Congenital insensitivity to pain: the controversy and possible pathophysiology model in progress

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Abstract. Congenital insensitivity to pain (CIP) is a disorder that emphasizes the critical role of nociception in protecting against tissue damage and is characterized by repeated injuries, burns, and poor wound healing. CIP is a developmental defect caused by pathogenic genetic variants in multiple genes. Current treatment modalities for patients with CIP are primarily symptomatic, but the first targeted therapies are being tested. Interestingly, this area of research offers new ideas for slow-moving pain, one of the great challenges still unresolved by the medical community.

Keywords: Genetic Pain Loss, Congenital insensitivity to pain (CIP)

1. Introduction

Pain is a warning sign that often represents an unpleasant sensation and emotion, usually accompanied by existing or impending tissue damage or because of such damage. Pain is considered a sensory and perceptual phenomenon, nociception, a feeling that is essential for survival because of its ability to signal danger and avoid it in the future. For physiologists, pain is a sensation that starts from the receptors and ends in the cerebral cortex. This physical sensation, pain, can be confirmed by electrophysiological methods, but it is still a subjective sensation. Its intensity and quality come from various internal and external factors, so although the stimulus may be the same, it may be experienced differently by different people in different environments and physical and mental conditions [1]. The evolutionary hypothesis nowadays suggests pain as a protection method; acute pain can promptly indicate danger, while chronic pain can indicate an injury and thus allow better recovery. For instance, patients with fractures suffer from slow pain during recovery, thus avoiding movement of the injured area to achieve faster recovery.

Congenital insensitivity to pain (CIP) is a rare disease or human phenotype in which an individual cannot experience pain but has normal other brain functions such as hearing or speaking. The first report on CIP can trace back to 1900 by E. K.Westlake [2], and the first detailed report of CIP patients can trace back to 1932 by George Van Ness, who described a fifty-four-year-old Prague Bohemian man, not with any mental disorder but could not respond to pain. For example, the person was able to stay awake and calm during the procedure without any anesthesia [3]. Although the exact definition of CIP is still the subject of a few debates, here this article describes CIP only, rather than congenital insensitivity to pain with anhidrosis (CIPA). CIPA is also known as hereditary sensory and autonomic neuropathy type IV (HSAN4/HSAN IV); patients with CIPA are unable to perceive pain or perceive pain minimally and are also unable to perceive temperature correctly [4]. Compared to patients with CIP who are only unable to perceive pain but have a normal body and mental function, CIPA patients usually have deficient development in autonomic sympathetic neuronal system, central nervous system, and bidirectional communication between the immune system and nervous system [5].

However, a complete inability to perceive pain does not make an individual human with superhuman abilities; instead, CIP leads to a higher mortality rate and injury chance compared to normal individuals, especially during brain development in young children. At the same time, CIP patients, especially younger infants and children, are often not diagnosed promptly because the disease is often asymptomatic. CIP is usually diagnosed after the patient has already received a physical injury. For example, some infants with CIP often cause injury to themselves when they are building their first cognition, such as damage to fingers, toes, lips, etc., due to curious gnawing. CIP

patients are often unable to learn to avoid injury until they have the full cognitive ability and are usually more likely to experience burns, bone damage, etc., during childhood while developing cognitive ability. Due to their inability to feel pain, CIP patients are not only more prone to injury in their daily lives but also unable to identify the extent of their injuries, resulting in injuries to their bones and joints that are often overlooked due to a lack of careful examination such as radiology examinations. Thus, injuries to bones and joints often leave CIP patients disabled in adulthood [6]. This article will briefly introduce what CIP is and the current research results on CIP.

2. How pain is started and transmitted

When a stimulus is present, the basic pain mechanism undergoes three events-transduction, transmission, and modulation. Subtypes of peripheral sensory neurons mediate the sensations of temperature, touch, pressure, vibration, pruritus, and pain, which are transduced. Nociceptive neurons are sensory neurons that detect tissue damage. During conduction, stimuli are converted into chemical events, which are subsequently converted into electrical events by the neurons. Transmission between neurons begins after the completion of the transmission to the neuron. Transmission of electrical events along the neuronal pathway occurs as neurotransmitters in the synaptic cleft transmit information from the postsynaptic terminal of one cell to the presynaptic terminals of another cell. The signal for nociception is then projected to the dorsal of the spinal cord. After processing in complex spinal cord circuits, the projection neurons transmit this information to relays, such as the thalamus, and ultimately to distributed cortical networks. Two parts of this make up the identification and response to pain, the primary sensory cortex, which processes the title of pain, and the anterior cingulate and insula cortices, primarily responsible for processing the emotional response to pain. This ultimately forms what we perceive as pain [7]. This is where sodium channels and gene variants in epigenetics and transcription are often closely linked to CIP [8].

