Neuropathic Pain: Mechanisms and Treatment Approaches

Zhaniya Turganova

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Neuropathic pain is a debilitating condition resulting from nervous system dysfunction, involving both peripheral and central mechanisms. Peripheral mechanisms involve structural and functional alterations in peripheral nerves, leading to heightened pain sensitivity and transmission. Central mechanisms encompass neuroplastic changes in the spinal cord and brain, resulting in the amplification and spread of pain signals. Current therapies target both peripheral and central mechanisms, employing pharmacological interventions such as antidepressants and anticonvulsants, alongside non-pharmacological approaches like physical therapy and transcutaneous electrical nerve stimulation. Limited understanding the underlying details of central and peripheral mechanisms that initiate and maintain neuropathic pain in patients with neurodenegerative diseases hinders the development of targeted treatment approachees. The aim of this review is to enhance our understanding of the structural and functional alterations in peripheral nerves, neuroplastic changes in the central nervous system, and evaluate the effectiveness and limitations of current therapeutic approaches for neuropathic pain management.

Keywords: Neuropathic pain, Dorsal root ganglion, Peripheral and central sensitization.

Introduction

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory nervous system"[1] or "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". It is characterized by abnormal hypersensitivity to stimuli (hyperalgesia) and nociceptive responses to non-noxious stimuli (allodynia)[2]. Neuropathic pain stems from nerve damage within the peripheral or central nervous system, making it particularly detrimental due to its severe, enduring nature and resistance to conventional analgesics[3]. The physical pain is further aggravated by the financial burden[4]. Even with ongoing treatment, individuals with neuropathic pain frequently visit their doctors and continue to struggle with discomfort that interferes with their daily lives[5].

It's important to recognize that chronic pain is not merely an extension of acute nociceptive signals; instead, it results from a maladaptive functioning of the nervous system[6].

Despite the availability of multiple treatments, neuropathic pain in degenerative diseases remains a significant problem due to its chronic and often refractory nature, leading to increased morbidity and healthcare costs[2]. A limited understanding of the specific mechanisms underlying neuropathic pain hampers our ability to pinpoint potential targets for drug development and to create other interventions that could alleviate pain and enhance symptom management[7]. Moreover, there are currently no objective tests that can confirm neuropathic pain with 100% accuracy[8] and not all aspects of neuropathic pain have been extensively studied or supported by high-quality evidence.

This literature review will involve a comprehensive search of relevant research articles, reviews, and meta-analyses published in scientific journals. The goal is to identify and critically assess the existing knowledge on the pathophysiology of neuropathic pain, focusing on the molecular and cellular mechanisms at play, and the roles of both peripheral and central sensitization in the development and perpetuation of chronic pain. In addition, the review will explore potential therapeutic targets for the treatment of neuropathic pain, including both pharmacological and non-pharmacological interventions.

Pathophysiology and etiology of neuropathic pain

Pain is an essential mechanism that serves as a warning system to the body, signaling the presence of tissue damage, injury, or other harmful stimuli[9]. While pain typically serves as a normal response to injury that resolves as the body heals, it can sometimes become chronic, persisting beyond the expected healing period and leading to ongoing discomfort and a diminished quality of life[10].

Normal pain evolves through several stages, starting with the transduction of a noxious stimulus by specialized sensory neurons called nociceptors. These neurons are found in the skin, muscles, and organs, and they respond to mechanical, thermal, and chemical stimuli associated with tissue damage or injury. Once activated, nociceptors generate an electrical signal that is transmitted to the spinal cord, where it is relayed to other neurons in the pain pathway. At this stage, the signal can be

modulated by various factors, including the release of neurotransmitters and neuromodulators, before being transmitted to the brain for processing and interpretation.

The percentages of neuropathic pain of overall experienced pain by patients with degenerative disease have shown that it is indeed an alarming problem in the field: 70% for Parkinson's disease, 50% for amyotrophic lateral sclerosis (ALS), around 25% for Alzheimer's disease and 58% of overall pain experienced in multiple sclerosis is neuropathic[11]. Neuropathic pains do not respond to NSAIDS and are generally poorly responsive to opiates[12]. Another characteristic of neuropathic pain is the emergence of allodynia, where pain is perceived in response to stimuli that are typically not painful, and hyperalgesia, which is an increased sensitivity to painful stimuli (see Figure 1). In peripheral sensitization, inflammatory mediators lower nociceptor thresholds, in central sensitization, increased excitability in the spinal cord and brain amplifies pain signals.

