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Study on the Correlation between Expression and Pain of Nav1.7 in Dorsal Root Ganglion

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Abstract: With the further study on pain, many scholars believe that voltage-gated sodium channels play a key role in the generation and development of pain. Of dorsal root ganglion coding Nav1. 7 gene mutations can lead to many diseases that pain, tip in the dorsal root ganglion Nav1. 7 expression closely relationship with pain, in this article, through analysis in recent years in the dorsal root ganglion Nav1. 7 pain expression and correlation of research, explore new drug targets for pain treatment.

Keywords: Dorsal root ganglion; Nav1.7; Pain

1. Introduction

1.1. Voltage-gated sodium ion channel Nav1. 7

Nav1.7 is a transmembrane protein encoded by the SCN9A gene selectively expressed in the dorsal root ganglion (DRG), sympathetic ganglia (high expression on the upper cervical ganglion neurons), Schwann On the membranes of cells and neuroendocrine cells, the expression level of central nerve cells was low, and the expression of Nav1.7 was also detected in cells such as smooth muscle, metastatic breast cancer, and prostate cancer. SCN9A is located on the long arm of chromosome The nucleotide sequence of hNav1.7 is composed of an open reading frame. The read sequence contains 113. 5 kb bases and 26 exons encoding 1977 amino acids. [1].The unique activation and homeostatic inactivation of Nav1.7 is fundamentally different from other voltage-dependent sodium channels and is the basis for this channel to play an important role in the transmission of pain signals: Nav1.7 is characterized by slow opening and slow closing inactivation. Therefore, Nav1.7 remains functional when a slow, depolarizing current below the activation threshold reaches the neuron. Experiments confirmed that at a low voltage of about -65 mV, Nav1.7 can generate sustained inward currents that are sensitive to TTX. This feature can increase the level of depolarization of neurons to external stimuli, thereby expanding impulses and activating nerve endings. The nociceptors increase the sensitivity of neurons to external stimuli. [2]

2. Dorsal Root Ganglion Nav1. 7 with Pain

2.1. Inflammatory pain and Nav1. 7 channels in dorsal root ganglion

When inflammatory pain occurs, it produces many inflammatory mediators, such as prostaglandins, adenosine, and hydroxytryptamine, all of which affect the electrophysiological properties of voltage-gated sodium channels. These inflammatory mediators increase the intensity of the current, resulting in the activation of sodium ion channels at hyperpolarization potentials and increase channel activation and inactivation rates. Therefore, inflammation can sensitize nociceptive neurons. In an experimental model of inflammatory pain—injection of substances that cause inflammation in the hind limbs of rats, upregulation of nociceptive neurons in dorsal root ganglia, axons of these neurons extend into the inflammatory region, and upregulation of these neurons increases the number of these cells. Excitability. In summary, transcription and translation levels of Nav1.7 are significantly increased in animal models of inflammation pain, and NGF and inflammatory cytokines are closely related to the increase in Nav1.7 transcription and translation levels, resulting from inflammatory cytokines. The resulting high expression of Nav1.7 in DRG may increase neuronal excitability and result in painful behavioral manifestations. [3]

2.2. Neuropathic pain and Nav1. 7 channels in dorsal root ganglion

Neuropathic pain is a chronic disease that affects millions of people worldwide. It is characterized by pain allergies, including spontaneous persistent or intermittent burning-like pain, exaggerated responses to painful irritations, and pain for normal, harmless stimuli. It is generally believed that neuropathic pain is caused by alterations in the expression and function of receptors, enzymes, and voltage-gated sodium channels in the nociceptive pathway in the peripheral nerve and dorsal root ganglia. Neurons express

multiple ion channels or receptors. These channels and receptors have at least three functions: transduction (eg, expression of transient receptor potential channels that transduce noxious stimuli into electrical impulses in the distal regions of the neurons, sodium channels, acid-sensitive ion channels, and sensitive receptors.), conductance (for example, sodium and potassium channels participate in the propagation of action potentials), modulation of synaptic transmission (for example, expression of voltage-gated calcium channels and glutamate receptors in the primary afferent postsynaptic terminals of the dorsal horn Regulates neurotransmitter release). After injury, both injured and uninjured neurons become more excited and show ectopic discharges. The sodium channel NaV1.7 is widely expressed in dorsal root ganglia and is mainly distributed in nociceptive neurons, which helps to amplify the activation potential and increase the nociceptive excitability. [4]

