

# Sodium Channel Inhibitors (Nav1.7, 1.8, And 1.9) For Neuropathic Pain Management

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**Abstract.** This paper explores the potential of voltage-gated sodium channels, specifically Nav1.7, Nav1.8, and Nav1.9, in the management of neuropathic pain. Neuropathic pain, a complex and chronic condition resistant to conventional treatments, poses a significant clinical challenge. Recent research has shed light on the role of these sodium channel isoforms, predominantly found in peripheral sensory neurons, as novel targets for analgesic development. In this study, we delve into the structural and functional aspects of these channels, their involvement in action potential generation and propagation, and their contribution to neuropathic pain. Furthermore, we review the development and clinical efficacy of selective sodium channel inhibitors, addressing associated challenges and discussing potential future directions in this promising field. Our paper aims to emphasize the potential of sodium channel blockers as a promising approach to neuropathic pain treatment, highlighting their role in providing targeted pain relief with potentially fewer side effects. The contributions of this study include new insights into the role of specific sodium channel isoforms, the evaluation of selective inhibitors, and an overview of the challenges and opportunities in this field of pain management.

**Keywords:** Neuropathic Pain; Sodium Channels; Nav1.7; Nav1.8; Nav1.9; Sodium Channel Blockers; Pain Management.

## 1. Introduction

Neuropathic pain poses a significant clinical challenge, affecting a substantial number of individuals worldwide [1]. It is a complex and chronic condition resulting from damage or dysfunction of the nervous system. Despite the availability of various treatment options, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants, effective management of neuropathic pain remains elusive for many patients [2]. Current treatments often come with a host of side effects and offer limited efficacy in providing relief.

According to recent data, neuropathic pain affects an estimated 7% of the global population, with a prevalence expected to rise due to an aging population and an increase in chronic diseases [3]. This highlights the urgency to explore novel therapeutic approaches to address this unmet medical need.

In this context, there has been growing interest in the role of voltage-gated sodium channels, specifically Nav1.7, Nav1.8, and Nav1.9, in the conduction of pain signals and their potential as targets for neuropathic pain management [4-8]. These sodium channel isoforms are predominantly expressed in peripheral sensory neurons involved in pain signaling, making them attractive candidates for the development of analgesics with enhanced specificity.

However, despite the promise of sodium channel blockers, there are challenges to overcome, such as ensuring selectivity, managing individual patient variability, and guaranteeing long-term safety and efficacy [9]. To address these challenges and explore the potential of sodium channel inhibitors as a promising approach to neuropathic pain treatment, this paper aims to provide a comprehensive review of the current understanding of sodium channels, their involvement in pain signaling, the development of selective inhibitors, and the associated clinical efficacy and challenges. By highlighting the shortcomings of current treatments and the potential of sodium channel blockers, this study aims to contribute to the advancement of neuropathic pain management.

Overall, a deeper understanding of the specific context and background of neuropathic pain, coupled with the potential of sodium channel blockers, will pave the way for the development of more effective and targeted interventions for individuals suffering from this debilitating condition.

## 2. Sodium Channels

### 2.1. Overview of Sodium Channels

Voltage-gated sodium channels (Nav) play a critical role in the generation and propagation of action potentials in neurons. These transmembrane ion channels are essential for the transmission of electrical signals in the nervous system and are therefore important targets for the development of drugs used to treat neuropathic pain. Sodium channels consist of  $\alpha$ -subunits, which form the pore through which sodium ions pass, and auxiliary  $\beta$ -subunits, which modulate channel function.

Sodium channels can be classified based on their sensitivity to the neurotoxin tetrodotoxin (TTX) [10]. TTX-sensitive channels include Nav1.1, Nav1.2, Nav1.3, Nav1.4, Nav1.6, and Nav1.7, which can be blocked by nanomolar concentrations of TTX. On the other hand, TTX-resistant channels such as Nav1.5, Nav1.8, and Nav1.9 require micromolar concentrations of TTX for blockage, making them effectively resistant to TTX under physiological conditions.

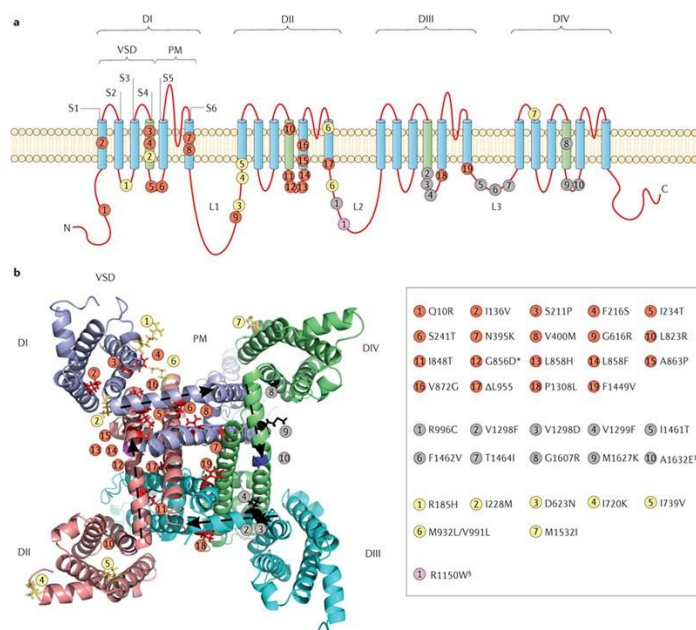
### 2.2. Specific Isoforms: Nav1.7, Nav1.8, and Nav1.9