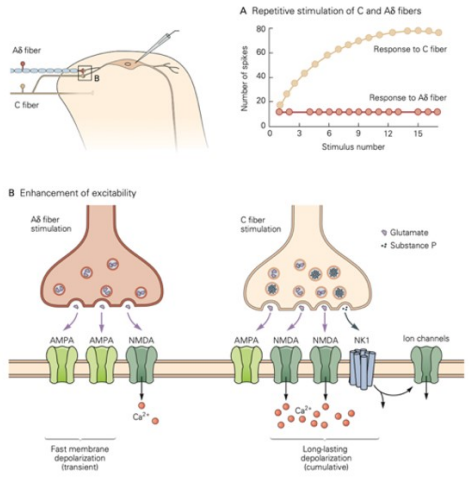

Fig. 1 Allodynia and hyperalgesia's effect on pain sensation and stimulus intensity. Note. From "A clinical perspective on a pain neuroscience education approach to manual therapy" by A. Louw, J. Nijs, & E. J. Puentedura, 2017, Journal of Manual & Manipulative Therapy.

Types of neuropathic pain include:

- Postherpetic neuralgia (PHN)
- Complex Regional pain Syndrome (CRPS)
- Painful diabetic neuropathy
- HIV-associated neuropathy
- Peripheral nerve injury pain
- Drug-induced neuropathy
- Amputation- (stump and phantom limb pain)
- Cancers
- Trigeminal neuralgia (TN)
- NP after spinal cord injury (SCI)

One common misconception is that neuropathic pain has a single, uniform etiology[13]. Its highly heterogeneous nature, with various etiological, genetic, and environmental factor contributing to its development, create a complex pain profile[14,15]. Moreover, in recent years, there has been a growing focus on the etiological roles of miRNAs, lncRNAs, and circRNAs in peripheral nerve injury or noxious stimuli induced NP[16], oxaliplatin in cases of chemotherapy-induced neuropathic pain (CINP)[17–19], mitochondrial dysfunction-associated neuropathy[20–23] and one of the newest discoveries is the role of the anterior cingulate cortex (ACC) in different types of neuropathic pain[24–26]. Shifting the focus from etiology to the reaction to the etiological pathology is an advantageous approach to gain insight into developing dual therapeutical tactics that target both the etiological factors and initiated maladaptive plasticity[27]. In other words, considering neuropathic pain as a manifestation of pathological neural plasticity could aid in understanding the underlying issues that lead to neuropathic pain[13,27].

It is important to be familiar with the specialized peripheral sensory neurons known as nociceptors to gain full understanding of peripheral mechanisms that initiate and maintain NP. Nociceptors in the skin, muscles, joints, and visceral receptors can be classified into two major categories based on the myelination of their afferent fibers: unmyelinated C fibers and myelinated A fibers[12,28]. Aδ fiber nociceptors, which are innervated by thinly myelinated Aδ fibers, produce sharp, prickly, short-latency pain, while Aβ fibers are predominantly involved in transmitting signals related to non-painful touch and proprioception. Because they are activated by sharp objects that pierce, squeeze, or pinch the skin, the majority are known as mechanical nociceptors or high-threshold mechanoreceptors (HTMRs)[12]. Numerous Aδ fibers react to temperatures above 45°C (113°F) and express the TRPV1 heat-sensitive channel, while C fiber-innervated nociceptors respond to thermal, mechanical, and chemical stimuli, producing a burning, dull pain that is diffusely localized and poorly tolerated. The emergence of secondary hyperalgesia and central sensitization is thought to be caused by the activation of silent nociceptors in the viscera[12,29]. Their firing threshold is substantially reduced by inflammation and different chemical agents, and they are not normally activated by noxious stimulation[12,30].

In cases of continuous injury, C fibers repeatedly activate and the reaction of neurons in the dorsal horn intensifies over time, as shown in the figure[12]. The progressive increase in sensitivity of dorsal horn neurons is known as "windup" and is thought to involve N-methyl-D-aspartate (NMDA) receptors that respond to glutamate, as depicted in Figure 2[31,32].

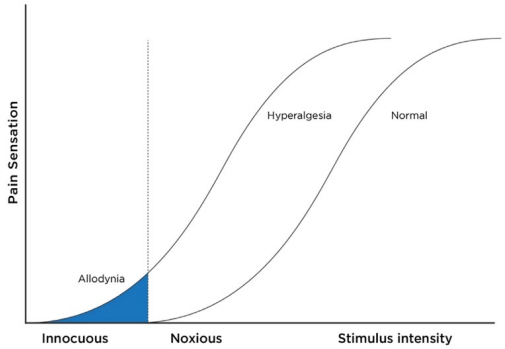

Fig. 2 Progressive increase in sensitivity of dorsal horn neurons. Note. From Principles of Neural Science (5th ed., p. [page number]), by E. R. Kandel, J. H. Schwartz, & T. M. Jessell, 2013, McGraw-Hill.

