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CRITICAL ROLE OF VOLTAGE GATED SODIUM CHANNELS IN THE DEVELOPMENT OF NEUROPATHIC PAIN

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ABSTRACT

The different etiological factors are involved in the pathobiology of neuropathy pain. Among the notable factors are diabetes, overconsumption of alcohol, deficiency of vitamins, and certain drug treatments like anticancer agents severely deteriorates the normal physiology of somatosensory nervous system. The genesis and time duration of painful neuropathy is complex phenomenon creating the hurdles in the treatment guidelines with the presently available drugs. Therefore, the management of neuropathy is becoming a challenging task for the researchers. Outcome of the pain research have revealed that differences in the functions, and mutations in genes responsible for genesis of neuropathic pain plays a vital role, and involved in the modulation of responses to the many analgesic drugs. In this context, the understanding the complete physiology of sodium channel is becoming quite obvious task for the successful management of neuropathic pain. The current review highlighted the involvement of different types of sodium channels, their correlation with development of neuropathy which will reveals the different possible opportunities in the direction of management of neuropathic pain.

Key words: Sodium channels, neuropathic pain, tetrodotoxin (TTX)

1. INTRODUCTION

The different modalities of pain are a repeatedly experienced phenomenon observed in the peripheral neuropathy condition. The alterations in the somatosensory nervous system function leads to the development of characteristic symptoms like hyperalgesia, and allodynia in neuropathic pain [1]. Almost 10% peoples across the globe are suffering from chronic pain, as these peoples are refractive to the present available treatment creating burden on the life of suffered peoples [2]. The different types of sodium channel causes exaggeration of nociceptors that directly mediate the neuropathic pain. Currently, nine different types of voltage gated channel isotypes have been identified in neuropathic pain that severely causes increased responses in affected neurons [3]. But, their exact role in neuropathic pain is poorly understood. Among the important type of sodium channels are Nav 1.3, Nav 1.7, and Nav 1.8 [4]. Currently, many analgesics shows poor responses in neuropathic pain which creates great opportunities for the new researchers to come up with better and effective treatment options [5]. Taking account of these factors, the present review mainly highlighted the role of different sodium channels in neuropathic pain that helps to find new therapeutic remedies in the management of neuropathic pain.

2. Role of sodium (Na^+) channels in neuropathic pain

Neuronal cytoskeleton of voltage gated Na^+ channels contain three glycoprotein components like central pore forming α-subunit and two auxiliary β_1 and β_2 subunits ($1\alpha:1\beta_1:1\beta_2$). Functionally, α-subunit regulate proper functioning of channel and β-subunits not only modify the biological and physiological properties of channels but also helps in both regulation and anchoring of these channels to the plasma membrane [6]. On the contrary, depending on communication with α-subunits, the β-subunits are categorized into two subdivisions like disulfide linkage involving β_2 and $\beta_4$and non-covalent bond forming β_1 and β_3. The α subunits is a potential subunit which is centrally encoded by the ion pore [6,7]. These highly processed subunits are heterologously expressed and generally made from 2000 amino acid residues. These amino acid residues are structured into four homologues backbone each containing six transmembrane segments with hairpin loop like an intracellular pore. This cytoskeleton of α subunits plays a vital role in the inactivation of Na^+ channels and forms the basis for binding site for numerous

categories of drugs in the management of neuropathic pain and its associated complications [8]. In the event of nerve action potential during neuropathic pain, these Na^+ channels cause influx of Na^+ current and helps in the both generation and propagation of action potential along the sensory nerves. Based on voltage dependency, both activation and inactivation kinetics and response to Na^+ channels inhibitors like tetrodotoxin (TTX), the Na^+ currents are categorized as TTX-sensitive (TTX-S), TTX-resistant (TTX-R) and intermediate type. Also, based on common architecture, arrangement of sequence of amino acid residues, different kinetic profile, and differences in voltage-based dependency, there are nine potential isoforms of Na^+ channels are identified as shown in Figure 1. [6-9] An extensive literature has focused the role of Na^+ channels in the development of neuropathic pain. Fundamentally, the neuropathy mainly causes changes in expression pattern of Na^+ channels and alters their trafficking mechanism. Also, it causes phosphorylation of Na^+ channel proteins like Nav1.6 to Nav 1.8. In the domain of Na^+ channels activity, neuropathy is mainly responsible for the shifting the Na^+ channel derived conductance of TTZ-S and TTX-R current towards leftward direction followed by increased expression of Nav1.3 & Nav1.7 and decreased expression of Nav1.6 and Nav1.8. All these sequential event causes increased spontaneous firing behaviour of sensory neurons with reduced firing threshold and accelerated the potential oscillations in membrane. The detailed role of various isoforms of Na^+ channels in neuropathic pain is summarized in below given Table [6-10].