Among the various isoforms of sodium channels, Nav1.7, Nav1.8, and Nav1.9 have gained particular attention for their role in pain signaling. These isoforms are predominantly expressed in peripheral sensory neurons involved in nociception and are implicated in the transmission of pain signals from the periphery to the central nervous system.

#### 2.2.1 Nav1.7

Nav1.7 is primarily expressed in dorsal root ganglion (DRG) neurons and sympathetic ganglion neurons [11]. Functionally, Nav1.7 channels have a low activation threshold, making them particularly sensitive to small, slow depolarizations near the resting membrane potential (see in Fig. 1) [12]. This property allows Nav1.7 channels to amplify weak stimuli, contributing to their role in pain signaling.

Genetic studies have provided strong evidence linking Nav1.7 to pain perception. Mutations in the SCN9A gene, which encodes Nav1.7, can cause a range of pain disorders, underscoring the crucial role of Nav1.7 in pain signaling. Additionally, individuals with loss-of-function mutations in SCN9A experience congenital insensitivity to pain, further highlighting the significance of Nav1.7 in pain perception.



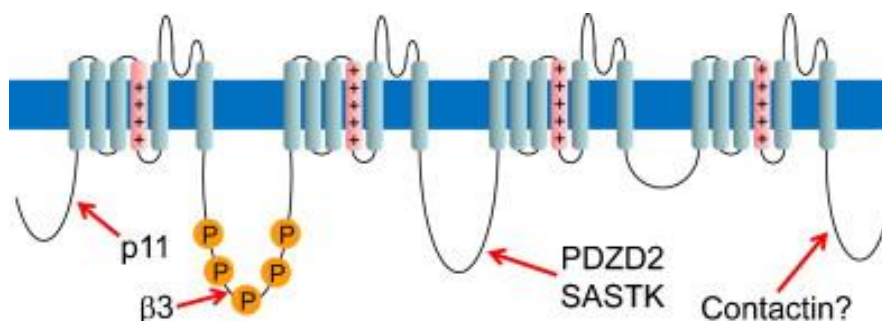
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**Fig. 1** The Nav1.7 sodium channel: from molecule to man [12].

### 2.2.2 Nav1.8

Nav1.8 channels are predominantly found in DRG neurons (see in Fig. 2) [13]. Unlike Nav1.7, these channels have a much higher activation threshold and are less sensitive to membrane depolarizations. Nav1.8 channels are also slower to inactivate and more resistant to blockage by the sodium channel inactivator tetrodotoxin. These properties allow Nav1.8 channels to remain active during prolonged stimuli and may contribute to their role in chronic pain.

Studies using genetic deletion and pharmacological approaches have demonstrated the involvement of Nav1.8 in pain signaling. Genetic deletion of Nav1.8 has been shown to reduce neuropathic and inflammatory pain in animal models, highlighting its potential as a therapeutic target.



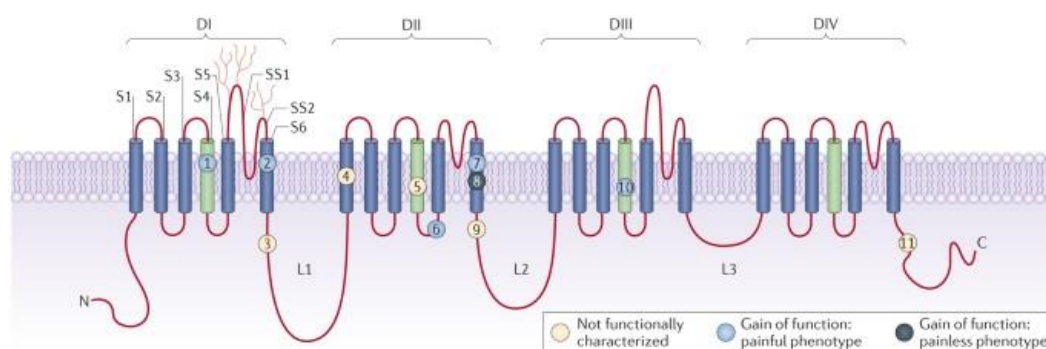
**Fig. 2** Structure of the Nav1.8 [13].