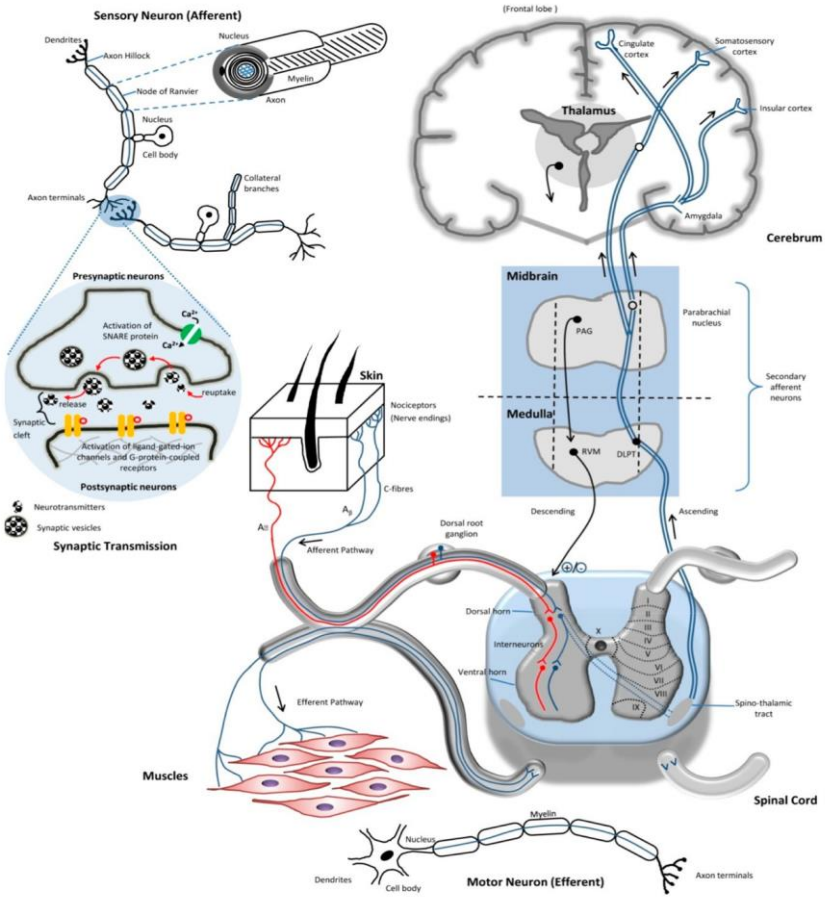

Figure 1. An overview of neural synaptic transmission is shown on the left side of the figure.

Nerve injury will induce brief and intense action potentials first reported by Wall et al. in 1974 [9]. Later on, with the advantage of molecular cloning, other researchers have found that these neural channels play a critical role in nociception which is known as voltage-gated sodium channels (VGSCs) [10]. VGSCs are transmembrane proteins consisting of a sizeable pore-forming a-subunit and one or two smaller a-subunits that are the essential components of the VGSC [11]. A-subunits are arranged into four homologous structural domains, each with six transmembrane segments (Figure 2). The ion-conducting pore of the sodium channel is formed by the P-loop region between the helical segments S5 and S6 of each repeating structural domain, which are tightly packed in the center of the quaternary structure. VGSCs have three different states: the resting closed state, the activated open state, and the inactivated closed state [12]. The S4 segment (each of the four structural domains) possesses multiple positively charged amino acid residues, thus responding to membrane voltage changes accordingly. Upon exceeding a critical threshold, the positively charged residues in the S4 segment move outward to a position close to the cell membrane's outer surface, which triggers a series of conformational changes leading to the activation of the channel [13].

