Channeling Pain

In what ways does the sodium channel Nav1.7 effect inherited and acquired neuropathic pain syndromes?

Abstract

Throughout the world, individuals suffer from inherited and neuropathic pain disorders. Congenital insensitivity to pain (CIP) is a dangerous inherited syndrome that makes the body immune to feeling the sensation of pain. Erythromelalgia, paroxysmal extreme pain disorder (PEPD) and small fiber neuropathy are all inherited pain disorders that cause the individual to feel extreme bursts of pain. All of these disorders are caused by mutations in the gene SCN9A, an alpha subunit of sodium channel Nav1.7. Through blocking this sodium channel, an acquired neuropathic syndrome include, post-amputation pain (PAP), can be treated. After a patient has a limb surgically removed, they can experience three different kinds of PAP: phantom limb pain (PLP), residual limb pain (RLP), and phantom sensations (PSs). PLP includes a pain in the already amputated limb while RLP consists of stump pain. PSs is not a painful sensation, but causes the individual to feel sensations or movement of the already amputated limb. The research of these disorders raises the question: In what ways does the sodium channel Nav1.7 effect inherited and acquired neuropathic pain syndromes? The sodium channel causes the inherited pain due to an inherited gene mutation, and the sodium channel treats PAP through sodium channel blockers, but a malfunction has been found in sodium channels that can cause PAP. When the limb is surgically removed and the nerves are cut, the sodium channels continue to send pain signals to the already amputated limb, thus causing PAP. Through regulating sodium channel firings during amputation and hours after the surgery, doctors may be able to end PAP. After further research, doctors may be able to regulate sodium channel firings when an individual encounters something that inflicts pain on the body, thus diminishing the sensation of pain. Since the cause of PAP and inherited pain syndromes are very similar, sodium channel

blockers may be able to be used to treat inherited pain syndromes. This astounding discovery can save many people from feeling excruciating sensations of pain.

Introduction

Describe pain. The International Association for the Study of Pain (ISAP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."[1] Anyone who has experienced pain though, understands that there is much more to it than a sensation. Pain can be excruciating such as in labor or even irritating when it is frequent and constant. Pain can also be helpful such as when a child touches a hot stove and immediately pulls their fingers away, bursting into tears. They understand not to keep their hand on the hot stove and therefore save themselves from severe burns. For the people who suffer from an inherited neuropathic pain syndrome, they understand the significance of pain for the body. When metabolic disorders such as diabetes, autoimmune diseases. physical injuries, or viral infections attack nerve cells, the nerves can be set off by a mild touch such as bed sheets. Around 20 million people in the United States are affected by these pathological pain extremities.[2] Since the nerves are so sensitive, the pain signals are sent frequently and are pointless, since the body is not in any real danger and does not need to feel pain. They live in horror of moving or touching anything since they do not want that excruciating sensation. On the opposite end of feeling intense, frequent pain, there are conditions that cause the complete absence of pain. Some individuals in northern Pakistan do not feel pain in any part of their body. By the age of 4, six children had injuries on their lips due to excessive biting. Fractures, bruises, and broken bones

[1] Theile, Jonathan W., and Theodore R. Cummins. "Recent Developments Regarding Voltage-Gated Sodium Channel Blockers for the Treatment of Inherited and Acquired Neuropathic Pain Syndromes." *National Center for Biotechnology Information*. U.S. National Library of Medicine, 04 Oct. 2011. Web. 05 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3185237/>.

[2] Ehrenberg, Rachel. "Hurt Blocker: The Next Big Pain Drug May Soothe Sensory Firestorms without Side Effects." *Science News* 30 June 2012: 24. Print.

also occurred, and were only found when the child was incapable to use that limb. Scientists found that the children could feel the sensations of hot and cold, tickling and pressure. Some of the children had been scalded since they feel the warmth but not the pain of the hot liquid. One of the children would put knives through his arms and walk on hot coals as street entertainment. He passed away by jumping off of a building.[3] The children were still able to injure their bodies, but due to their lack of pain they did not understand the depth of the injuries. Humans need pain to protect their bodies. Other than inherited pain, there are other people who acquire neuropathic pain syndromes throughout their lifetime. People who must have an amputation suffer from pain in the stump or even suffer from the mystery of a painful sensation in a limb that they do not even have anymore. About 185,000 upper and lower limb amputations are performed in the United States alone. Three categories of pain are usually felt after the amputation: residual limb pain (RLP), phantom limb pain (PLP), and phantom sensations (PSs). In a study by scientist Ephraim and his colleagues, of the 914 individuals with limb loss, 95% of them experienced one of the three categories of pain. These mysterious painful sensations, therefore, effect a wide range of U.S citizens.[4] Research shows that these different pain syndromes are connected to the sodium channel Nav1.7 in a certain way. This astounding discovery raises the question: In what ways does the sodium channel Nav1.7 effect inherited and acquired neuropathic pain?