### 2.2.3 Nav1.9

Nav1.9 channels are primarily expressed in small-diameter DRG and trigeminal ganglion neurons, which are typically associated with nociception [14]. Similar to Nav1.7, Nav1.9 channels have a low activation threshold. However, they produce a persistent sodium current that is not rapidly inactivated, helping to set the resting membrane potential and modulate the response to depolarizing stimuli.

Mutations in the SCN11A gene, which encodes Nav1.9, have been associated with human pain disorders, further implicating the role of Nav1.9 in pain perception. Nav1.9 channels contribute to shaping the action potential threshold and firing frequency in nociceptors, making them potential targets for therapeutic interventions.

By understanding the structural and functional characteristics of specific sodium channel isoforms, such as Nav1.7, Nav1.8, and Nav1.9, researchers can gain insights into their roles in pain signaling and develop targeted strategies for neuropathic pain management. The next sections will delve into the distribution of sodium channels across the nervous system and further explore their involvement in action potential generation, neurotransmission, and pain signaling.



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**Fig. 3** Nav1.9: a sodium channel linked to human pain [14].

## 2.3. Sodium Channel Distribution across the Nervous System and Classifications

### 2.3.1 Distribution across the Nervous System

Voltage-gated sodium channels are expressed throughout the nervous system. Their distribution varies by isoform, with different isoforms being expressed in different types and locations of neurons.

Central Nervous System (CNS): Nav1.1, Nav1.2, Nav1.3, and Nav1.6 are primarily expressed in the CNS neurons. They play a crucial role in the initiation and propagation of action potentials in these neurons.

Peripheral Nervous System (PNS): Nav1.7, Nav1.8, and Nav1.9 are predominantly expressed in the peripheral nervous system, particularly in the dorsal root ganglion (DRG) neurons and trigeminal ganglion neurons involved in pain signaling.

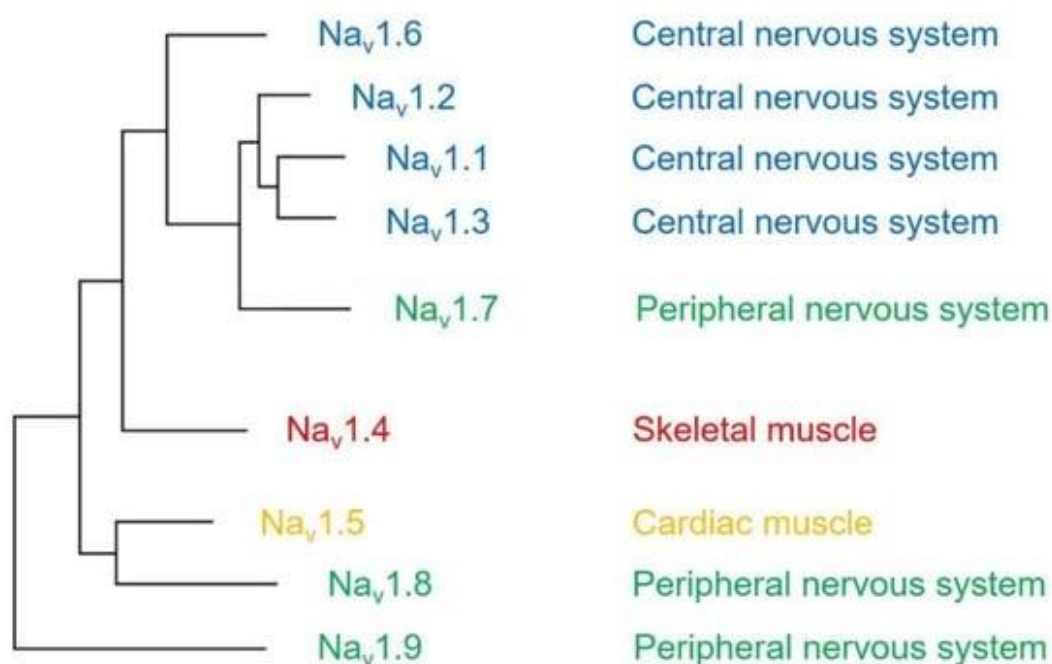
### 2.3.2 Classifications of Sodium Channels

Voltage-gated sodium channels can be classified in several ways, including by their sensitivity to the neurotoxin tetrodotoxin (TTX).

TTX-sensitive channels: These include Nav1.1, Nav1.2, Nav1.3, Nav1.4, Nav1.6, and Nav1.7. As the name suggests, these channels can be blocked by nanomolar concentrations of TTX.

TTX-resistant channels: These include Nav1.5, Nav1.8, and Nav1.9. These channels require micromolar concentrations of TTX to be blocked, making them effectively resistant to TTX under physiological conditions.

