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Review Article

Research progress on the mechanism of chronic neuropathic pain

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ABSTRACT

Chronic neuropathic pain (CNP) refers to pain that lasts for more than three months due to a disease or an injury to the somatosensory nervous system. The incidence of CNP has been increasing in the world, causing it to become a global concern and patients often experience spontaneous pain, hyperalgesia, abnormal pain or even abnormal sensation as some of its main symptoms. In addition to serious pain and poor physical health, CNP also negatively affects patients' mental health, thus impacting the overall quality of their lives. The pathogenesis of CNP is not clear, but some studies have proved that central sensitization, peripheral sensitization, neuroinflammation, dysfunction in descending nociceptive modulatory systems, oxidative stress reaction, activation of glial cells and psychological factors play an important role in the occurrence and development of CNP. In this context, this article summarizes the current research progress on the mechanism of CNP to provide a basis for further research in preventing and treating the disease.

1. Introduction

Over the past few years, growing public awareness regarding health issues, along with the development of medical technology, allowed people to become more conscious about chronic neuropathic pain (CNP). This condition significantly affects both the physical and psychological health of patients and with a prevalence rate of 6.9–10% among the world population, CNP is now considered to be a global disease (Vos et al., 2017).

According to the International Association of the Study of Pain (IASP), CNP refers to pain that lasts for more than three months and which occurs as a result of pathological changes or diseases that affect the somatosensory system (Cohen et al., 2021; Nicholas et al., 2019). Various nerve damaging stimuli in the peripheral or central nervous system can lead to neuropathic pain (NP), such as metabolic diseases, neurodegenerative diseases, tumors, infections, poisoning, trauma, etc. Negative symptoms of CNP include numbness, weakness, and loss of deep tendon reflexes in the affected neural area. Positive symptoms of CNP include spontaneous pain, stimulus-dependent pain and other symptoms such as paresthesia, and characteristic paresthesia of CNP is the key to correctly diagnose this disease and distinguish it from other pain types (Finnerup et al., 2021; Baron et al., 2010; Gilron et al., 2006). Pain is the main positive symptom of CNP, and it can still be accompanied by pain in the corresponding innervation area after the damage factors are eliminated. For example, the persistent tearing and burning pain after herpes zoster, often accompanied by autonomic symptoms, such as irritability, restlessness (Bannister et al., 2020).

The treatment of neuropathic pain remains a challenge because of the complexity and diversity of its mechanisms. Currently, the recognized treatment methods include drug therapy and intervention therapy, which can relieve pain to varying degrees, but cannot cure the disease (Gilron et al., 2015). In clinical practice, the complexity of this mechanism is addressed by an interdisciplinary approach that includes cognitive behavioral therapy, physical and occupational therapy, and others (Baron et al., 2010). Opioids and non-steroidal anti-inflammatory drugs are commonly used. Since many patients have varying degrees of mood disorders, drug therapy is often combined with antiepileptic drugs and antidepressants (Bannister et al., 2020). The main interventional

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therapies include nerve block, transcutaneous electrical stimulation, spinal cord stimulation, etc (Finnerup et al., 2021; Gilron et al., 2015).

CNP does not refer to a single disease, but is instead a clinical syndrome caused by various diseases and lesions (Cohen et al., 2021). In addition to great physical pain, patients having this condition also suffer from mental health issues, resulting in emotional distress in the form of anxiety or depression (Finnerup et al., 2021; Kremer et al., 2021). Moreover, it has been reported that patients may even develop sleep disorders which further aggravate pain, thereby disrupting not only their overall quality of life but also the effectiveness of potential therapies (Meints et al., 2017). Effectively preventing and treating neuropathic pain is therefore of great importance but for this purpose, there is the need to first understand the pathogenesis of the disease so that, depending on the mechanism involved, the appropriate targeted treatment can be administered.

