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Review Article

Chronic pain, Sodium channel and Gene mutation

Dr Santanu Mallik DA*[1], Dr V. G Sawant[2]
[1]Department of Anatomy Dr D Y Patil Medical College, Navi Mumbai, India
[2]Head & Professor, Department of Anatomy, Dr D Y Patil Medical College, Navi Mumbai, India

***Corresponding author**
Dr Santanu Mallik DA
Email: drmallick@rediffmail.com

Abstract: Anatomy of human pain pathway is complex. It starts with the primary sensory neurons in the periphery, conduction to the spinal cord through afferent neurons, and processing at multiple higher levels that include the dorsal horn, spinal projections, thalamus, and cortex. Transmission of painful stimulus and its processing involves different ion channels, receptors, and various chemical mediators. Different sodium channels, especially Nav1.7 are expressed preferentially in most slowly conducting nociceptive neurons and in sympathetic neurons. Dysregulated expression of voltage-gated sodium channels can produce neuronal hyperexcitability associated with severe pain, whereas loss of the Nav1.7 channel in patients leads to indifference to pain. Interestingly, certain factors of human pain perception can be inherited like acute pain thresholds, efficacy of analgesics, inclination of developing chronic pain, etc. Mutation of the genes encoding for ion channels can cause heritable pain disorders by abnormal channel function or expression. Discovery of genetic mutations and of additional variants that likely to be identified in the future will open up the possibility of understanding chronic pain accurately, at the molecular level. The understanding of the pain pathway at the molecular level may lead to new therapeutic strategies that will bring us closer to more effective treatments for pain.
Keywords: Chronic pain, Sodium channel (Nav), Dorsal root ganglion, inherited pain disorders, inherited erythromelalgia

INTRODUCTION

Sodium channels are integral membrane proteins that form ion channels, conducting sodium ions (Na^+) through a cell's plasma membrane present in excitable cells such as neurons, myocytes, responsible for the rising phase of action potentials[1,2]. Pain pathways start with primary sensory neurons of dorsal root ganglion and trigeminal neurons. The peripheral stimulus that develops pain perception depends on the presence of functional voltage-gated sodium channels. Several studies shown that, after injury to their axons, neurons can display changes in excitability due to increased sodium channel expression. Though studies showed that, in some pain syndromes, hyperexcitability or increased baseline sensitivity of these cells leads to abnormal bursting that can produce chronic pain but the underlying molecular mechanisms are not fully understood [3-5].

Changes in Dorsal root ganglion after injury

Early studies [6,7] described that, after injury to their axons, motor neurons show changes in excitability, suggesting increased sodium channel expression over the cell body and the dendrites, and subsequently similar changes were observed in sensory neurons[8,9]. Abnormal sodium channel aggregation at the tips of injured axons also has been observed[10-12] that abnormally increases in sodium conductance which can lead to inappropriate, repetitive firing[13-15] causing chronic pain. These observations, together with experimental and clinical observations on partial efficacy of sodium channel blocking agents in neuropathic pain, established a link between sodium channel activity and sensory neuron hyperexcitability producing pain [16-19].

Sodium Channels in Sensory Neurons

Over the past decade, a family of nine structurally related Voltage-gated sodium channels is encoded within mammals by different genes. Dorsal root Ganglion (DRG) neurons, which had been known to display multiple, distinct sodium currents [20-23] express at least six sodium channel transcripts [24]. Out of nine pore-forming voltage-gated sodium channel (Nav 1.1 to Nav 1.9), Sodium Channel Nav 1.7 and Nav 1.8 are important in nociceptive pathway. Nav 1.7 has been detected in DRG (A-Beta and C fibers), trigeminal ganglion and sympathetic ganglion neuron (superior cervical ganglion). Its presence is less in CNS, smooth myocytes [25].

Sodium Channel Gene Expression Is Altered After Injury to DRG Neurons

Waxman *et al* observed that in addition to production of excess channels, there is a switch in the type of channels produced cause a significant up-regulation of expression of the previously silent sodium channel gene ((SNSyPN3, NaN, PN1, and NaG) in DRG neurons after axotomy. This finding was followed by demonstration of down-regulation of the gene expression, which can persist as long as 210 days [26], which is consistent with the long-lasting changes in gene expression that have been described in these cells [27]. These changes may poise DRG neurons to fire spontaneously, or at inappropriately high frequencies, after injury. Increased sodium channel densities, in themselves, will tend to lower threshold [14].