The different isoforms of sodium channels also have different biophysical properties (such as activation and inactivation thresholds, and recovery from inactivation), which contribute to their specific roles in neuronal excitability (see Fig. 4) [15].



**Fig. 4** A phylogenetic tree and tissue distribution of voltage-gated sodium channels. Isoforms predominantly expressed in the central nervous system (blue), peripheral nervous system (green), skeletal muscle (red), and cardiac muscle (orange) are highlighted [15].

## 2.4. Na<sup>+</sup> Channel's Role in Action Potential and Neurotransmission

Voltage-gated sodium (Na<sup>+</sup>) channels play a crucial role in the generation and propagation of action potentials in neurons, thereby facilitating neurotransmission.

### 2.4.1 Generation of Action Potentials

Action potentials are the primary means of long-distance communication within the nervous system. They are initiated at the axon hillock of a neuron, a region with a high density of voltage-gated Na<sup>+</sup> channels.

When a neuron is at rest, the voltage-gated Na<sup>+</sup> channels are closed, maintaining the resting membrane potential. Upon receiving a stimulus, the neuron depolarizes, and when a certain threshold

is reached, the voltage-gated Na<sup>+</sup> channels open. This allows a rapid influx of Na<sup>+</sup> ions into the cell, causing further depolarization and generating the upstroke of the action potential.

#### **2.4.2 Propagation of Action Potentials**

The depolarization caused by the influx of Na<sup>+</sup> ions during an action potential spread to adjacent regions of the neuron's membrane. This opens more voltage-gated Na<sup>+</sup> channels in these regions, causing the action potential to propagate down the neuron's axon. This wave of depolarization, followed by repolarization, is the basis for the propagation of action potentials.

#### **2.4.3 Neurotransmission**

The action potential eventually reaches the axon terminals, where it triggers the opening of voltage-gated calcium channels. The influx of Ca<sup>2+</sup> ions into the neuron prompts the release of neurotransmitters into the synaptic cleft. These neurotransmitters then bind to receptors on the post-synaptic neuron, eliciting a response that can either excite or inhibit the post-synaptic neuron.

#### **2.4.4 The Role of Different Na<sup>+</sup> Channel Isoforms**

Different isoforms of voltage-gated Na<sup>+</sup> channels contribute to different aspects of the action potential and neurotransmission. For example, TTX-sensitive channels like Nav1.7 are often involved in initiating action potentials, while TTX-resistant channels like Nav1.8 and Nav1.9 are more often involved in modulating action potential firing and pain signaling.

### **3. Nav's Role in Pain Signaling**

#### **3.1. Mechanism of Neuropathic Pain**

Neuropathic pain is a type of chronic pain that is caused by damage, disease or dysfunction of the nervous system. It can be associated with conditions such as diabetes, herpes zoster infection (shingles), cancer, stroke, multiple sclerosis, and trauma, among others.

The mechanisms underlying neuropathic pain are complex and multifaceted. They involve changes in the function and structure of neurons that enhance or prolong pain signals. These changes can occur at various levels of the nervous system, from the peripheral nerves to the spinal cord and brain.

Neuropathic pain often involves "peripheral sensitization" and "central sensitization". In peripheral sensitization, the threshold for activating peripheral nociceptors (pain-sensing neurons) decreases, meaning they can be activated by weaker stimuli. In central sensitization, neurons in the dorsal horn of the spinal cord become hyperresponsive to peripheral input, amplifying pain signals to the brain.

#### **3.2. The Role of Sodium Channels in Neuropathic Pain**

Voltage-gated sodium channels play a key role in the generation and propagation of action potentials in neurons (see in Fig. 5) [16]. They are thus integral to the transmission of pain signals from the peripheral nervous system to the central nervous system.

Specific isoforms of sodium channels, namely Nav1.7, Nav1.8, and Nav1.9, have been implicated in pain signaling. These channels are predominantly expressed in peripheral sensory neurons involved in pain signaling.

Nav1.7: Mutations in the SCN9A gene that encodes Nav1.7 can cause a range of pain disorders, suggesting that Nav1.7 plays a crucial role in pain signaling. Moreover, individuals with loss-of-function mutations in SCN9A experience congenital insensitivity to pain, further highlighting the role of Nav1.7 in pain perception.

Nav1.8: Nav1.8 channels are important for the generation of action potentials in nociceptive neurons, especially under conditions of inflammation or nerve injury. Genetic deletion of Nav1.8 can reduce neuropathic and inflammatory pain in mice.

Nav1.9: Mutations in the SCN11A gene that encodes Nav1.9 have been associated with human pain disorders. Nav1.9 channels help to shape the action potential threshold and firing frequency in nociceptors.