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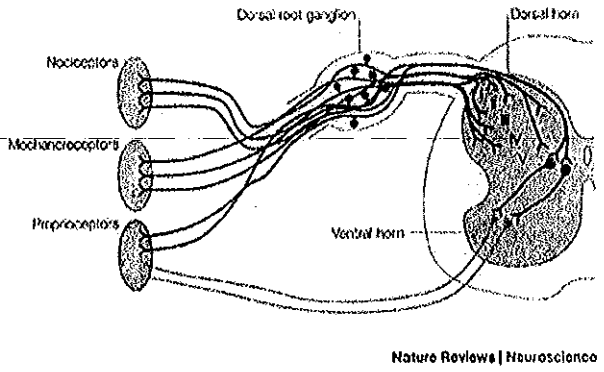
[3] Ehrenberg, Rachel. "Hurt Blocker: The Next Big Pain Drug May Soothe Sensory Firestorms without Side Effects." *Science News* 30 June 2012: 22. Print.

[4] Cohen, SP., and E. Hsu. "Postamputation Pain: Epidemiology, Mechanisms, and Treatment." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23426608>.

The Sodium Channel and Inherited Pain

Voltage-gated sodium channels transport positively charged sodium ions into cells which gives the cells the ability to generate and transmit electrical signals to the brain. They have been used as treatment for inherited and acquired neuropathic pain disorders. There are nine sodium channel isoforms, but four of them- Nav1.3, Nav1.7, Nav1.8 and Nav1.9- amaze researchers through their contributions to chronic pain disorders. The most famous channel, Nav1.7 (Na representing sodium and v for voltage-gated channel) rests on pain-sensing nerves called nociceptors. These nerves are part of the peripheral nervous system, which connects the brain and spinal cord to cells that detect pain, touch, and smell. The center of nociceptors (cell bodies) are located in the dorsal root ganglion in the spinal cord and are mainly used for transporting pain signals. Throughout the cell bodies, axons detect sensory information. Then, these fibers send the information to the dorsal root ganglion which sends it to the brain. [5] [6] [7]



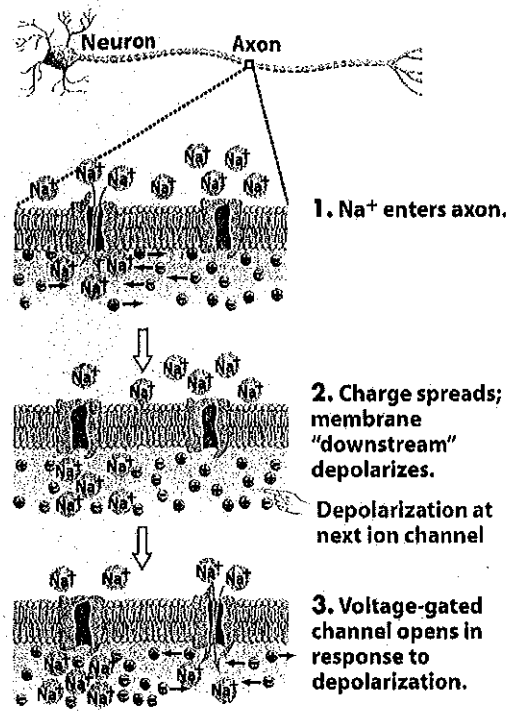
A schematic of the spinal cord. The nociceptors and dorsal root ganglion are labeled. [8]

[5] Cohen, SP., and E. Hsu. "Postamputation Pain: Epidemiology, Mechanisms, and Treatment." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23426608>.

[6] Waxman, SG., Et Al. "Expression of Nav1.7 in DRG Neurons Extends from Peripheral Terminals in the Skin to Central Preterminal Branches and Terminals in the Dorsal Horn." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23134641>.

[7] "SCN9A." *Genetcs Home Reference*. N.p., 2012. Web. 18 Mar. 2013. <http://ghr.nlm.nih.gov/gene/SCN9A>.

[8] Caspary, Tamara, and Kathryn V. Anderson. "Figure 1: Organzation of the Spinal Cord."



