Review Article

Open Access Journal of
Biomedical Science
ISSN: 2690-487X

Analgesic Potential Sodium Channel SCN9A

Claudia Mancilla-Simbro[1]*, José Emmanuel Hurtado-Madrid[2], Sandra Ortíz-González[3], G Gerardo Aguirre-Espindola[3], José Alfredo Galicia Domínguez[3], Dajiehdy Perdomo-Martínez[4], Citalli Gamboa-Estéves[5], Alberto Ramírez-Mata[6] and Erwin J Pérez-Cortés[2]

[1]*Laboratorio de Biofísica Cardiaca, Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla, México*

[2]*Departamento de Ciencias de la Salud, Universidad de las Américas Puebla, México*

[3]*Facultad de Medicina Veterinaria y Zootecnia, Benemérita Universidad Autónoma de Puebla*

[4]*Escritora independiente, México*

[5]*Centro de Investigaciones en Ciencias Microbiológicas, Benemérita Universidad Autónoma de Puebla, México*

[6]*Laboratorio de Neurofisiología, Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla, México*

ABSTRACT

Chronic pain is one of the most complex clinical conditions to manage, it can affect approximately 20% of the population and it has a high economic cost. In recent years, the voltage-gated sodium channel Nav1.7 has been proposed as a possible therapeutic target against pain, due to the evidence that certain mutations in the gene that encodes it are associated to chronic pain or the absence of this, depending to its nature. Several molecules have been discovered - both synthetic and natural-with selective inhibitory potential, which may to contribute in searching an effective treatment without side effects against chronic pain.

KEYWORDS: Sodium channel; Nav1.7. pain; Analgesic

INTRODUCTION

The sensitive receptors to pain receive stimuli (the channel allows sodium to pass, and this leads to the action potential, the nociceptive stimulus is transduced into electrical signals), these have evolved in complex organisms to alert about cellular and tissue damage. The sensation of pain results in the adoption of behaviors that remove the body from a "dangerous environment" to stop or minimize tissue damage. Thus, the pain alert protects us from our environment, teaching us what are the possible situations and behaviors that can cause injuries. Pain pathways operate at numerous levels in the nervous system and are under voluntary, but also involuntary, control. The neural process through which organisms encode the noxious stimulus is called nociception, and it is mediated by the activation of sensory terminals called nociceptors. Blocking these processes with analgesics has been a major pharmaceutical achievement.

Voltage-Gated Sodium Channels and Pain

Humans have nine subtypes of voltage-gated sodium (Nav) channels, denoted from Nav1.1 to Nav1.9 and expressed in various organs: the Nav1.1, Nav1.2, Nav1.3, and Nav1.6 channels. they predominate in the central nervous system; while Nav1.7, Nav1.8 and Nav1.9 are expressed mainly in the peripheral nervous system; Nav1.4 channels are expressed in skeletal muscle; and Nav1.5 in the heart. Of all of them, the Nav1.7, Nav1.8 and Nav1.9 channels play an important role in pain signaling.

The Nav1.7 channel has been shown to play a crucial role in pain sensation and there is interesting genetic evidence linking Nav1.7 and the gene that encodes it, SCN9A, with pain disorders in humans Focken et al. [1]. Here I recommend writing what has been found about the sodium channel and pain.

Quick Response Code:

Address for correspondence: Claudia Mancilla-Simbro, Laboratorio de Biofísica Cardiaca, Instituto de Fisiología. Benemérita Universidad Autónoma de Puebla, México

Received: December 23, 2021 **Published:** January 18, 2022

How to cite this article: Claudia MS, José EHM, Sandra OG , Gerardo GAE, José AGD, Dajiehdy PM, Citalli GE, Alberto RM, Erwin JPC. Analgesic Potential Sodium Channel SCN9A. 2022- 4(1) OAJBS.ID.000378. **DOI:** 10.38125/OAJBS.000378

Channel Nav1.7

Voltage-gated sodium channels are transmembrane proteins that are made up of an alpha (α) subunit composed of approximately 2,000 amino acid residues. This subunit is organized into four homologous domains that make up the pore for Na + flux. Each domain is made up of 6 transmembrane segments; 1 through 4 form the voltage sensor domains (VSDs) and segments 5 and 6 of each domain form the central module of the pore. The sodium channel β subunits are composed of an N-terminal extracellular immunoglobulin-like fold, a single transmembrane segment, and a short intracellular segment in Figure 1; Catterall [2].