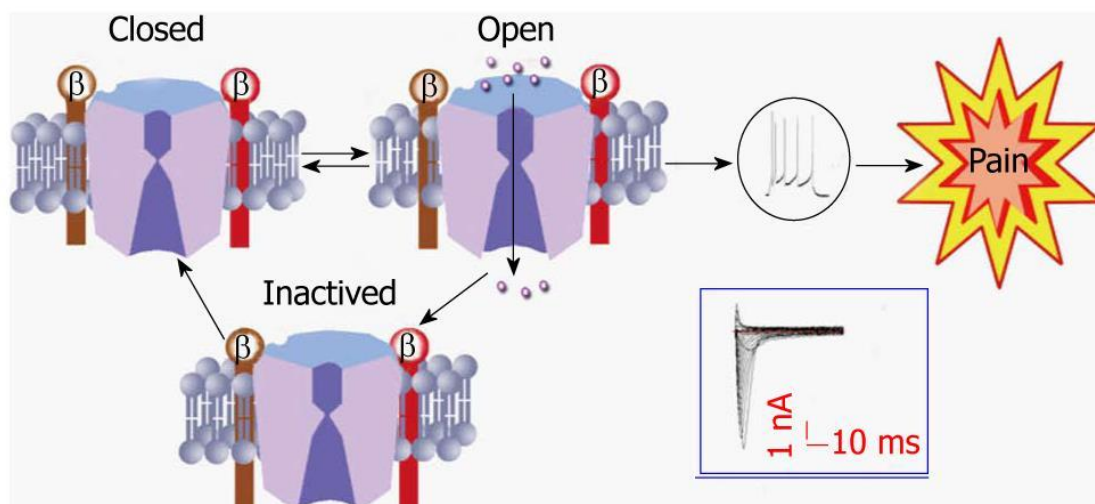


Fig. 5 A model showing the three states of the sodium channel [16].

### 3.3. Nav 1.7, 1.8 and 1.9 Rationale as a Therapeutic Target

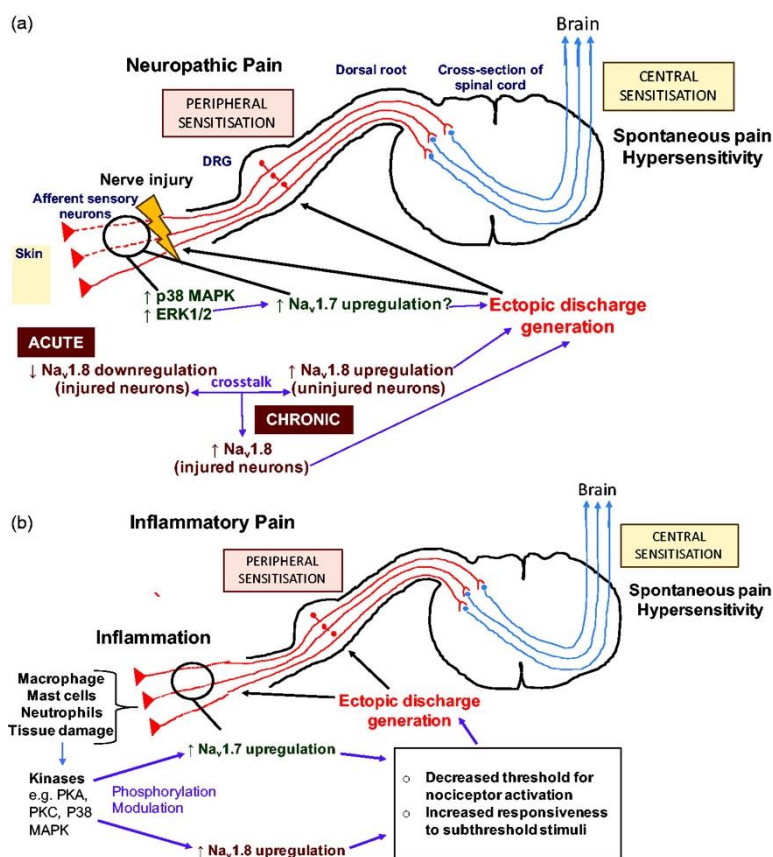


Fig. 6 Proposed mechanisms of the role of Nav1.7 and Nav1.8 in the pathophysiology of neuropathic pain and inflammatory pain [17].

Given their role in pain signaling, Nav1.7, Nav1.8 [17], and Nav1.9 have emerged as promising targets for the development of new analgesics for neuropathic pain.

Nav1.7: Given the strong genetic evidence linking Nav1.7 to pain, Nav1.7 inhibitors could potentially provide effective pain relief. Several pharmaceutical companies are developing Nav1.7 inhibitors, and some of these drugs are currently being tested in clinical trials.

Nav1.8 and Nav1.9: While the role of Nav1.8 and Nav1.9 in pain is less well defined than that of Nav1.7, these channels are still considered potential targets for pain management. Nav1.8 and Nav1.9 inhibitors could potentially be useful for treating conditions characterized by chronic pain.