However, there is still no consensus on how CNP occurs or develops. But what is certain is that there is not one, but several, mechanisms that contribute to CNP. Different mechanisms may be involved in the same patient, and the combination of these mechanisms leads to the occurrence and development of CNP, which not only demonstrates the complexity of CNP, but also highlights the importance of identifying the underlying pain mechanisms in the individual patient. Many studies have proposed that central sensitization, peripheral sensitization, neuroinflammation, dysfunction in descending nociceptive modulatory systems, oxidative stress response and the activation of glial cells could be some of the main mechanisms responsible. In addition to these, CNP has also been linked to psychosocial factors (Sun et al., 2021a; Teixeira-Santos et al., 2020; Ho et al., 2020; Sommer et al., 2018; Koga et al., 2016; Jensen and Turk, 2014; Hickey et al., 2014; Loeser and Treede, 2008). Using the above information as background, this article summarizes the progress made by current research in unveiling the mechanism of CNP, in view of providing a theoretical basis for further research on the prevention of the disease.

2. Central sensitization

Based on existing studies, it is now known that the central nervous system plays an important role in causing CNP as pain can only be sensed when the central nervous system is intact. The development of CNP is influenced by the central sensitization process which also represents an important feature of many patients suffering from chronic pain (Quesada et al., 2021; Arendt-Nielsen et al., 2018). Central sensitization, as an overexcited state of the central nervous system, occurs when intense nociceptive stimulation increases the ability of nociceptors within the central nervous system to respond to normal or subliminal afferent information.

During central sensitization, nociceptive sensory neurons can produce or increase spontaneous activity, decrease the peripheral stimulation threshold that can activate neurons, increase the response to suprathreshold stimulation and enlarge the receptive field (Baron et al., 2013). At this time, only the neurons specific to nociceptive stimuli (nociceptive sensory neurons) were converted into wide-dynamic neurons that could respond to both nociceptive and non-nociceptive stimuli, the response to repeated non-nociceptive stimuli gradually increased and the receptive field expanded, and these changes of neurons still existed after the end of stimulation (Yunus, 2008; Neblett et al., 2013).

The main substrate for the central sensitization is activation of the N-methyl-D-aspartate (NMDA) receptor for glutamate. NMDA receptor channels are normally blocked by Mg^{2+} ions and activated because the blockade is abolished by membrane depolarization caused by nociceptive afferent input. Activation of NMDA receptors increases synaptic efficiency and causes Ca^{2+} influx, thus activating intracellular signaling pathways, and ultimately initiating and maintaining central sensitization (Ji et al., 2018, 2003; Liu et al., 2019; Woolf and Salter, 2000). This process also relies on epinephrine-β ligand, calcitonin gene-related peptide (CGRP), brain-derived neurotrophic factor (BDNF), the neuromodulator substance P and glutamate neurotransmitters which together activate various intracellular signaling pathways within the dorsal horn neurons. Including the phosphatidylinositol-3-kinase (PI3K) pathway, the mitogen-activated protein kinase (MAPK) pathway, etc (Latremoliere and Woolf, 2009).

In a diseased state, pain-related central and peripheral neural networks display great plasticity. Neuroplasticity is a compensatory change that occurs when the nerve is injured to adapt to the functional characteristics of neurons, which is of great significance for the maintenance of normal physiological function. Central sensitization can lead to changes in membrane excitability, synaptic plasticity and inhibition of neurons. It can also increase neuronal function while creating loops in pain transmission pathways to cause pain. In addition to the damaged area, central sensitization can further lead to pain caused by harmless stimulation of the area around the injured tissue (Basbaum et al., 2009). It has been reported that glial cells can also be involved in central sensitization, with activated microglia releasing and responding to various chemokines and cytokines to regulate neuroinflammation and mediate CNP (Sun et al., 2021b; Watkins, 2007).

3. Peripheral sensitization

Peripheral sensitization refers to a condition whereby nociceptors in the body or visceral structures are activated and display increased excitability and sensitivity, along with a decreased threshold in response to harmful stimuli. Tissue injury or nociceptive stimulation can induce the release of a large number of chemicals from non-nerve cells and primary afferent terminals in local tissues, which participate in the activation and sensitization of nociceptors. Such products include arachidonic acid metabolites, serotonin(5-HT), bradykinin, nerve growth factor(NGF), nucleotides, and so on (Woolf and Salter, 2000; Davies et al., 1984; Allison et al., 2016; Liu et al., 2020; Choi and Hwang, 2018). The following examples will illustrate the role and mechanism of these factors in CNP.