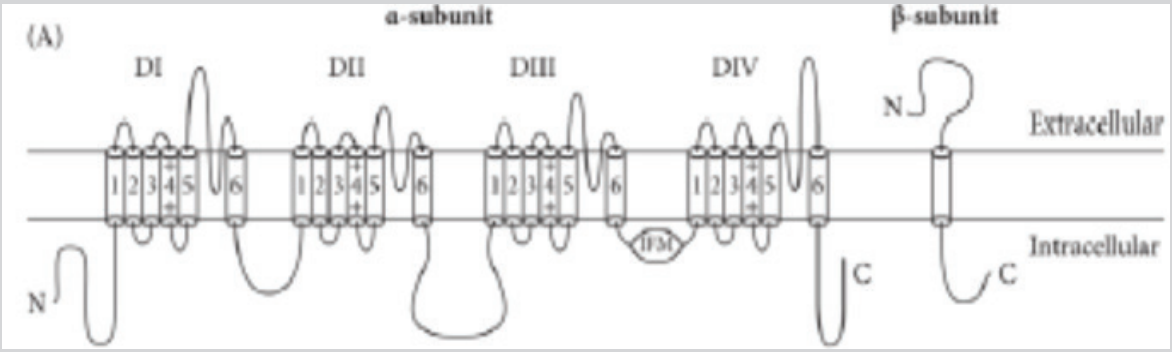

Figure 1: Voltage-dependent sodium channel structure.

Focusing specifically in the Nav1.7 channel, it is highly expressed in the soma, axons and peripheral endings of the nociceptive neurons of the spinal and trigeminal ganglia, in the olfactory neurons and in the neurons of the sympathetic ganglion. It is also expressed in the central nervous system, liver, heart muscle, and spinal cord.

Nav1.7 is designated as a low-threshold channel and is expressed on the surface of peripheral pain-sensitive or nociceptor neurons (in about 85% of? Neurons), where it allows Na + flux in response to depolarizations of the cell membrane, generated in turn by potentially tissue-damaging events or stimuli. The sodium flux modifies the electrical properties of the membrane transiently, and consequently an action potential is produced. These momentary changes in the cell membrane spread through the neurons that make up the nociceptive pathways and reach the cerebral cortex. Nav1.7 could also be seen as an amplifier of pain signals generated by receptors in nociceptor terminals, where type C and A delta fibers are those that receive nociceptive stimuli, later (it is not yet clear exactly how) the Channel Nav1.7 (which not only transmits pain signals). When activated, it lets in sodium, and this allows electrical changes in the membrane to propagate the action potential (transduction). The "signal" is amplified for several reasons: 1) adjacent receptive fields, secondary neurons; localization of pain, if it is chronic, it is diffuse, if it is acute, it is more localized.

Mutations in the SCN9A gene associated with gain and loss of canal function have been reported to result in different conditions: in gain of function there is evidence of painful diseases such as hereditary erythromelalgia, paroxysmal extreme pain disorder and idiopathic small fiber neuropathies; whereas, a loss of function is related to a rare disorder called congenital insensitivity to pain, characterized by the complete loss of the ability to feel pain stimuli Wu [3]. The important role of Nav1.7 in pain generation has created immense interest in this channel as an analgesic target.

A Brief History

The first hint that Nav1.7 might play an important role in pain signaling was given by a research group in 2004, who showed that patients of three generations of a Chinese family with a persistent pain syndrome called primary erythromelalgia (a rare disease). characterized by severe burning with redness and warmth in the extremities in response to moderate exercise) had nonsense mutations in the SCN9A gene ((T2573A, L858H) Yang et al. [4].

The following year Dib-Hajj et al. Discovered that the mutation that changes phenylalanine for valine at position 1449 in Nav1.7, which is invariant in all mammalian sodium channels, is the one associated with the gain of function in the canal, causing hypersensitivity to pain Dib-Hajj et al. [5].

Around the same time, researchers at the University College of London examined the role of Nav1.7 in pain pathways using Knockout mice, which were found to be insensitive to inflammatory pain, demonstrating that mutations associated with loss of function nullify pain perception.