In conclusion, voltage-gated sodium channels Nav1.7, Nav1.8, and Nav1.9 play key roles in pain signaling and represent promising targets for the development of new neuropathic pain treatments. A better understanding of these channels and their roles in pain could lead to the development of more effective and safer analgesics.

## **4. Inhibitors for Pain Management**

### **4.1. General Classification**

Pain management involves a range of drugs, from over-the-counter analgesics to prescription medications [18]. Among them, sodium channel blockers have been used for many years to manage pain. They can be broadly classified into two categories:

**Non-selective Sodium Channel Blockers:** These drugs, which include local anesthetics like lidocaine and carbamazepine, a drug used to treat neuropathic pain and epilepsy, block sodium channels non-selectively. They don't target a specific Nav isoform, which can lead to a variety of side effects.

**Selective Sodium Channel Blockers:** More recently, drugs that selectively target specific Nav isoforms have been developed. These selective blockers aim to offer pain relief with fewer side effects.

### **4.2. Existing Sodium Channel Blockers for Nav1.7, Nav1.8, and Nav1.9: Mechanism of Action**

In the context of neuropathic pain, Nav1.7, Nav1.8, and Nav1.9 have emerged as promising targets for the development of new analgesics [19]. Several inhibitors have been developed to selectively target these channels:

**Nav1.7:** Given the strong genetic evidence linking Nav1.7 to pain, many pharmaceutical companies are developing Nav1.7 inhibitors. These inhibitors work by binding to the Nav1.7 channel and preventing it from opening in response to a voltage change, thus blocking the propagation of pain signals.

**Nav1.8:** A selective Nav1.8 blocker, A-803467, has shown efficacy in animal models of inflammatory and neuropathic pain. It works by binding to the Nav1.8 channel and blocking the influx of sodium ions, thereby reducing the excitability of pain-sensing neurons.

**Nav1.9:** Currently, there are no specific Nav1.9 blockers available. However, ongoing research aims to develop drugs that target Nav1.9 due to its involvement in modulating the excitability of nociceptive neurons.

### **4.3. Clinical Trials and Efficacy Data**

Several Nav1.7 blockers are currently in clinical trials. For example, Biogen's BIIB074 (vixotrigine) has shown efficacy in reducing pain in patients with trigeminal neuralgia, a severe facial pain disorder, in phase II trials.

For Nav1.8, while A-803467 showed efficacy in preclinical models, it has not been tested in humans due to its poor bioavailability.

### **4.4. Side Effects and Concerns**

The main concern with sodium channel blockers, especially non-selective ones, is their potential for side effects [20]. These can include dizziness, nausea, and alterations in heart rhythm. This is due to the widespread distribution of sodium channels in the body and their crucial role in many physiological processes.

Selective sodium channel blockers are designed to minimize these side effects by targeting specific isoforms of sodium channels that are primarily involved in pain signaling. However, even these drugs can have side effects, as the targeted channels may also be expressed in other tissues. For example, Nav1.7 is expressed not only in peripheral sensory neurons but also in olfactory sensory neurons, and

there are reports of individuals with Nav1.7 loss-of-function mutations experiencing anosmia (loss of smell).

Moreover, while selective sodium channel blockers offer the promise of better efficacy with fewer side effects, achieving sufficient selectivity in a drug is a significant challenge.

## 5. Benefits and Drawbacks of Targeting Sodium Channels to Treat Neuropathic Pain

Voltage-gated sodium channels, in particular Nav1.7, Nav1.8, and Nav1.9, have emerged as promising targets for the development of new treatments for neuropathic pain. However, like all therapeutic strategies, targeting these channels has both benefits and potential drawbacks [21].

### 5.1. Benefits

**Evidence-Based Approach:** There is strong genetic evidence linking certain sodium channels, particularly Nav1.7, to pain. Individuals with gain-of-function mutations in the SCN9A gene (which encodes Nav1.7) experience severe pain disorders, while those with loss-of-function mutations in the same gene exhibit congenital insensitivity to pain.

**Targeted Pain Relief:** Sodium channels are crucial for the generation and propagation of action potentials in neurons. By selectively blocking certain sodium channels that are predominantly expressed in pain-sensing neurons, it may be possible to achieve targeted pain relief.

**Potential for Fewer Side Effects:** Non-selective sodium channel blockers can have a variety of side effects due to the widespread distribution of sodium channels in the body. By contrast, selective sodium channel blockers have the potential to minimize these side effects by specifically targeting channels that are primarily involved in pain signaling.

### 5.2. Drawbacks

**Challenges in Drug Development:** Developing drugs that selectively target specific sodium channels is a significant challenge. It requires a thorough understanding of the structure and function of these channels, as well as sophisticated drug design techniques.