A schematic of how voltage gated sodium channels transmit pain. [9]

In the cell membrane, there are different ion channels, such as sodium ion channels and potassium ion channels, where only that ion may pass through. The cell membrane is negatively charged and when a chemical, mechanical, or electrical disturbance affects the cell membrane, positively charged ions flow out of the sodium channel and into the cell, thus making the cell less negative and depolarizing it. When the electrical potential in the membrane reaches =+40mV, the sodium channels close. This membrane change is sent down entire length of the axon, thus the nerve signal is transmitted down the nerve cell.[10]

Nav1.7 is the main topic of interest due to mutations in the gene called SCN9A, which encodes the alpha subunit of the sodium channel. The official name for the SCN9A gene is sodium channel, voltage-gated, type IX, alpha subunit. Loss-of-function mutations in the gene are associated with congenital insensitivity to pain (CIP). On the opposite end of the pain

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8. *Nature.com*. Nature Publishing Group, n.d. Web. 05 Sept. 2013. http://www.nature.com/nrn/journal/v4/n4/fig_tab/nrn1073_F1.html

[9] "The Body's Communication Systems: The Endocrine And Nervous Systems." *The Body*. N.p., n.d. Web. 05 Sept. 2013. http://www.uic.edu/classes/bios/bios100/lectures/nervous.htm

[10] Freudenrich, Craig. "How Nerves Work." *HowStuffWorks*. N.p., n.d. Web. 05 Sept. 2013. http://science.howstuffworks.com/life/human-biology/nerve4.htm

spectrum, gain-of-function mutations in gene SCN9A correspond to pain that causes erythromelalgia and paroxysmal extreme pain disorder (PEPD). Other than these inherited pain disorders, Nav1.7 also contributes to common persistent pain that follows nerve damage. [11] [12] [13]

Congenital insensitivity to pain (CIP) is a very rare inherited pain syndrome that creates a complete absence of pain for the individual. CIP is inherited in an autosomal recessive pattern, which means that both copies of the gene have mutations. There have been 13 mutations in the SCN9A gene found that cause CIP. The mutation sends a premature stop signal in the creation of the alpha subunit. This creates a shortened, nonfunctional alpha subunit in the Nav1.7 sodium channel. The subunit cannot be incorporated into the channel and creates loss-of-function Nav1.7 sodium channels. This loss-of-function mutation hinders the channel from transmitting pain signals from the injured area to the brain causing an insensitivity to pain. As an example, a mutation in the olfactory sensory neurons causes the sense of smell to not be transmitted, leading to the complete loss of smell, called anosmia. [14]

Erythromelalgia is referred to as the "man on fire syndrome." It causes episodes of pain, redness, and swelling in various parts of the body. The condition is inherited in an autosomal dominant pattern, meaning that one copy of the gene is altered and creates the syndrome. The individual may inherit the syndrome from a parent who already had the mutation in their genes or a new mutation may occur that causes an individual to have the syndrome without any family history of it. There are more than 10 mutations in the SCN9A gene that cause erythromelalgia.

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[11] Cohen, SP., and E. Hsu. "Postamputation Pain: Epidemiology, Mechanisms, and Treatment." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23426608>.

[12] "SCN9A." *Genetcs Home Reference*. N.p., 2012. Web. 18 Mar. 2013. <http://ghr.nlm.nih.gov/gene/SCN9A>.

[13] Cohen, SP., and E. Hsu. "Postamputation Pain: Epidemiology, Mechanisms, and Treatment." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23426608>.

[14] "SCN9A." *Genetcs Home Reference*. N.p., 2012. Web. 18 Mar. 2013. <http://ghr.nlm.nih.gov/gene/SCN9A>.

The mutation makes the Nav1.7 channel open more easily than normal and stay open longer than usual. This increases the amount of sodium ions that flow into the cells and therefore enhances the transmission of pain signals. This then creates the characteristics of erythromelalgia. [15]

Paroxysmal extreme pain disorder (PEPD) is also known as familial rectal pain, the rare, lifelong condition that causes attacks of excruciating pain in different parts of the body, such as the eyes, genitalia, rectum, limbs and jaw. It also creates redness and warmth (flushing) in the skin. The syndrome is inherited in an autosomal pattern. Around 10 mutations in the SCN9A gene have been found to cause PEPD. The mutations change amino acids in the alpha subunit of the Nav1.7 sodium channels. This causes the channel to not fully close when it is "turned off," and the sodium ions to flow into nerve cells abnormally. This enhances the transmission of pain signals, and creates pain attacks. [16]