Arachidonic acid is a polyunsaturated fatty acid present in large amounts within phospholipids of cell membranes, and arachidonic acid metabolites include prostaglandins, leukotrienes, and thromboxane. These substances can enhance the pain sensation by increasing the frequency of action potentials triggered by normal stimuli or endogenous chemicals (Davies et al., 1984). Prostaglandins have been shown to be detectable in inflammatory exudates in pain models and interact with other inflammatory mediators to cause hyperalgesia (Allison et al., 2016). 5-HT is a monoamine released by platelets and mast cells and widely distributed in the nervous system. It has been proved that 5-HT can regulate pain, and 5-HT can not only inhibit but also promote pain sensitivity. Whether the effect is to facilitate or inhibit pain transmission is closely related to the receptor subtypes and the sites of action. 5-HT1, 5-HT2, 5-HT3 and 5-HT7 receptors are the most studied receptors in neuropathic pain. Activation of 5-HT1A and 5-HT7 receptors shows antinociceptive effect in neuropathic pain. 5-HT2A receptors promote local neuropathic pain but inhibit spinal hyperalgesia. The spinal 5-HT3 receptors played both facilitatory and inhibitory roles in neuropathic pain which might related to its binding rate (Liu et al., 2020). Bradykinin is a strong endogenous nociceptive substance released into tissue fluid by mast cells and eosinophils in injured tissues, which can excite and sensitize nociceptors. Through intracellular signaling, mostly composed of G-protein coupled ones, it has been hypothesized that bradykinin may finally augment the depolarizing activities of some specific effector ion channels expressed in the nociceptor neurons (Choi and Hwang, 2018).

Indeed, the release of these peripheral substances from nociceptors not only assists the inflammatory process, but is also involved in injury-related pain by interacting with receptors or ion channels on sensory nerve endings, thus causing primary nociceptive neurons to exhibit enhanced reaction or excitation to stimuli (Gold and Gebhart, 2010). In addition, these chemicals can further activate intracellular signaling

pathways by phosphorylating receptors and pain receptor terminals, change the kinetics of the pathways and even act on tyrosine kinase receptors or G protein coupled receptors to increase the sensitivity and excitability of pain receptor terminals (Julius and Basbaum, 2001).

It has been reported that the transduction of a nociceptive stimulus depends on a number of voltage-gated channels, including those of sodium, potassium and calcium amongst others. A change in conductance in the nociceptive receptors due to depolarization suggests that transduction of a stimulus could involve the closure of potassium channels. Moreover, depolarization also produces a resting membrane potential in pain receptors. Sodium ion is considered to be the transmitter of nociceptive signals which regulate the excitability of neurons and the formation of the depolarization phase of action potential. This was supported by some experiments whereby the loss of voltage-gated sodium channels in rats' sensory neurons was shown to reduce pain sensitivity. In addition, while the calcium channel was lightly expressed in dorsal root ganglions, the expression increased significantly after nerve injury, thus proving that, for the auxiliary voltage-gated calcium channel, its subunits were closely related to abnormal pain (Sun et al., 2021b; Julius and Basbaum, 2001; Wang et al., 2021; MacDonald et al., 2021; Liu and Wang, 2019; Peng et al., 2017).

4. Neuroinflammation

When inflammatory reaction occurs, macrophages and Schwann cells can release pro-inflammatory cytokines such as IL-1β, IL-6, TNF-αand anti-inflammatory cytokines such as IL-4, IL-10 to regulate inflammatory process. Increasing evidence points to the fact that these factors contributes to the occurrence of CNP (Ji et al., 2014, 2016; Biet et al., 2021). Feeling pain is usually linked to inflammation which basically refers to the body's multi-system response to tissue damage or stimulation. Indeed, after injuries to tissues, it involves increased vascular permeability, leukocyte infiltration, glial cell activation and the production of inflammatory mediators such as tumor necrosis factor, interleukin-1 (IL-1) and interleukin-6 (IL6) which are related to fever, prostaglandin, bradykinin and substance P which are linked to pain, histamine, bradykinin and nitric oxide which cause vasodilation as well as oxygen free radicals and lysosomal enzymes which are related to tissue injury. Interestingly, these inflammatory factors exert multiple effects on tissues and cells, with one example being the ability of IL-6 to promote both inflammatory response and the development of blood cells.