2.3. Neuropathological pain not associated with Nav1.7 channels in dorsal root ganglions

Although acute pain and some types of inflammation and neuropathic nerve pain are Nav1.7 dependent, not all pain states depend on Nav1.7. Recently, examples of pain states that do not rely on Nav1.7 expression have been identified in mice and humans. In mice, bone cancer pain and oxaliplatin-induced mechanical and cold allodynia occurred normally in Nav1.7 null mice. Mice usually develop mechanical and cold allodynia after oxaliplatin treatment. This suggests that the expression of Nav1.7 in DRG or sympathetic neurons is not required for this pain syndrome [5]. Similarly, global loss of Nav1.3, Nav1.8, or Nav1.9 does not diminish mechanical or cold allodynia in this model, although the Descoeury study suggests that Nav1.7 expression is enhanced and may induce oxaliplatin induction Cold pain [6], however, in the majority of Minett et al. [7] mice with Nav1.7 deletion, both mechanical and cold allodynia occurred normally. Therefore, the oxaliplatin model produces pain and does not require the presence of Nav1.7. In a mouse model of metastatic cancer pain induced by intrastrand injection of syngeneic LL/2 lung cancer cells, as with oxaliplatin-induced pain, deletion of Nav1.7 expression in the peripheral nervous system did not result in the loss of pain. Although deletion of Nav1.7 in the peripheral nervous system has significant behavioral deficits in all models of acute, inflammatory, and surgically-induced neuropathic pain [8], it does not reduce the incidence of cancer-induced bone pain. There is increasing evidence that cancer-induced skeletal pain is mechanically different from other chronic pain states such as neuropathic pain and inflammatory pain. The neurochemical changes observed in the spinal cord in cancer-induced skeletal pain models differ from those observed in inflammatory and neuropathic states [9]. Although the inflammation model showed an increase in the levels of substance P and calcitonin gene-related peptides in the spinal cord, the cancer-induced bone pain model did not show changes in these neuropeptide levels. Emery [10] thought that the sodium channel blocker mexiletine prevented oxaliplatin-induced pain, but Shcherbatko [11] demonstrated that Nav1.6 plays an important role with delayed rectifier potassium channels in oxaliplatin-induced pain It is consistent. Therefore, there was no significant correlation between Nav1.7 channels and oxaliplatin-induced pain and bone metastases.

3. Research Progress of Nav1.7 Related Animal Models

3.1. Nav1.7 knockout mouse strain production

A large number of Nav1.7 knockout mouse strains are currently produced using the Cre-loxP system. Navl.7Advill mice comprising Nav1.7Nav1.8 mice, Nav1.7Wntl mice expressing the Wntl promoter, and the Advillin promoter expressed in DRG neurons. The effect on the pain behavior of the three types of mice was examined after performing a chronic constriction injury (CCI) of the sciatic nerve or a spinal nerve transaction (SNT) of the fifth lumbar segment. Both surgical models can produce intense cold and mechanical allodynia. The results suggest that: Nav1.7Nav1.8 mice do not produce acetone-induced cold allodynia, but there is normal mechanical allodynia. In contrast, the removal of Nav1.7 from all DRG neurons attenuated cold and mechanical allodynia. It was shown that Nav1.7 expression in DRG neurons is not critical to cold or mechanical allodynia in the sympathetically-mediated SNT model. Nav1.7Nav1.8 and Nav1.7Advill mice usually develop cold and mechanical allodynia after SNT surgery, indicating that the pain associated with the SNT model is not directly generated by Nav1.7-positive nociceptors, in addition, Nav1.7Wnt1 is small Neither cold nor mechanical allodynia occurred in mice, indicating that Nav1.7 expressed in peripheral sympathetic neurons is essential for SNT-induced mechanical and cold v allodynia. [7]

3.2. Deletion of Nav1.7 in adult mice reverses neuropathic pain

People with a loss of latent capacity for Nav1.7 mutations are an important mechanism for the development of painlessness, but specific high-affinity antagonists of Nav1.7 have so far produced no apparent analgesia ([12]. Lae et al. .7 Intrauterine developmental defects may be used to explain some of the problems of Nav1.7-dependent pain. To solve this problem, they used Advillin-CreERT2 [13] to generate inducible DRG-specific Nav1.7 knockout mice. The strain (Nav1.7 ADERT2) Lae et al., the results showed that after tamoxifen induction, Advillin-CreERT2 has the same expression pattern

as Advillin-Cre, uninduced Nav1.7 ADERT2 mice after CCI surgery with their littermates Mechanical allodynia was produced in the same manner, however, mechanical allodynia was reversed in Nav1.7 ADERT2, but after tamoxifen treatment Advox-CreERT2-negative, homozygous floxed (Scn9a) Nav1.7 were in the same fossa The results were reversed in pups, and these data further validated Nav1.7 as a target for the development of analgesic drugs for adults.Emery et al [10] found that knocking out Nav1.7 in Nav1.8-positive nociceptors resulted from mouse experiments. Acute injury However, Minett et al. found that knocking out Nav1.7 in all sensory neurons not only resulted in the above-mentioned symptoms, but also a loss of temperature sensation. This can be seen in Nav1 of the dorsal root ganglion. .8 Negative neuronal Nav1.7 plays a crucial role in acute temperature stimuli, but Emery et al. found that knocking out Nav1.7 expression in the dorsal root ganglion of mice did not affect the behavior of neuropathic pain. The role of Nav1.7 in the dorsal root ganglion in mice remains unclear and there is no consensus on this, which requires further investigation.