Sodium Channel Expression in Inflammatory Pain Models

Several studies have demonstrated that inflammatory molecules such as prostaglandins and serotonin can modulate sodium currents in DRG neurons [29], possibly acting through a cyclic AMP-protein cascade [30]. However, whether sodium channel gene expression is affected in inflammatory models of pain had not been addressed. But some studies have shown a persistent increase in sodium channel in DRG neurons within 24 hrs of injection of carageenan[31] in rat . The mechanism responsible for this inflammation-associated change in sodium channel expression is not known. Interestingly, Nerve Growth Factor (NGF) normally is produced in peripheral target tissues by supporting cells that include fibroblasts, Schwann cells, and NGF production is stimulated in immune cells, and increased NGF levels have been observed in the local area, raising the possibility that inflammation may indirectly trigger changes in sodium channel gene expression via changes in neurotrophin levels [32,33].

Now it is clear to us that, dysregulated expression of several sodium channels has been associated with chronic pain induced by trauma, inflammation or metabolic disorders (e.g. diabetes) and blocking of sodium channels can ameliorate pain symptoms [34-37]. However, one particular sodium channel isoform Nav1.7, has emerged as a major focus in studies on pain, in large part because recent studies have identified Nav1.7 as a key contributor to nociceptive neuronal excitability, which is linked to different human pain disorders [38-40].

Certain factors of human pain experience are found to be inherited like acute pain thresholds, efficacy of analgesics. Mutation of the genes encoding for ion channels can cause heritable pain disorders by abnormal channel function or expression. These diseases caused by these gene mutations are rare but refractory to conventional treatment.

Contribution of Nav1.7 to pain: human studies

Inherited sodium channelopathies underlie several neurological and muscular diseases [41-44]. In 2004 a painful syndrome erythromelalgia (also called erythermalgia) was found in two Chinese families with two independent mutations in SCN9A, the gene that encodes Nav1.7 [45]. Since 2004, several more mutations in SCN9A have been linked to inherited erythromelalgia [46]. Additionally, other mutations in SCN9A have been linked to inherited paroxysmal extreme pain disorder [47] and, more recently, individuals with complete loss of functional Nav1.7 have been reported to be 'indifferent' to pain [48,49].

Inherited erythromelalgia

Life-long symptoms of early-onset (as early as 1 year-old) are characterized by episodes of burning pain triggered by mild warmth or exercise, together with erythema and mild swelling in the hands and feet and sometimes in the ears or face [50-53]. The frequency and severity of pain episodes increase with age, with each episode lasting minutes to hours. Typically, patients with early-onset inherited erythromelalgia do not report autonomic abnormalities, such as orthostatic hypotension or gastrointestinal symptoms. Partial relief of symptoms comes from cooling the affected extremities. Linkage analysis identified the disease locus on chromosome 2 (2q31–32) [54] where a cluster of voltage-gated sodium-channel genes, including SCN9A, is known to exist and, subsequently, the molecular target was identified as Nav1.7[55]. Indeed, two independent mutations (I848T and L858F) in two sporadic early-onset erythromelalgia cases from China [55,56], which have also been reported from multigeneration French (I848T) and Canadian (L858F) families[54]. Familial adult-onset erythromelalgia has been described recently in a family from the USA in which coding mutations of Nav1.7 were excluded as the causative factor [57]. Thus, it is possible that mutations in noncoding regions of the SCN9A gene that cause increased expression of the channel or indeed other target genes might cause inherited erythromelagia.