Small fiber neuropathy is a condition where the individual feels painful sensations beginning in their feet or hands. As the individual grows older they will experience the pain attacks in different regions of their body. The pain may consist of burning or stabbing sensations or even tingling and itching. Some people affected by small fiber neuropathy cannot feel pain in a concentrated area, but only in general (hyperalgesia). Sometimes people cannot feel warm or cold sensations or these sensations may trigger a pain attack. This condition affects the peripheral nervous system. Individuals inherit this condition in an autosomal dominant pattern. In small fiber neuropathy, a mutation in the SCN9A gene causes Nav1.7 sodium channels to not close completely when the channel is not in use. The increase in sodium ions flowing into the nociceptors, enhances the transmission of pain, thus making the person extremely sensitive to

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[15] "SCN9A." *Genetcs Home Reference*. N.p., 2012. Web. 18 Mar. 2013. <http://ghr.nlm.nih.gov/gene/SCN9A>.
[16] "SCN9A." *Genetcs Home Reference*. N.p., 2012. Web. 18 Mar. 2013. <http://ghr.nlm.nih.gov/gene/SCN9A>.

sensations that may not cause pain for an individual without this condition. The small fibers connected to nociceptors that transmit pain signals degenerate over time. The degeneration is thought to cause the inability to perceive temperature. [17]

Mutations in the gene SCN9A are also found to cause febrile seizures, which are seizures that occur when a child has a fever. Later on in life the individual may experience seizures when they do not have a high body temperature. Various mutations can also cause Dravet syndrome, a condition where in infancy the individual will experience convulsive seizures. In childhood, the individual will not experience seizures, but a loss of consciousness for short periods of time. It has not been discovered yet what exact mutation in the SCN9A gene causes the syndrome or what problems in the Nav1.7 sodium channels occur.[18]

The Sodium Channel and Acquired Pain

Other than dealing with the pain disorders of CIP, erythromelalgia and PEPD, the individuals are completely normal. This suggests that the sodium channel Nav1.7 is a vital component in human perception of pain and that the channel's function is redundant. Therefore, researchers believe that through targeting this sodium channel, there is a possibility of almost complete analgesia. Experiments in rats and humans have found that different sodium channels prefer certain regions of the body. While one may transport sodium ions to cells in heart muscles, another may transport them mainly to the brain. This discovery supports the idea of sodium channels as pain blockers. Through blocking one channel, pain in just one area of the body can be suppressed.[19] Experiments of patients with post-amputation pain have shown that sodium

[17] "SCN9A." *Genetcs Home Reference*. N.p., 2012. Web. 18 Mar. 2013. <http://ghr.nlm.nih.gov/gene/SCN9A>.
[18] "SCN9A." *Genetcs Home Reference*. N.p., 2012. Web. 18 Mar. 2013. <http://ghr.nlm.nih.gov/gene/SCN9A>.
[19] Ehrenberg, Rachel. "Hurt Blocker: The Next Big Pain Drug May Soothe Sensory Firestorms without Side Effects." *Science News* 30 June 2012: 22-25. Print.

channel blockers decrease the pain in their lost limb or stump. Based on this research, scientists believe that by binding local anesthetics with sodium channels, this will diminish the peripheral neural activity, and therefore decrease PAP sensations. [20]

The use of sodium channel blockers as a pharmacotherapy treatment for post-amputation pain (PAP) is one of many approved treatments. PAP consists of three types of pain: phantom limb pain (PLP), residual limb pain (RLP), and phantom sensations (PSs). Phantom limb pain (PLP) is a painful sensation felt in the already amputated limb. The character of pain can vary from a sharp, electrical-like pain to a dull type of cramping and squeezing. Although the pain usually occurs within 6 months of the amputation, 85% of individuals complain that the pain persists for years after surgical amputation. Residual limb pain (RLP) is also known as stump pain, creating sharp, electrical-like pain in the body part remaining after amputation. 74% of amputees experience RLP even years after the amputation, just like PLP. PSs are defined as non-painful perceptions that affect the lost limb after amputation. One-third of patients experience PSs 24 hours after the amputation, three-quarters of patients within four days, and 90% of patients complain of PSs six months after surgery. The amputation of the body part is essential for the experience of PSs, unlike PLP and RLP. There is kinetic, kinesthetic, and exteroceptive perceptions of PSs. Kinetic sensations involve the individual feeling either willed or spontaneous movement in the already amputated body part (such as toes moving on the already amputated foot). Kinesthetic perception deals with the individual sensing a change in size, shape, or position of the lost limb (such as the arm moving). Exteroceptive perception refers to pressure, touch, itch, temperature, tingling, and vibratory sensations. Many times these sensations are felt