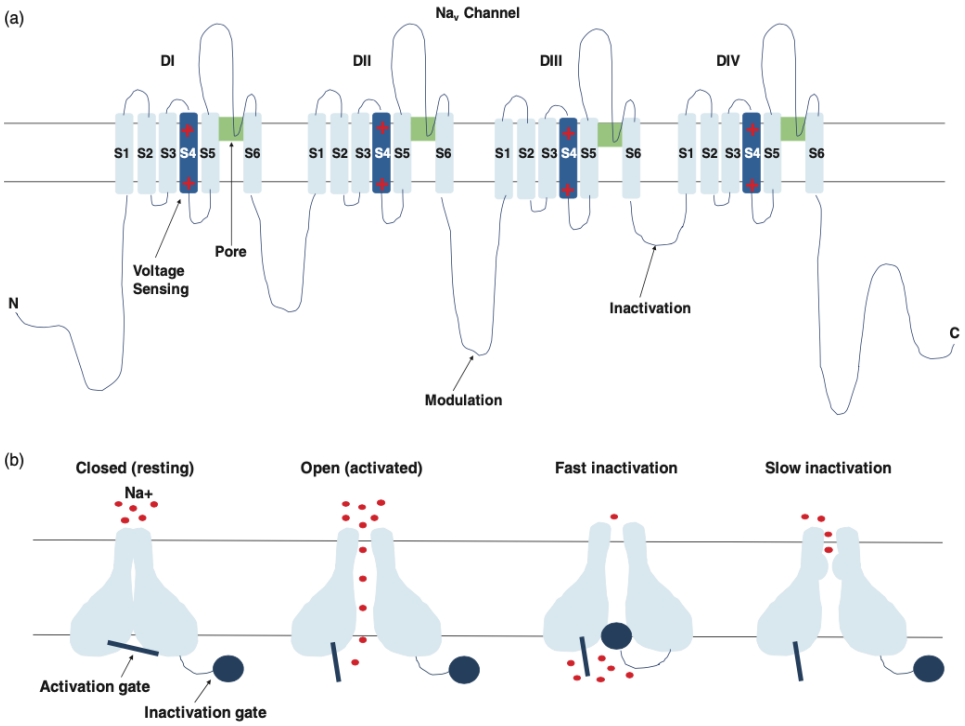

Figure 2. VGSCs in different states.

And a series of subsequent studies found that there are nine isoforms of NaV channels in mammals, and these are named in order from the first to the ninth, NaV1.1, NaV1.2, ... NaV1.9. NaV1.7, NaV1.8, and NaV1.9 are very common in sensory neurons. In 1997, Toledo-Aral JJ et al. studied neuronal cells by culturing PC12 cells on a culture medium. They then found that the PN1 gene was expressed at high levels throughout the peripheral nervous system [14].

In 2004, Nassar MA et al. initiated a more detailed investigation of the role of NaV1.7 after finding that the mice that lost NaV1.7 died shortly after birth. By genetic editing of embryonic stem cells from mice, they obtained mice with artificially deleted NaV1.7-expressing genes and subjected such mice to a series of tests. They used a hot plate on the mice to measure their response to pain. They found that under heat stimulation, the mice that lost NaV1.7 showed much less pain behavior to the hot plate (~20% or so). Also, Nassar MA et al. found that the response of these mice to mechanical pain stimuli was significantly reduced. Hence, they inferred that NaV1.7 sodium channel controls are closely linked to the pain response. They also found that NaV1.7 is closely related to NaV1.8 in the process of pain reaction. Their study provides a non-negligible theoretical basis for further studies on NaV to follow [15].

In a study of the NaV1.7 cassette NaV1.8 from 2018, Shannon DS et al. genetically deleted mice to obtain mice that were artificially knocked out of the NaV1.7 gene, which does not express NAV1.7 and are ideal animal models for studying pain and other responses. Through a series of tests such as noxious mechanical stimulus, noxious cooling stimulus (Acetone cooling test), thermally evoked response, mechanically evoked response, Hotplate test, etc., the reaction time of mice was observed for analysis. The experiment revealed that NaV1.7 and NaV1.8 have entirely different reactions to temperature, especially cold and heat. This experiment demonstrated that NaV1.7 is mainly responsible for burning pain, while NaV1.8 is responsible for extreme cold pain. At the same time, NaV1.7 and NaV1.8 were retested in response to mechanical, inflammatory, and other stimuli (Figure 3). This experiment not only further improved the knowledge of NaV1.7 and NaV1.8 but also speculated that there may be two completely different mechanisms for tactile and nociceptive sensation [16].

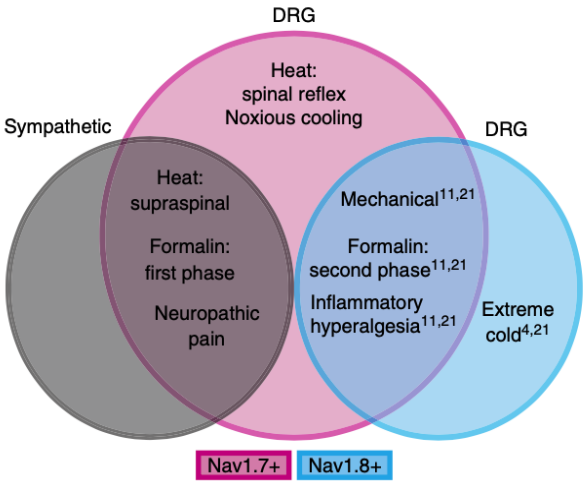

Figure 3. The neuron-specific role of Nav1.7 different pain states.