4. Antagonist Drug Research Progress

In 2006, James Cox and Geoff Woods [14] found that loss-of-function recessive mutations in Nav1.7 caused insensitivity to congenital pain (CIP) [14]. This amazing discovery has attracted the attention of the majority of scholars in this field, focusing on the development of new sodium channel subtypes of analgesic drugs, in principle should be no side effects. Since global sodium channel blockers are effective analgesics, a key issue in the development of these drugs is the specificity of Nav1.7, which has become an important element that many Nav1.7 drug development projects lack. The expression pattern of Nav1.7 is mainly limited to the peripheral nervous system and is an important route for pain transmission. Selective inhibition of them can reduce central nervous system and heart side effects. Therefore, the selective inhibition of these channels becomes a new target for pain therapy. At present, some companies have begun specific Nav1.7 blocking agent clinical trials, such as vaccines. It was reported that Nav1.7 specific small molecule inhibitor (BZP) can inhibit the expression of peripheral VGSCs and less penetrated into the central nervous system. It was also confirmed that oral BZP can relieve inflammatory and neuropathic pain in animal models, and that CNS-related side effects are lighter than Mexilet. [15]

In 2012, AstraZeneca's application of the proprietary small molecule compound AZD3161 produced a dose-dependent analgesic effect on NaV1.7 in rats and produced a significant analgesic effect at a dose of 49 mg·kg-1. Pharmacokinetic studies have shown that AZD3161 rats have an oral bioavailability of 44% and a half-life of 4.8 hours [16]. There are also NaV 1.7 blockers with better subtypes and less toxic effects in natural products. The selectivity of scorpion toxin μ-SLPTX-Ssm6a for NaV 1.7 was more than one hundred times higher than that of other subtypes. In mouse experiments, one- and two-phase pain responses due to 4% formaldehyde were dose-dependently reduced (1, 10 and 100 nmol·kg-1). In the rat model of acetic acid writhing and hot plates, the efficacy of scorpion toxin was comparable or even better than that of equimolar doses of morphine, while an analgesic dose of 10 times did not affect the blood pressure, heart rate, and motor function of the mice. Studies have found that the analgesic effects of some epilepsy and convulsive medications such as gabapentin and rufinamide are related to N a V 1.7 [17]. Gabapentin (daily 50 mg·kg -1 ,iv) was effective for 1 week to effectively relieve hyperalgesia and mechanical hyperalgesia in diabetic rats. Part of the mechanism of analgesia was related to decreased expression of NaV1.7 in DRG[18] Lufenamide (50 mg·kg-1, po) has a good therapeutic effect on mechanical hyperalgesia in surgically induced SNI mouse models. Electrophysiological results showed that rufamide effectively reduced the peak current of NaV1.7, shifted the steady-state inactivation curve of NaV1.7 towards hyperpolarization, and prolonged the recovery time of NaV1.7 from rapid inactivation, which was dependent on Inhibition of NaV1.7 [19].

The IC50 of the monoclonal antibody targeting NaV 1.7 SVmab1 against NaV1.7 was 30.9 nmol·L-1. This antibody allows the voltage-dependent activation of the channel to move in the direction of depolarization, reducing the peak current of NaV 1.7, and reducing the pain-induced mouse pain response in a dose-dependent manner. Animal experiments showed that SVmab1 (10 and 50 mg·kg-1, iv) can effectively reduce the mechanical hyperalgesia induced by compression injury in rat neuropathic pain model, and the efficacy was up to 24 h, [20] but related to neutralization of Nav1. The claim that .7's monoclonal antibody is an effective analgesic does not continue. Recent studies have shown that the higher the selectivity of Nav1.7 (such as protoxin II) inhibitors, the worse the analgesic effect, while the less selective antagonists (such as CNV-1014802 and lidocaine) may be broader spectrum The sodium channel is very effective. [13]

5. Conclusion

In recent years, research on ion channels and pain has been devoted to scientists from various countries. Ion channels have selective permeability to charged ions, and ion channels play a complex and changing role in the process of pain. The role of voltage-gated sodium channels in the conduction of noxious stimulation is increasingly affected by various countries. Researcher's attention. Although there is currently no clear and complete understanding of the role of sodium channels in pain, its

research has allowed people to discover the important role of NaV1.7 in pain and is working hard to make it a new treatment for pain. The target. It is believed that as scientists continue to work hard to explore and in-depth research on voltage-gated sodium channels, they will be able to provide comprehensive and effective treatment methods for clinical treatment of pain and voltage-gated sodium channel-mutant pain and other diseases.