Neuroinflammation in CNP is usually the result of peripheral damage to primary sensory neurons and overactivity within the neural network. Inflammatory mediators can directly stimulate the pain receptors on the primary afferents in surrounding tissues, making them increasingly sensitive to stimuli. Such overactivity of the primary afferents subsequently causes more neurotransmitters to be released, leading to the overactivity of postsynaptic nociceptive neurons (Ji et al., 2014). Furthermore, neuroinflammation also activates microglia such as Schwann cells which, in turn, activate mitogen activated protein kinase (MAPK) and extracellular regulated protein kinase (ERK) at the beginning of a nerve injury to trigger the expression of those inflammatory mediators that lead to chronic pain (Napoli et al., 2012). It is also well known that during the early stages of acute inflammation, neutrophils are among the first cells that infiltrate damaged tissues where they phagocytize bacteria and foreign bodies. Hence, some studies involving these inflammatory cells have shown that their accumulation in injured nerves could contribute to the early occurrence of peripheral neuropathic pain. This is presumably because immune cells release various algesic mediators which can sensitize or excite primary nociceptive afferents elicit hyperalgesia and contribute to the generation of neuropathic pain disorders (Perkins and Tracey, 2000).

5. Dysfunction in descending nociceptive modulatory systems

The brain coordinates a top-down pain modulation system that can promote or inhibit nociception from the periphery. Descending nociceptive modulatory systems, including descending nociceptive inhibition system and descending nociceptive facilitation system, plays an important role in the generation and maintenance of pain. Growing evidence supports that chronic pain is associated with dysregulation of the descending pain regulation systems.Disruption of the balance of descending regulatory systems activate the descending facilitation system may promote and maintain chronic pain.Impaired function of the descending inhibition system may be an important factor in determining whether pain is likely to become chronic (Ossipov et al., 2014).

The descending facilitation system includes the anterior cingulate cortex, hypothalamus, amygdala, periaqueductal gray (PAG), rostral ventromedial medulla (RVM), nucleus of solitary tract and dorsal reticular nucleus. In physiological state, the activation of descending facilitation system is to improve the response ability to nociceptive stimuli by lowering pain threshold. After nerve injury, the descending facilitation system can be activated through two pathways. One is to excite neurons in the superficial layer of spinal dorsal horn, which transmits information to amygdala and hypothalamus, indirectly causing RVM activation. The other is that the nerve fibers in the injured area and the adjacent uninjured area produce spontaneous discharge, which is transmitted to the higher center through the gracile nucleus to activate the descending facilitation system (Ossipov et al., 2014; Wei et al., 1999). The RVM also plays an important role in the descending inhibitory system and exerts a bidirectional pain modulatory effect, both inhibiting and facilitating pain.

The descending inhibitory system is composed of the projection of the periaqueductal gray matter from the ventral lateral aqueduct to the rostral ventromedial medulla as well as the connection between the above structures, the upstream cortical and subcortical brain regions and the downstream spinal cord neurons. Descending inhibitory pathways mainly include the brainstem descending inhibitory system composed of PAG-RVM-dorsal horn of spinal cord/spinal trigeminal nucleus, the mesolimbic analgesic circuit composed of PAG-nucleus accumbens-habenular nucleus-PAG circuit and thalamic subcentral nucleus-ventrolateral frame cortex-PAG circuit, the cerebral cortex descending inhibitory pathway composed of hypothalamic arcuate nucleus pain modulation system, and the descending pain modulation system of limbic system via habenular nucleus (Eippert et al., 2009). PAG is the center, RVM is the relay station, and then it goes down to the dorsal horn of spinal cord through the dorsal lateral tract of spinal cord to regulate pain. As a descending nerve fiber that extends from the reticular structure to the spinal cord's anterior horn cells, this descending inhibitory system whose neurons are housed within many different nuclei such as the nucleus raphe magnus, the nucleus raphe dorsalis, the locus ceruleus, the periaqueductal gray, the reticular formation, the hypothalamus and the somatosensory cortex, is actively involved in transmitting peripheral nociceptive sensation to the central nervous system (Kuner, 2010; Bouchet and Ingram, 2020).