In 2006 researchers from the University of Cambridge reported that children from different families in Pakistan seemed unable to experience pain. The first of them, 10 years old, acted in a "street theater" placing knives through his arms and later walked on hot coals without feeling any type of pain. The little one died at the age of 14 before being part of the study. Subsequently, they studied 6 children (between 6 and 12 years old) from three other families who were consanguineous to the first with similar stories, who had never felt any pain in any part of their body, despite having wounds, for example, on the lips or the tongue as a consequence of self-mutilation in the first four years of life, fractures and even osteomyelitis; Despite this, all the children were found to have normal vision, hearing and appearance. Genome sequencing of these individuals showed the disruption of one gene, SCN9A, causing loss-of-function mutations of Nav1.7 and the complete loss of nociceptive entry.

It is important to note, apart from the inability to feel pain, loss of smell (anosmia) is another sensory disability in individuals with channelopathy. These studies paved the way to propose and study the Nav1.7 channel as a therapeutic target to develop drugs that could serve as an analgesic by selectively blocking it.

Why is the Nav1.7 Channel a Therapeutic Target for Pain?

If the various sodium channel subtypes are related to particular

pain mechanisms, then specific antagonists of those subtypes could, in theory, produce pain management without side effects. Specifically, there are three binding sites that appear to offer the highest potential for the discovery and optimization of selective inhibitors of Nav1.7: 1) the extracellular vestibule of the pore, tetrodotoxin (TTX) and saxitoxin (STX) binding sites; 2) the extracellular loops of domain II of the voltage sensor (VSD2) AND 3) the extracellular loops of domain IV of the voltage sensor (VSD4).

Channel Inhibitory Molecules

The discoveries about the mutations associated with the gain of function of Nav1.7 that generate intense pain and the mutations related with loss of function of the same channel that generate absence of pain have put Nav1.7 in the therapeutic target as a new e important target for the development of analgesics, for which a channel antagonist is required.

Despite the peculiarity and promise of the Nav1.7 channel, the use of ion channel blockers for pain management is not new. For years, sodium (Na+), calcium (Ca++) and potassium (K+) channel blockers, such as local anesthetics, antiarrhythmics or antiepileptic drugs, have been used as adjuvants in the treatment of neuropathic pain. The problem lies in the low selectivity of these drugs, in the adverse cardiac, neurological, hematological and digestive effects that limit their use, and in the interindividual variability, which, together with the particular susceptibility to develop chronic pain, limit their efficacy, for Therefore, the challenge facing Nav1.7 inhibitor molecules is that they must be extremely selective, for which the three previously described binding sites have been proposed. Some of the compounds so far studied and proposed as selective inhibitors of Nav1.7 are described below. Therefore, it is relevant that diseases related to mutations in the Nav1.7 channel, such as small fiber neuropathy (SFN small-fiber neuropathy), characterized by the loss of myelination of small fibers, produces a combination of sensory dysfunction and neuropathic pain. Gain-of-function variants in the sodium channel Nav1.7 produce neuronal hyperexcitability of the dorsal root ganglion (DRG), present in 5% to 10% of patients with idiopathic painful SFN Chen [6].

Small Molecules as Sodium Channel Blockers

In recent years, small molecules have been developed that seek to selectively inhibit domain IV of the voltage sensor, among which are arylsulfonamides. In 2012, arylsulfonamide, shown in Figure 2, was shown to bind in the extracellular region of domain IV of the Nav1.7 channel voltage sensor. Likewise, in 2015, Focken et al. Demonstrated that this same arylsulfonamide selectively blocks Nav1.7 and with greater efficacy on Nav1.5 (a channel expressed in the heart and in which its blockage can cause arrhythmia) and Nav1.3; Focken et al. [1].

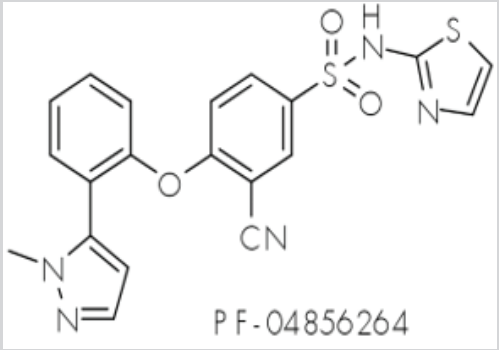

Figure 2: Nav1.7 inhibitory aryl sulfonamide.

Vixotrigine also called raxatrigine (Figure 3) is another Nav1.7 channel blocker under clinical investigation to treat peripheral neuropathic pain conditions, including trigeminal neuralgia, which is characterized by brief episodes of severe pain in one or more branches. of the trigeminal nerve. Results from clinical trials suggest that vixotrigine at a dose of 150 mg three times a day may be an effective and safe treatment for trigeminal neuralgia pain, with only dizziness and headache as side effects; even a phase III study suggests that a higher dose (250 mg three times a day) may provide additional benefits to those who do not show an adequate response to the first dose [7-10]. Vixotrigine is still in clinical development.