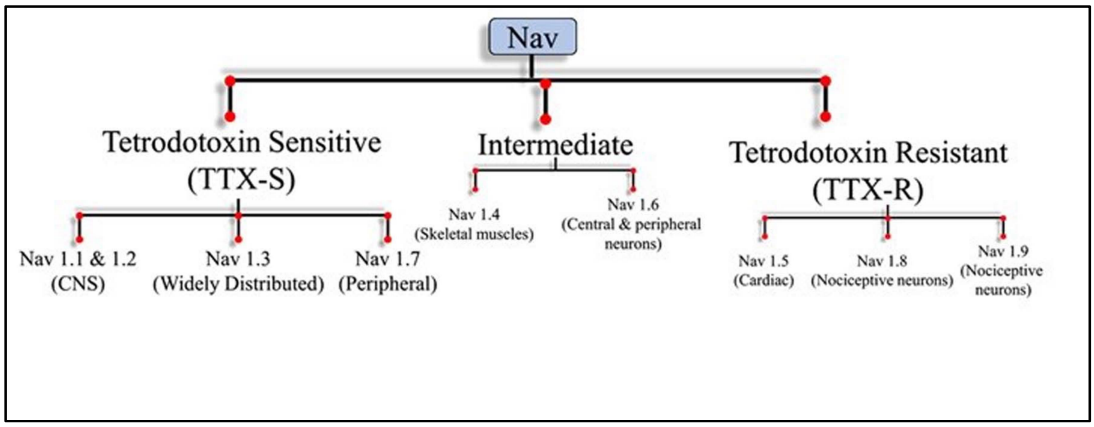

Figure 1: Potential isoforms of Na^+ channels

The sodium channel induced action potential initiates electrical stimuli and causes hyperexcitability in the neurons forming the platform for development of peripheral neuropathic pain. The sensory neurons located in dorsal root ganglia and

spinal cord becomes hyperresponsive in response to peripheral injury, thereafter develops the symptoms of neuropathic pain like allodynia and hyperalgesia. Following lesion to axons of these neurons, initially voltage gated Na^+ channels are activated which is responsible for the development of increased the sodium current. The peripheral nerve injury initiates expression of Nav 1.3 and Nav 1.8 isoforms of Na^+ channels that principally play a vital role in development and maintenance of neuropathic pain. The other isoform like Nav 1.8, mediate and transmit the mechanical stimuli from peripheral area to CNS but do not play role in the transmission of thermal stimuli [11]. The numerous preclinical models of neuropathic pain have revealed the potential role of sodium channels in the pathogenesis of neuropathic pain. According to previous reports with chronic constriction injury (CCI) of sciatic nerve, it was observed that neurons located in dorsal horn not only abnormally expresses the mRNA but also increases the protein level of Nav 1.3 isoform subunit [12]. Other findings with spinal cord injury (SCI) revealed the excess level of mRNA and protein concentration of Nav 1.3 isoform of sodium channel in dorsal horn and thalamic neurons. This sequence of event is correlated with elevated firing of action potential along the pain pathway and responsible for hyperresponsiveness of these neurons to innocuous and noxious mechanical and thermal stimuli. Enhanced stimulation of Nav 1.3 amplify and regulate the transmission of peripheral pain and central pain through development of TTX-S current induced greater neuronal firing in lesioned neurons than normal neurons. The SNL model of neuropathy revealed the fact about sodium channel and its association with development of ectopic discharge-based pain behaviour and upregulated TTX-S channel expression within the somata of DRG neurons [13]. Abnormal injury causes accumulation of sodium channels and the sodium channel blockers inhibit the ectopic discharges, reduced abnormal sensation in neuropathic pain patients as well as reduces pain behavior in animal models of neuropathic pain. The possible mechanism of development of neuropathic pain is depicted in Figure 2.