Although pain signals are transmitted around neural networks, the descending inhibition system blocks the transmission at the spinal cord to relieve pain, with this process being beneficial to the body under certain physiological conditions. However, when nociceptive stimulation persists, neuroplastic changes can occur in the neurons of the rostral ventromedial medulla of the descending inhibitory system, leading to the continuous transmission of pain signals which further aggravates feelings of pain (Zhuo and Gebhart, 1997).

The above antinociceptive effect exerted by the descending modulatory systems occurs at the spinal cord level mainly through descending 5-hydroxytryptamine (5-HT) and noradrenergic projection fibers (Yamaguchi et al., 2021; Kaswan et al., 2021). The central and peripheral nervous systems, especially areas such as the amygdala, the prefrontal cortex and the thalamus that are involved in pain processing, are

characterized by the high expression of α and β adrenergic receptors which mediate the effects of norepinephrine. When noxious stimulation activates the endogenous descending modulatory system, 5-HT, as the main neurotransmitter in that system, is released in the spinal cord's dorsal horn to downregulate pain levels (Bravo et al., 2019; Bannister et al., 2017). The descending regulatory system could potentially be involved in various non-drug-based methods of CNP, including transcutaneous nerve electrical stimulation, acupuncture and hypnosis (Kuner, 2010).

6. Oxidative stress reaction

Oxidative stress (OS) occurs as a result of an imbalance between the body's oxidative processes and its anti-oxidant mechanisms, thereby leading to inflammation (e.g., neutrophils infiltration) as well as the production of various intermediates, with the most common ones being intracellular reactive oxygen species (ROS), superoxide dismutase (SOD), intracellular glutathione (GSH) and malondialdehyde (MDA). Under normal physiological conditions, the amount of reactive oxygen species is regulated by antioxidant systems to carry out signal transduction in normal cells. However, under pathological conditions, reactive oxygen species are produced in larger quantities and even promote further production of ROS, along with inflammatory factors through specific signal pathways. For instance, damage to the central nervous system and the resulting increase in extracellular levels of glutamate causes excessive activation of N-methyl-D-aspartate (NMDA) receptors. This, in turn, leads to an influx of calcium ions which eventually produces large amounts of ROS (Yang et al., 2021; Mata-Bermudez et al., 2021). Altogether, these processes damage cells irreversibly and may even lead to apoptosis.

Given that reactive oxygen species helps in transmitting neuropathic pain after nerve injury, an increase in its concentration after spinal cord injury can downregulate the transmission of γ-aminobutyric acid (GABA) within the dorsal horn, resulting in various diseases (Zhou et al., 2021; Gwak et al., 2013). Studies of capsaicin models have shown that large amounts of superoxide free radicals are produced by dorsal horn neurons, with ROS levels being correlated to the level of secondary hyperalgesia. The experimental results further showed that central sensitization was also influenced by superoxides (Bittar et al., 2017; Schwartz et al., 2009). Finally, based on models of neuropathic pain, it has been reported that the administration of non-selective ROS scavengers could reduce the overexcitation of nociceptive neurons in the spinal dorsal horn to reduce their hypersensitivity (Grace et al., 2016).

7. Activation of glial cells

Glial cells which are closely involved in CNP can be divided into either microglia that mainly exist around blood vessels and in the parenchyma of the central nervous system or astrocytes which are derived from neuroectoderm and form close synapses with neurons (McMahon and Malcangio, 2009; Hulsebosch, 2008). Within the central nervous system, microglia, as the main innate immune cells, get activated in response to stimulations, including mild ones.

In fact, microglia are likely to be involved when a nerve injury leads to neuropathic pain which is characterized by signal transduction after increased excitability in the dorsal horn. This enhanced excitability is produced by a complex transmission process resulting from communications between microglia, astrocytes, dorsal horn neurons and primary afferents (Ellis and Bennett, 2013). Indeed, after peripheral nerve injury, stimulated nociceptors can induce significant proliferation as well as activation of microglia, alongside a significant upregulation of microglial markers in the spinal cord (Ji et al., 2016). The activation of intracellular signaling pathway, especially the MAPK pathway, is a key step in glial activation in persistent pain, with many mediators such as growth factors and matrix metalloproteinases also playing a role in the direct communication between damaged primary afferent nerves and microglia (Ji et al., 2018; Calvo and Bennett, 2012).