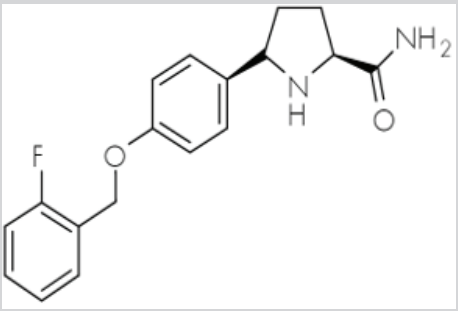

Figure 3: Voxotrigine.

Toxins as Sodium Channel Blockers

On the other hand, studies have been developed with different toxins for a therapeutic benefit, finding that they bind to VSD2, a different domain than small molecules; for example, ProTx-II, a spider venom peptide, was the first Nav1.7 inhibitor reported to have more than 50-fold selectivity over the other Nav isoforms. In 2019, ProTx-II from the Peruvian green velvet tarantula (Figure 4) was studied, verifying that it shows 30 to 100 times more selectivity on the Nav1.7 channel than on the other Nav isoforms, and they also demonstrated that this toxin is the most potent inhibitor available, testing its structural bases in the search to accelerate the design of new modulators [11,12].

Figure 4: Peruvian green velvet tarantula.

CONCLUSION

The voltage-gated sodium channel Nav1.7 has been shown to play an important role in human pain signaling through neuronal excitability. Studies of different rare diseases suggest that certain mutations of the SCN9A gene, which codes for this channel, are associated with its gain or loss of protein function, which has demonstrated its intrinsic relationship with pain. This has led to the Nav1.7 channel being an interesting therapeutic target to develop analgesics, although a large catalog of channel antagonists have been discovered, there is still no certainty for their medical

prescription; However, there is ample and promising research in clinical trials to exploit the characteristics of Nav1.7 and there will be, in the future, specific drugs that relieve patients of severe pain, thus improving their quality of life.

REFERENCES

1. Focken T, Liu S, Chahal N, Dauphinais M, Grimwood ME, et al. (2016) Discovery of aryl sulfonamides as isoform-selective inhibitors of NaV1.7 with efficacy in rodent pain models. ACS Med Chem Lett 7(3): 277-282.
2. Catterall WA (2017) Forty years of sodium channels: Structure, function, pharmacology and Epilepsy. Neurochem Res 42(9): 2495-2504.
3. Wu X, Hong L (2021) Calmodulin Interactions with Voltage-Gated Sodium Channels. International journal of molecular sciences 22[18].
4. Yang Y, Wang Y, Li S Xu Z, Li H, et al. (2004) Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. Journal of medical genetics 1(3): 171-174.
5. Dib-Hajj SD, Waxman SG (2019) Sodium channels: Inhuman pain disorders: Genetics and pharmacogenomics. Annu Rev Neurosci 42: 87-106.
6. Chen L, Wimalasena NK, Shim J, Han C, Lee, et al. (2021) Two independent mouse lines carrying the Nav1.7 I228M gain-of-function variant display dorsal root ganglion neuron hyperexcitability but a minimal pain phenotype. Pain 162(6): 1758-1770.
7. Edward CE, Ana PL, John NW (2016) Nav1.7 and other voltage-gated sodium channels as drug targets for pain relief. Expert Opinion on Therapeutic Targets (8): 975-983.
8. SD Dib-Hajj, AM Rush, TR Cummins, FM Hisama (2005) Gain-of-function mutation in Nav1.7 in familial erythromelalgia induces bursting of sensory neurons (Pt 8): 1847-1854.
9. James JC, Frank R, Adeline KN, Gemma T (2006) An SCN9A channelopathy causes congenital inability to experience pain, Nature 7121: 894-898.
10. Mohammed AN, Caroline S, Greta F, Baker D, Elizabeth AM, et al. (2004) Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain, Proceedings of the National Academy of Sciences 101(34): 12706-12711.
11. Nuvia PC, María CMT, Ivette DM (2017) Canalopatías, un novedoso enfoque en la fisiopatología del dolor, Revista Cubana de Pediatría 89(3).
12. Pimienta F, Mercado F, Almanza A (2016) Insensibilidad congénita al dolor: sufriendo sin dolor. Elementos 101