References

[1] Liu huili, li ping, and li min, the research progress of sodium ion channel Nav1.7 with voltage gated sodium channels. Basic medicine and clinic, 2012(12): p. 1484-1487.

[2] Abdel-Magid, A.F., Nav1.7 Inhibitors: Potential Effective Therapy for the Treatment of Chronic Pain. ACS Med Chem Lett, 2015. 6(9): p. 956-7.

[3] Zhong he jiang and Yang tiande, dorsal root ganglion sodium channel and pain. Chinese clinical rehabilitation. 2003(04): p. 617-619.

[4] Wang lifang, et al., voltage gated sodium channel and neuropathic pain. Journal of china-japan friendship hospital. 2016(05): p. 301-303.

[5] Minett, M.S., et al., Endogenous opioids contribute to insensitivity to pain in humans and mice lacking sodium channel Nav1.7. Nat Commun, 2015. 6: p. 8967.

[6] Descoeur and A.H. Dickenson, Osteoarthritis-dependent changes in antinociceptive action of Nav1.7 and Nav1.8 sodium channel blockers: An in vivo electrophysiological study in the rat. Neuroscience, 2011. 295: p. 103-16.

[7] Minett, M.S., et al., Pain without nociceptors? Nav1.7-independent pain mechanisms. Cell Rep, 2014. 6(2): p. 301-12.

[8] Abrahamsen, Neuroimmune interactions in itch: Do chronic itch, chronic pain, and chronic cough share similar mechanisms? Pulm Pharmacol Ther, 2008. 35: p. 81-6.

[9] Honore, et al., Mouse DRG Cell Line with Properties of Nociceptors. PLoS One, 2015. 10(6): p. e0128670.

[10] Emery, E.C., A.P. Luiz, and J.N. Wood, Nav1.7 and other voltage-gated sodium channels as drug targets for pain relief. Expert Opin Ther Targets, 2016. 20(8): p. 975-83.

[11] Shcherbatko, A., et al., Engineering Highly Potent and Selective Microproteins against Nav1.7 Sodium Channel for Treatment of Pain. J Biol Chem, 2016. 291(27): p. 13974-86.

[12] Rolyan, H., et al., A painful neuropathy-associated Nav1.7 mutant leads to time-dependent degeneration of small-diameter axons associated with intracellular Ca2+ dysregulation and decrease in ATP levels. Proc Natl Acad Sci U S A, 2016. 12.

[13] Laedermann, C.J., H. Abriel, and I. Decosterd, Post-translational modifications of voltage-gated sodium channels in chronic pain syndromes. Front Pharmacol, 2015. 6: p. 263.

[14] Cox JJ, R.F., Nicholas AK, et al, An SCN9A channelopathy causes congenital inability to experience pain. Nature, 2006. 444(7121): p. 894.

[15] Miao ,The effect of BZP on the expression of Nav1.7 in the dorsal root ganglion of diabetic neuropathic pain. Chinese journal of pain medicine, 2014(04): p. 203-207.

[16] K.I.C.G.M.I.N.f.M.S.L.S.K.e., Structure and activity relation-ship in the (S) -N-chroman-3-ylcarboxamide series of voltage-gated sodium channel blockers. Bioorg Med Chem Lett, 2012. 22(17): p. 5618.

[17] Wu baohong, wang yongan, and zheng jianquan. The toxin of the chilopoda can relieve the neuropathic pain through the specific blocking of sodium ion channels., 2014(03): p. 189-193.

[18] Z.J.Y.J.Z.J.L.R.W.J.J.J.e., Gabapentin reduces allodynia and hyperalgesia in painful diabetic neuropathy rats by decreasing expression level of NaV1. 7 and p-ERK1/2 in DRG neurons[Brain Res, 2013. 1493: p. 13-18.

[19] I,S.M.K.G.L.C.A.H.D., Rufinamide attenuates mechanical allodynia in a model of neuropathic pain in the mouse and stabilizes voltage-gated sodium channel inacti- vatedstate. Anesthesiology, 2013. 2013(1): p. 160.

[20] L.J.P.C.C.G.H.Q.X.R.L.T.e., A monoclonal antibody that targets a NaV1.7 channel voltage sensor for pain and itch relief. Cell, 2014. 157(6): p. 1393.