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[20] Cohen, SP., and E. Hsu. "Postamputation Pain: Epidemiology, Mechanisms, and Treatment." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23426608>.

in the hands and feet of the patient and can occur not only after amputation, but also after a spinal cord injury.[21]

The Connection Between Inherited and Acquired Pain

Many scientists and neurobiologists believe that post-amputation pain, and especially phantom limb pain are due to the mental idea of the patient fully believing that the lost limb is still there and still functioning. For the treatment of phantom limb pain, scientist and neurobiologist Ramachandran uses mirror therapy. The patient places their healthy, working limb on one side of a mirror, thus creating a reflection, tricking the mind into believing that there are two arms still attached to the body. The patient is not able to see the stump of their lost limb. The individual then moves and twitches their working arm and they say that the pain in their lost limb vanishes. This therapy completely deals with the mental mechanism of post-amputation pain, but there is a physical aspect that deals with the sodium channels. There is a peripheral mechanism that contributes to PAP in which spontaneous neuronal activity occurs in the proximal end of the cut nerves. The patients explain that when injected with local anesthetic, the pain of the phantom limb vanishes. "Axonal nerve damage during the surgery causes inflammation...Altered expression of transduction molecules, upregulation of voltage-sensitive sodium channels, downregulation of potassium channels, and the development of new nonfunctional connections between axons all serve to spontaneous afferent input to the spinal cord...These changes may lead to spontaneous pain." (PAP) This mechanism proves that even when the nerves are cut, they are still trying to send pain signals to the lost limb, even though they are not needed. In the inherited diseases, paroxysmal extreme pain disorder (PEPD) and

[21] Cohen, SP., and E. Hsu. "Postamputation Pain: Epidemiology, Mechanisms, and Treatment." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23426608>.

erthromelalgia, the mutation causes Nav1.7 channels not to close thoroughly and to stay open longer than needed, thus creating a spontaneous pain sensation. The peripheral mechanism causes spontaneous painful sensations in the phantom limb and thus the sodium channel almost inherits a mutation through the cutting of the nerves. In phantom sensations (PSs), the patients feel the sensations in their hands and feet. In the inherited pain syndrome of small fiber neuropathy, the individual feels pain in their hands and feet due to the Nav1.7 sodium channel not closing completely, and thus creating a rush of pain. The peripheral mechanism explains that these phantom sensations could be caused by the cutting of the nerves creating a malfunction in the sodium channel that is similar to small fiber neuropathy. [22] If this one sodium channel, Nav1.7, is the cause of inherited pain and potentially surgical pain, then surgeons need to look into methods of regulating sodium channel firing for amputation. Through this development, 185,000 people per year just in the United States can feel less pain after a surgical amputation.

Conclusion

In the inherited pain syndromes, congenital insensitivity to pain (CIP), erythromelalgia, paroxysmal extreme pain disorder (PEPD), and small fiber neuropathy, pain takes on a completely new meaning. The mutations in the SCN9A gene in sodium channels Nav1.7 hinder the channels from sending pain signals, thus creating CIP. The mutations can cause the channels to open too easily or to not close fully, thus sending a rush of sodium ions into the cells abnormally, and creating bursts of pain. In acquired neuropathic pain syndromes, such as post-amputation pain (PAP), the nerves cut off during surgery do not fully stop sending pain signals, thus there is a malfunction in the sodium channels, since they

[22] Cohen, SP., and E. Hsu. "Postamputation Pain: Epidemiology, Mechanisms, and Treatment." *National Center for Biotechnology Information*. U.S. National Library of Medicine, n.d. Web. 19 Mar. 2013. <http://www.ncbi.nlm.nih.gov/pubmed/23426608>.

continue to transmit signals to the already amputated limb. If surgeons are able to find a method to regulate sodium channel firings during amputation, then the next research step would be to find a way to regulate sodium channel firings whenever a person comes in contact with something that will inflict pain on their body. Since sodium channel blockers are used as a pharmacology treatment for phantom limb pain, and the cause of PLP and inherited pain syndromes are similar, these sodium channel blockers may be able to treat inherited pain. Individuals with inherited disorders such as small fiber neuropathy and paroxysmal extreme pain disorder have similar symptoms of amputees, thus sodium channel blockers can diminish the side effects of inherited pain syndromes. This will create a completely new perspective in the world of medicine on how to treat pain.