**Potential Side Effects:** Even selective sodium channel blockers can have side effects, as the targeted channels may also be expressed in other tissues. For example, Nav1.7 is expressed not only in peripheral sensory neurons but also in olfactory sensory neurons, leading to a risk of anosmia (loss of smell) with Nav1.7 blockers.

**Variable Patient Response:** There is considerable variability in the way patients with neuropathic pain respond to sodium channel blockers, and some patients may not respond at all. This can be due to genetic differences, the specific nature and location of the nerve damage causing the pain, and other factors.

**Unknown Long-Term Effects:** The long-term effects of blocking specific sodium channels are not fully understood. While these drugs may provide pain relief in the short term, it is possible that they could have unexpected effects over the long term.

In summary, while targeting sodium channels offers a promising approach to treating neuropathic pain, there are significant challenges to overcome, and a thorough understanding of both the benefits and drawbacks of this strategy is crucial. Further research and clinical trials will be essential for fully exploring the potential of this approach.

## 6. Challenges and Future Directions

Despite the potential of targeting sodium channels for neuropathic pain management, several challenges need to be addressed:

## 6.1. Challenges

**Selective Targeting:** Achieving selective targeting of specific sodium channels remains a significant challenge. Although selective inhibitors for Nav1.7, Nav1.8, and Nav1.9 have been developed, improving their selectivity and minimizing off-target effects is a crucial area of ongoing research.

**Drug Delivery:** Efficient and targeted delivery of sodium channel blockers to the nervous system is another challenge. Overcoming the blood-brain barrier or targeting peripheral nerves without affecting central nervous system function is difficult.

**Individual Variability:** There is considerable variability in how patients with neuropathic pain respond to sodium channel blockers. Understanding the genetic and physiological factors that contribute to this variability will be important for predicting which patients are most likely to benefit from these drugs.

**Long-Term Safety and Efficacy:** The long-term safety and efficacy of selective sodium channel blockers are not yet fully understood. More long-term clinical trials are needed to assess the risks and benefits of these drugs.

## 6.2. Future Directions

Despite these challenges, the future of sodium channel blockers for neuropathic pain treatment is promising. Here are a few potential directions for future research:

**Personalized Medicine:** As we learn more about the genetic factors that influence pain sensitivity and response to sodium channel blockers, it may be possible to use genetic testing to guide treatment decisions, a strategy known as personalized medicine.

**Combination Therapies:** Sodium channel blockers might be combined with other types of pain medications to increase efficacy and minimize side effects. This could be particularly useful for patients who do not respond to sodium channel blockers alone.

**New Drug Delivery Methods:** Advances in drug delivery technology, such as nanoparticle-based delivery systems, could potentially be used to deliver sodium channel blockers more efficiently and specifically to their targets.

**Understanding Resistance Mechanisms:** Some patients may develop resistance to sodium channel blockers over time. Understanding the mechanisms of resistance could lead to the development of more effective therapies.

In summary, although there are several challenges to overcome, the targeting of sodium channels remains a promising approach for the treatment of neuropathic pain. Ongoing research in this area is likely to lead to the development of more effective and safer treatments in the future.

## 7. Conclusion

Voltage-gated sodium channels, particularly Nav1.7, Nav1.8, and Nav1.9, are crucial entities in the conduction of pain signals. As such, they present potentially effective targets for the management of neuropathic pain. The genetic linkage of these channels, especially Nav1.7, to various pain disorders supports this therapeutic approach.

Selective sodium channel blockers represent a promising leap forward in pain management, potentially offering targeted pain relief with fewer side effects compared to non-selective blockers. However, the journey from promising targets to effective, safe, and selective drugs is fraught with challenges. These include achieving true selectivity, ensuring efficient drug delivery, managing individual patient variability, and guaranteeing long-term safety and efficacy.

The future of sodium channel blockers in neuropathic pain treatment lies in overcoming these challenges through innovative research and development. Areas of focus could include personalized medicine, combination therapies, novel drug delivery methods, and understanding resistance mechanisms.

In conclusion, while the road to fully realizing the potential of sodium channel blockers in neuropathic pain management is still being paved, the direction of travel holds considerable promise. With continued research and clinical trials, it's hoped that new treatments will emerge that offer effective pain relief for the many patients worldwide who live with chronic neuropathic pain.