Paroxysmal extreme pain disorder (PEPD)

A different set of mutations in Nav1.7 has been associated with another autosomal dominant painful disorder, PEPD[40], which was known as familial rectal pain previously [58,59]. PEPD is characterized by life-long pain episodes, accompanied by tonic posturing and immediately followed by flushing of the lower limbs, in a uni- or bi-lateral fashion, which start within the first days after birth and are triggered by defecation or probing of the anal or genital areas. The frequency of the rectal-pain episodes decreases with age; ocular and mandibular pain are sometimes triggered by cold or irritants, becoming more prominent complaints. In contrast to inherited erythromelalgia, which is generally refractory to pharmacological treatment, PEPD patients respond to

treatment with carbamazepine with almost complete cessation of spontaneous or induced attacks [40,58]. This patient has more severe symptoms compared with his father and with patients in another family carrying the R996C mutation alone [60].

Congenital indifference to pain (CIP)

Patients with congenital insensitivity (or indifference) to pain (CIP) show varying degrees of deficits in sensing, perceiving and reacting to painful stimuli but their other sensory modalities are intact[61,62]. The designation of patients as 'insensitive' or 'indifferent' to pain is a subject of controversy that has led to the use of the term channelopathy- associated CIP for a subset of these patients with null mutations in Nav1.763. Typically, these patients present with a history of not experiencing any form of pain anywhere on their bodies, even after burns, bone fractures or severe injuries to their lips and tongues, and they do not experience visceral pain [63-65]. Despite the fact that Nav1.7 is produced within sympathetic ganglion neurons [66-70], patients with channelopathy-associated CIP do not show apparent deficits in autonomic function, such as whole-body thermoregulation or cardiac or respiratory rhythm, and have a normal axon-reflex response to histamine [48,63]. Interestingly, channelopathy- associated CIP patients have deficits in the sense of smell [48]. Three loss-of-function mutations in SCN9A were identified initially in unrelated consanguineous Pakistani families63. Subsequently several other mutations , including deletions in coding sequence that truncate the protein and deletion of intronic sequences that suggest splicing defects, were identified in ethnically diverse patients [64]. Surprisingly, these cases included patients who were born into families that are apparently non-consanguineous, which suggests a de novo mutation of one of the alleles and the inheritance of the second mutant allele from one of the parents, who would be an asymptomatic carrier. This observation suggests that SCN9A-related CIP might underlie some cases of idiopathic CIP in non-consanguineous families [62].

Familial hemiplegic migraine (FHM)

It is a form of migraine headache that runs in families. It is inherited in autosomal dominant fashion, and aura symptoms may be associated with moderate to severe motor weakness, ataxia, and seizures. Mutations in the CACNA1A (on chromosome 19p3 coding for calcium channel Cav2.1) [71,72], ATP1A2 (encoding the Na+/K+ ATPase α2 subunit leads to impaired pump function there by leading to loss of ion gradient at channels), SCN1A gene mutation is in the highly conserved region of the sodium channel responsible for fast inactivation[73] , and PRRT2 genes are found to cause familial hemiplegic migraine. The function of the protein produced from the PRRT2 gene is unknown although it interacts with a protein that helps control interneuronal signaling.

Familial episodic pain syndrome (FEPS)

It is associated with episodes of upper body pain of severe intensity. The pain is triggered by fasting, physical stress, or fatigue. It was first found in a Colombian family and first disease linked with transient receptor potential channels (TRP channels). These are a group of ion channels located mostly on the plasma membrane of numerous human cell types and mediate a variety of sensations like pain, hotness, warmth, coldness, taste, pressure, and vision. A nonsense mutation in TRPA1 gene is found to be linked to the syndrome [74].

Irritable Bowel Syndrome (IBS)

Several studies suggest a strong genetic component causing familial IBS but association of the candidate genes are yet to be found [75].

CONCLUSION

Sodium channels are significant participants in electro-genesis within sensory neurons, including DRG and trigeminal nerves and they probably subserve multiple functions (transduction, signal amplification, action potential electrogenesis, etc.) and interact in a complex manner in trauma, inflammation or metabolic disorders (e.g. diabetes). Mutation of the genes encoding for ion channels can cause heritable pain disorders by abnormal channel function or expression. It is quite likely, in our opinion, that sodium channel blockade will emerge as a viable strategy for pharmacologic treatment of pain but require further careful studies. Discovery of genetic mutations and of additional variants that will likely be identified in the future open up the possibility of understanding chronic pain more fully, at the molecular level.

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