The two types of glial cells also release various growth factors, inflammatory factors and neuroregulators to induce neuroinflammation, with the release of these mediators further facilitating the transmission of pain signals and leading to neuropathic pain. However, this process is far from a simple passive one resulting from degenerated axonal terminals. Instead, this involves an active process which occurs when damaged neurons release signals in response to injuries (Ellis and Bennett, 2013). Sensitization of the central nervous system as well as greater release of inflammatory factors may also take place when glial cells are activated and this can eventually worsen the process of chronic pain.

8. Psychosocial factors

Psychosocial factors are also known to contribute to the occurrence and development of CNP (Meints and Edwards, 2018). Studies have already shown that chronic pain can lead to some degree of psychological and mental disorders, with many patients displaying varying degrees of anxiety, depression, sleep disorders or even strong suicidal tendencies (Kremer et al., 2021; Grocott et al., 2021; Melikoglu and Celik, 2017; Turk et al., 2016; Fishbain et al., 2014). Such psychological changes further increase the sensitivity of patients to pain, and patients showing pain intolerance is one of the important mechanisms of chronic pain. This also explains why anti-anxiety and antidepressant medications are added to the treatment against CNP (Boadas-Vaello et al., 2018).

At present, there are several theories to explain the psychological mechanism of neuropathic pain, mainly including fear-avoidance theory and operant conditioning theory. The fear-avoidance theory holds that people have two behavioral responses: confrontation and avoidance when facing the fear related to pain. Confrontation behavior will eventually lead to the reduction of fear, avoidance will lead to the maintenance and amplification of fear, and ultimately lead to various obstacles in the body (Crombez et al., 2012). Fear of pain may cause related dysfunction because fear can sensitize pain or lower the pain threshold. According to the operant conditioning theory, chronic pain is exacerbated by painful behaviors such as moaning.Pain and its consequences increase pain behavior and contribute significantly to pain persistence (Leeuw et al., 2007).

Furthermore, social factors, including trauma, interpersonal relationships, social support and race, can promote the occurrence, development and prognosis of CNP. For instance, a link between psychological or physical trauma during childhood and chronic pain in adulthood has been reported. Similarly, good social support and relationships can improve the physical capabilities of patients suffering from pain symptoms, reduce the pain intensity and even increase pain threshold. Finally, in terms of ethnicity, it has been reported that blacks displayed more sensitivity to pain than whites (Meints et al., 2017; Turk et al., 2016; Burke et al., 2017; Guillory et al., 2015).

9. Conclusions

CNP is a kind of disease with very complex mechanism caused by nervous system injury or disease. At present, there is no particularly effective treatment, which brings great adverse effects to the life of patients and aggravates the medical pressure of the society. The above summary provides a clear idea of the pathophysiology and psychosocial mechanism of CNP, while highlighting the fact that the occurrence and development of this disease is not caused by a single mechanism. Instead, it is the result of several processes which often occur together and influence each other. For example, neuroinflammation can lead to the activation of microglia, resulting in peripheral and central sensitization, with microglial activation further releasing inflammatory factors. Similarly, the intermediate products of oxidative stress injury can interact with inflammatory factors while at the same time, the social environment and patients' psychological factors can contribute to the

disease.

Our understanding of the underlying pathophysiological and psychological mechanisms of CNP has been greatly improved through the continuous efforts of many researchers and medical workers.Clarifying the pathogenesis of the disease is conducive to mining new therapeutic targets, developing new therapeutic methods, and improving the cure rate and discharge rate of patients.With advances in sequencing technology, the emergence of new molecular techniques, and the invention of various emerging approaches, the likelihood of a cure for CNP will increase dramatically.

Ethical statement

This article does not involve human or animal experiments, and all authors agree to publish it.

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Conflicts of interest

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