## References

- [1] Quintans JS, Antonioli AR, Almeida JR, Santana-Filho VJ, Quintans-Júnior LJ. Natural products evaluated in neuropathic pain models-a systematic review. *Basic & clinical pharmacology & toxicology*. 2014 Jun;114(6):442-50.
- [2] De Gray LC, Matta BF. Acute and chronic pain following craniotomy: a review. *Anaesthesia*. 2005 Jul;60(7):693-704.
- [3] Zghoul N, Ross EL, Edwards RR, Ahmed A, Jamison RN. Prevalence of chronic pain with neuropathic characteristics: a randomized telephone survey among medical center patients in Kuwait. *J Pain Res*. 2017 Apr 4; 10:679-687. doi: 10.2147/JPR.S123966. PMID: 28435312; PMCID: PMC5388267.
- [4] Wood JN, Boorman JP, Okuse K, Baker MD. Voltage-gated sodium channels and pain pathways. *Journal of neurobiology*. 2004 Oct;61(1):55-71.
- [5] Bennett DL, Clark AJ, Huang J, Waxman SG, Dib-Hajj SD. The role of voltage-gated sodium channels in pain signaling. *Physiological reviews*. 2019 Apr 1;99(2):1079-151.
- [6] Rogers M, Tang L, Madge DJ, Stevens EB. The role of sodium channels in neuropathic pain. In *Seminars in cell & developmental biology* 2006 Oct 1 (Vol. 17, No. 5, pp. 571-581). Academic Press.
- [7] Kühn H, Kappes L, Wolf K, Gebhardt L, Neurath MF, Reeh P, Fischer MJ, Kremer AE. Complementary roles of murine Nav1. 7, Nav1. 8 and Nav1. 9 in acute itch signalling. *Scientific Reports*. 2020 Feb 11;10(1):2326.
- [8] Okura D, Horishita T, Ueno S, Yanagihara N, Sudo Y, Uezono Y, Sata T. The endocannabinoid anandamide inhibits voltage-gated sodium channels Nav1. 2, Nav1. 6, Nav1. 7, and Nav1. 8 in *Xenopus* oocytes. *Anesthesia & Analgesia*. 2014 Mar 1;118(3):554-62.
- [9] Imbrici P, Liantonio A, Camerino GM, De Bellis M, Camerino C, Mele A, Giustino A, Pierno S, De Luca A, Tricarico D, Desaphy JF, Conte D. Therapeutic Approaches to Genetic Ion Channelopathies and Perspectives in Drug Discovery. *Front Pharmacol*. 2016 May 10; 7:121. doi: 10.3389/fphar.2016.00121. PMID: 27242528; PMCID: PMC4861771.
- [10] Nieto FR, Cobos EJ, Tejada MÁ, Sánchez-Fernández C, González-Cano R, Cendán CM. Tetrodotoxin (TTX) as a therapeutic agent for pain. *Marine drugs*. 2012 Jan 31;10(2):281-305.
- [11] Chang W, Berta T, Kim YH, Lee S, Lee SY, Ji RR. Expression and role of voltage-gated sodium channels in human dorsal root ganglion neurons with special focus on Nav1. 7, species differences, and regulation by paclitaxel. *Neuroscience bulletin*. 2018 Feb; 34:4-12.
- [12] Dib-Hajj, S., Yang, Y., Black, J. et al. The Nav1.7 sodium channel: from molecule to man. *Nat Rev Neurosci* 14, 49–62 (2013).
- [13] Swanwick, Richard & Pristerà, Alessandro & Okuse, Kenji. (2010). The trafficking of Na(V)1.8. *Neuroscience letters*. 486. 78-83. 10.1016/j.neulet.2010.08.074.
- [14] Dib-Hajj, S., Black, J. & Waxman, S. Nav1.9: a sodium channel linked to human pain. *Nat Rev Neurosci* 16, 511–519 (2015).
- [15] Qi FH, Zhou YL, Xu GY. Targeting voltage-gated sodium channels for treatment for chronic visceral pain. *World J Gastroenterol* 2011; 17(19): 2357-2364 [PMID: 21633634 DOI: 10.3748/wjg.v17.i19.2357]
- [16] Hameed S. Nav1.7 and Nav1.8: Role in the pathophysiology of pain. *Molecular Pain*. 2019;15. doi:10.1177/1744806919858801
- [17] Perrot S, Cittée J, Louis P, Quentin B, Robert C, Milon JY, Bismut H, Baumelou A. Self-medication in pain management: The state of the art of pharmacists' role for optimal Over-The-Counter analgesic use. *European Journal of Pain*. 2019 Nov;23(10):1747-62.
- [18] Lampert A, O'Reilly AO, Reeh P, Leffler A. Sodium channelopathies and pain. *Pflügers Archiv-European Journal of Physiology*. 2010 Jul; 460:249-63.

- [19] Alsaloum M, Higerd GP, Effraim PR, Waxman SG. Status of peripheral sodium channel blockers for non-addictive pain treatment. *Nature Reviews Neurology*. 2020 Dec;16(12):689-705.
- [20] Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, Freeman R, Truini A, Attal N, Finnerup NB, Eccleston C. Neuropathic pain. *Nature reviews Disease primers*. 2017 Feb 16;3(1):1-9.
- [21] Cheng Qiyun, Sun Caixin, Zhang Xiaoxing, et al. Short-Term load forecasting model and method for power system based on complementation of neural network and fuzzy logic. *Transactions of China Electrotechnical Society*, 2004, 19(10): 53-58.