead to a number of side effects. Therefore, lignocaine patch 5% is approved by the USFDA for the treatment of post herpetic neuralgia. Mexiletine is a close structural analogue of lignocaine and

found to be effective in painful diabetic neuropathy⁵².

Newer Classes of Sodium Channel Blockers

All currently used sodium channel blockers are non-selective, because they were not developed as analgesic agents. Moreover, the clinical usefulness of these drugs in the treatment of neuropathic pain is limited because of their CNS (ataxia, confusion and sedation) and cardiovascular side effects like arrhythmia. Recently, the development of newer classes of sodium channel blockers have focused on mainly two objectives: 1) preventing the drug distribution to CNS 2) Targeting the selective subtype sodium channels.

A-803467 is a selective Nav1.8 channel blocker, which shows voltage dependent blocking property. It acts by state dependent manner having more affinity towards inactivated state than resting state. *In vitro* study on injured sensory neurons showed reduction in action potential firing, while *in vivo* experiment revealed that A-803467 significantly attenuated the allodynic response in acute, inflammatory and neuropathic pain model⁵⁴. Recent study have shown that systemic administration of A-803467 decreased both mechanically evoked and spontaneous firing of spinal neurons in SNL model⁵⁵. Although A-803467 proved to be effective in blocking Nav1.8 current, the poor bioavailability limits its use in humans. However the identification of this compound has stimulated the development of subtype selective sodium channel blocker to improve efficacy for treatment of neuropathic pain.

Ambroxol is a secretolytic compound useful in respiratory disease, which blocks both recombinant and native sodium current. Interestingly, it inhibits TTX-resistant (Nav1.8) channels more effectively than TTX-sensitive channels in sensory neurons. The potency of sodium channel blocking activity is relatively high as compared to local anaesthetics (lignocaine or benzocaine)⁵⁶. In neuropathic and inflammatory pain model of rat, ambroxol effectively suppress the pain symptoms⁵⁷.

Benzazepinone derivative is a series of selective Nav1.7 channel blocker developed by Merck scientists using fluorescence resonance energy transfer (FRET) assay. It exhibits state dependent blocking property and inhibits

veratridine induced depolarization in HEK293 cells stably expressing Nav1.7 channel. Oral administrations of these compounds in rat model of neuropathic pain have attenuated the neuronal firing. However, some members of this family also demonstrate selectivity for Nav1.8 and the cardiac Nav1.5 channel⁵⁸.

CDA54, a peripherally acting sodium channel blocker has pronounced blocking action on inactivated state than resting state. It selectively blocks Nav1.7 and Nav1.8 channel and reduces spontaneous firing in nociceptive neurons. Interestingly, CDA54 has lower brain penetrating property and thus displayed low CNS side effects than mexiletine. Moreover, it significantly reduced neuropathic pain, but did not affect acute nociception, motor co-ordination and cardiac electrophysiological parameters including conduction⁵⁹. This finding suggests that sodium channel blockers having selectivity for subtype sodium channel and less CNS penetrating property display improved safety profile with minimal side effects.

Furan piperazine derivative blocks TTX-resistant current in rat sensory neurons and Nav1.8 current in HEK293 cells of recombinant mouse stably expressing human Nav1.8 channel. Moreover, these compounds were 100 to 1000 fold more potent in blocking Nav1.8 channel compared to mexiletine or lamotrigine. It also displayed efficacy in the chung model of neuropathic pain. However, some compounds from this family displayed modest selectivity for Nav1.2 and Nav1.5 channel in HEK293 cells⁶⁰.

Lacosamide is a newer anticonvulsant agent approved for partial seizures. It can differentiate between the resting and inactivated state of sodium channel and preferentially binds to the slow inactivated state of sodium channel. Lacosamide selectively block Nav1.3, Nav1.7 and Nav1.8 subtypes and found to be more effective than carbamazepine and lignocaine⁶¹. It produced dose dependent anti allodynic response in rat model of central and trigeminal neuropathic pain and also reduced chronic allodynia like behaviour in spinal injured rats⁶². It has shown positive results in phase 2 and 3 clinical trial in painful diabetic neuropathy⁶³.

M58373 is a novel compound, which acts by inhibiting neurotoxin binding to the site 2 of VGSC. Pre-clinical data suggest that M58373 inhibits the effect of veratridine-induced release of substance P from dorsal root ganglion cells. In addition, M58373 has shown more antinociceptive action and wider therapeutic window than mexiletine in neuropathic pain model⁶⁴.

2-[4-(4-Chloro-2-fluorophenoxy) phenyl]-pyrimidine-4-carboxamide (PPPA) is a broad spectrum, state-dependent Na channel blocker. It binds with high affinity to

the inactivated state of sodium channel. Recent study has shown that PPPA was approximately 1000 times more potent, 2000-fold faster binding kinetics and wider therapeutic window than carbamazepine and lamotrigine⁶⁵.

Ralfinamide (NW-1029) acts by blocking use dependent sodium channel. In addition, it has greater affinity for TTX-resistant than TTX-sensitive channels⁶⁶. It also displayed selectivity for Nav1.3, Nav1.8 and Nav1.9 channel and having affinity for site 2 of the sodium channels. It antagonizes NMDA receptor and inhibits the release of substance P. Ralfinamide attenuated allodynic response in animal models of inflammatory and neuropathic pain. It is under phase II clinical trial^{67, 68}.

4-arylimidazole carbamate derivative binds with high affinity to site 2 of the sodium channel and is proved to be efficacious in carrageenan induced hyperalgesia and chronic constrictive injury model of neuropathic pain⁶⁹.

μO-conotoxin (MrVIB), a 31 amino acid peptide from marine cone snails has higher affinity to block Nav1.8 channel than Nav1.9 or TTX-sensitive channel. MrVIB has at least 10-fold greater selectivity for Nav1.8 than other subtypes of VGSCs. Intrathecal infusion in neuropathic and chronic inflammatory pain model reduced the allodynic and hyperalgesic response without affecting motor function⁷⁰. TTX has proved to be efficacious for treating cancer pain in clinical trial and abolished repetitive firing in animal model of neuropathic pain, but the major drawback with TTX therapy is systemic toxicity⁷¹.

Conclusion

Neuropathic pain represents major unmet medical need which occurs due to diverse aetiologies. Therefore, specific treatment does not exist for the same. None of the currently available drug is said to be ideal or monotherapy to treat neuropathic pain. Now a days there are tremendous increase in the number of patients associated with neuropathic pain because of several factors such as diabetes, cancer and viral infection, which ultimately add the complications in treatment strategies and emphasizing the need of searching newer and better medication for this distressing condition. The currently available sodium channel blockers showed promising effects in some forms of neuropathic pain, while its wide spread use is limited by pharmacologically undesired off-target side effects and relatively narrow therapeutic window. Advancements in the molecular biology and relevant drug discovery and designing tools led to the development of subtype selective sodium channels blocker with minimal off target effects, which are found to be very effective in pre-clinical and clinical trials. Moreover, involvement of specific sodium channel subtypes in pain signalling is not fully understood and it is prerequisite to elucidate the

Review Article

molecular and structural interactions leading to painful neuropathies for the development of better and safer medication.

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