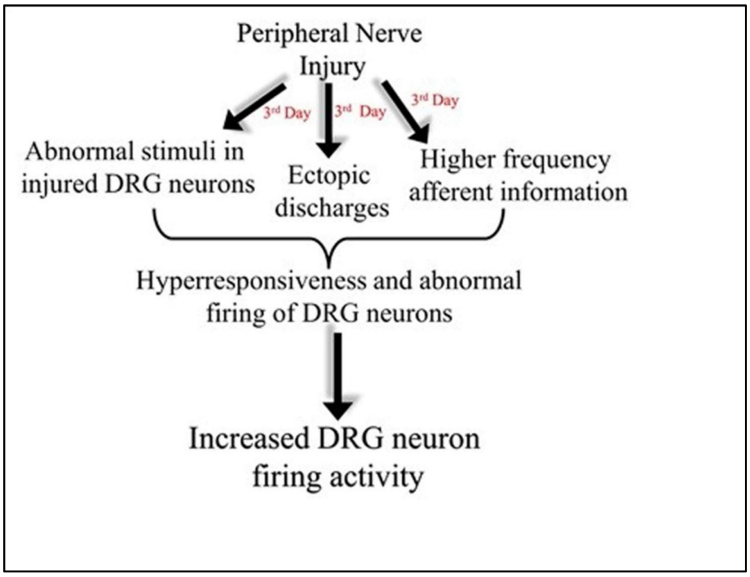

Figure 2: Possible mechanism of development of neuropathic pain by Na+ Channel

Table 1: Types and Properties of Na^+ Channels and Current

TTX-S	TTX-R			
➢ Low activation threshold ➢ Rapid inactivation ➢ Different inactivation kinetics with different fibers ➢ Determine shape of action potential ➢ Responsible for initial depolarization ➢ Inactivated during depolarized induced high frequency firing ➢ Produces action potential in nerve terminals of fast conducting Aδ fibers	➢ Located in small prominent, medium and large diameter DRG neurons ➢ Lined with nociceptive fibers ➢ Maintain action potential ➢ Regulate majority of upstroke and repolarizing phase ➢ Initiates action potential in nerve terminals of slow conducting C & Aδ fibers			
	TTX – R_1	TTX – R_2	TTX – R_3	TTX – R_4
	❖ High threshold ❖ Slow inactivation ❖ Encoded by Nav1.9 ❖ Small diameter DRGs ❖ Causes sustained action potential	❖ High threshold ❖ Slow inactivation ❖ Encoded by Nav1.9 with different gating mode	❖ Low threshold ❖ Rapid inactivation ❖ Encoded by Nav1.5	❖ Low threshold ❖ Small diameter DRGs ❖ Encoded by Nav1.5

Table 2: The detailed role of various isoforms of Na^+ channels in neuropathic pain

Type	Characteristics
Nav1.3	➢ Generate TTX-S current, has fast activation, and fast inactivation kinetics, rapid recovery from inactivation and responsible for persistent current. ➢ Causes 2 to 30 fold upregulation of Nav1.3 mRNA. ➢ Originate TTX-S current in injured DRG neurons with rapid recovery from inactivation (repiming) than that of normal DRG. ➢ Produces ectopic firing in large diameter Aβ and Aδ fibers. ➢ Upregulates Nav1.3 mRNA protein expression in medium and large diameter neurons in several models of neuropathic pain. ➢ Expressed in CNS of adult rats, primates and humans. ➢ Responsible for spontaneous ectopic discharges and regulation of sustained firing in injured neurons
Nav1.8	➢ Responsible for abnormal conduction of sensory inputs and facilitation of firing in DRG. ➢ Expression of Nav1.8 channel in uninjured fibers. ➢ Involvement of Nav1.8 in neuropathic pain may dependent of type of neuropathic pain model.

	e.g. SNL – causes 50% reduction of Nav1.8 expression. CCI – causes 25% reduction in Nav1.8expression. STZ – causes little reduction in Nav1.8expression
Nav1.7	**➢ Expressed in DRG, small C fibers and Aδ and Aβ fibers. ➢ Causes fast TTX-S current with slow repriming kinetics (inactivation) and activated by small depolarizing current as that of sensory nerve. ➢ Are localized to sensory endings therefore it may transmits painful stimuli. ➢ SNL model of neuropathic pain causes half reduction in expression of mRNA level. ➢ Diabetic neuropathy model causes characteristic increase in TTX-S current. ➢ The mutations in Nav1.7 due to erythromelagia causes burning pain and hot skin flashes, alteration in activation and deactivation kinetics, lowered threshold for spike inactivation and hyperexcitability in DRG neurons**
Nav1.9	**➢ Expressed in nociceptive neurons and fibers (e.g. C, Aδ & Aβ fibers). ➢ Produces persistent current. ➢ Neuropathic pain causes reduction in expression of Nav 1.9. ➢ SNL and CCI cause reduction in protein expression and persistent TTX-R current whereas trigeminal neuralgia model causes reduced mRNA level. ➢ Not involved in conducting neuropathic pain painful stimuli as they exist in an inactivated state.**

3. CONCLUSION

This review demonstrates the role of different types of sodium channels and function of the voltage-gated sodium channel along with their expression behaviour. Also, this article helps in screening of many analgesics for the management of neuropathic pain.

Conflict of Interest

The authors do not have any conflict of interest.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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