Lucy M et al. took it a step further in a 2019 experiment that recruited three human participants with a NaV1.7 gene mutation and CIP to further investigate the effects and function of NaV1.7 in humans. First, human responses were observed in CIP patients and healthy controls by applying topical pruritic agents such as mustard oil to the skin. All CIP patients showed much higher tolerance to these chemical stimuli. To further understand the role and mechanisms of NaV1.7, Lucy M et al. assessed the nature and characteristics of channel biophysics by whole-cell patch-clamp recordings. Lucy M et al. found that NaV1.7 mutations in all CIP patients caused a significant conductance loss, consistent with an almost complete loss of channel function. In addition, the Lucy M et al. team performed skin biopsies (a procedure to remove a small portion of skin cells) on CIP patients. They found that CIP patients had almost no epidermal nerve fibers, especially C-fiber nociceptors, but skin nerve fibers could still be observed. This implies that the presence of NaV1.7 is essential for the long-term structural integrity of the distal terminals of the nociceptors [17].

Other studies on PRDI-BF1 and RIZ homology domain containing (PRDM) have focused on PRDM12, which belongs to the PRDM protein family, characterized by the N-terminal PR domain related to the SET methyltransferase domain, and multiple zinc fingers that mediate sequence-specific DNA binding and protein-protein interactions. The PRDM family of proteins has an essential role in cellular transcription, especially during differentiation. PRDMs are often involved in localized cell differentiation by directing a series of chromatin modifications at target sites to promote or inhibit the developmental transition of cell states [18].

In 2015, Zhang S et al. identified five cases of CIP patients who had a PRDM12 deficiency and were intellectually normal and able to taste the type of food generally associated with pain sensation—for example, being able to recognize spicy foods as “hot." These CIP patients were able to feel the full range of normal emotions, including painful emotions, and had normal neurological

exams; these patients were able to report sensations including fine touch, deep touch, pressure, vibration, and itching and tickling [19].

Later in 2019, Desiderio S et al. found that mutations in PRDM12 lead to mutations in components of the tropomyosin receptor kinase A (TrkA) signaling pathway and that the team performed double immunostaining of mouse head and trunk ganglia at different embryonic stages after knockout mice to investigate the specific role of PRDM12 in neural development. They found that in mice, PRDM12 is often expressed in combination with the TrkA gene, a gene that is essential for nociceptive neurons. They also found that when PRDM12 was knocked out in mice, their ganglia tended to be smaller and accompanied by incomplete neuronal development. Subsequently, by sequencing spinal cord RNA from PRDM12 knockout mice and normal mice, they found that many neurogenic genes were affected by the deletion of PRDM12. Therefore, they determined that PRDM12 is essential in neuronal development [20].

In another 2019 study, Mark AL et al. found that PRDM12 knockout mice had normal embryonic development, but the pups usually died within a few hours after birth. Compared to normal pups, Mark AL et al. found that the dorsal root ganglia of these PRDM12 knockout mice were significantly smaller (about 68%). Furthermore, by tagging the TrkA, Mark AL's team successfully tracked the growth and activity of the nociceptor. By crossing Advillin mice with PRDM12 mice, the team was able to obtain a mouse that avoided expressing PRDM12 but was able to survive after production. These mice were then subjected to a series of tests that revealed a significantly reduced response to both temperature and physical and mechanical stimuli. At the same time, these mice had fewer nociceptors due to the loss of PRDM12. And in subsequent experiments, if the PRDM2 gene was knocked out in well-developed adult mice, these mice tended not to have a more sluggish response when they received extreme temperature stimuli, such as hot plates or mechanical stimuli. This also means that PRDM12 does not cause insensitivity to pain when knocked out in post-developmental mice. These experiments demonstrate that PRDM12 is essential for the development of Nociceptor neurons [21].

3. Conclusion

Although the current knowledge of CIP is still limited, the pathology and specific mechanisms involved are still unclear. The concept of CIP is still controversial, especially in diagnosis, where different physicians or researchers may have completely different opinions. However, learning about the field of CIP has provided new perspectives on treating chronic pain. The results of CIP research have provided new insights into the molecules and pathways critical for pain perception, providing new insights into the mechanisms by which nerves work on the senses. Although there are currently no therapeutic options for CIP patients that have shown significant results beyond targeted gene therapy, research in this area continues to have a substantial impact on the field of chronic pain, such as inflammatory and arthritic pain, by further dissecting the complexity of pain processing in humans, thus making it possible to provide specific drugs for specific pain. Current developments in microbiology, such as using viruses as vectors for therapeutic purposes, are also attracting more and more attention from researchers. In terms of diagnostics, although next-generation sequencing (NGS) technology currently provides molecular-based diagnostics in many developed and developing countries, it is still not widely available due to its high cost. However, the development of third-generation sequencing technologies provides a new perspective. Perhaps in the near future, the price of whole-genome sequencing could be significantly reduced, providing new insights into the diagnosis and potential therapies for CIP.

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