Table 1. Neuropathic pain mechanisms

Peripheral mechanisms

Peripheral mechanisms of neuropathic pain occur outside the central nervous system, typically at sites of nerve injury or damage, and involve the activation of nociceptors—specialized sensory neurons that detect and transmit pain signals. Nociceptor activation leads to peripheral sensitization, characterized by increased responsiveness and reduced pain threshold. Inflammatory mediators released at the site of injury contribute to peripheral sensitization and the development of hyperalgesia. Neuroplastic changes, such as alterations in ion channel expression and neurotransmitter release, further contribute to the development of neuropathic pain in the periphery. We will discuss phenomena such as peripheral sensitization, collateral sprouting, sympathetic-sensory coupling, inflammation of nerve trunks and related occurrences.

Peripheral sensitization

Peripheral sensitization is a phenomenon where sensory nerve fibers in the periphery become more sensitive to pain signals, leading to increased pain and tenderness in response to stimuli. It is an increase in the responsiveness of primary afferent nociceptors compared to baseline and is caused by many mediators[33]. The significance of any specific factor has proven difficult to determine given that many of these release others, resulting in a complex mix of factors. Chemicals released from damaged cells that accumulate at the site of tissue injury, such as peptides and molecules like H+, K+, bradykinin, substance P, nerve growth factor, ATP, histamine, serotonin (5-HT), prostaglandins, leukotrienes, and acetylcholine can trigger sensitization[34]. Some of the chemicals, for example, ATP and 5-HT directly activate the nociceptors by interacting with ligand-gated ion channels on the terminal, while H+ ions typically activate nociceptors via acid-sensing ion channels. They act together to decrease the threshold of nociceptor activation despite being released from distinct cell types. Theoretically, the process is reversible—once inflammatory mediators and cytokines subside, peripheral sensitization should decrease and eventually dissipate, as typically observed after surgery. However, there are situations where peripheral sensitization continues, for example, in the context of chronic inflammation, such as in rheumatoid arthritis[35] or inflammatory bowel disease[36]. Several factors can trigger spontaneous firing, including increased sub-threshold membrane oscillations in A-fibers, alterations in the membrane potentials of the dorsal root neurons, cross-excitation between nerve fibers (such as between A-fibers and C-fibers), and the upregulation or reorganization of sodium and calcium channels.

Upregulation of receptors

The stimulation of a diverse array of peripheral receptors leads to an increased sensitivity and excitability of nociceptor neurons by influencing the activity of different ion channels. These ion channels include transient receptor potential (TRP) channels like TRPA1, TRPV1, and TRPV4, as well as sodium channels such as Nav1.7, Nav1.8, and Nav1.9[37]. Additionally, mechanosensitive Piezo ion channels are also involved in this process[38,39].

Various allergenic or pain-inducing chemicals, such as serotonin, histamine, and prostaglandins, can activate specific molecular receptors located on nociceptive terminals. This activation triggers a cascade of enzymatic reactions, resulting in the upregulation or increased sensitivity of ion channels that normally respond to acidic, chemical, and mechanical stimuli; and nociceptive-specific sodium channels are also upregulated. The presence of these mediators enhances the responsiveness of these channels to the same concentration of chemicals or mechanical stimulation, leading to a heightened influx of ions. Consequently, the nociceptor is more likely to generate an action potential, thereby amplifying the sensation of pain through a process known as sensitization.

Role of subthreshold membrane oscillations and ectopic discharges

Subthreshold membrane potential oscillations are fluctuations in the membrane that do not reach the threshold necessary to trigger an action potential. Although these oscillations alone don't cause neurons to fire, they can facilitate the processing of sensory signals and promote synchronous activity among neighboring neurons[40]. Research has demonstrated that chronic nerve injury leads to an elevation in the number of neurons displaying subthreshold oscillations, amplifying the magnitude of the subsequent ectopic discharge, and thus leading to neuropathic pain syndromes[41–43]. In other words, a spinal nerve injury can increase subthreshold oscillations in dorsal root ganglion (DRG) neurons, leading to enhanced ectopic discharge, which in turn results in neuropathic paresthesia and pain.

Recent research indicates that ectopic discharges may be

critical in initiating neuropathic pain at the early stages, but their significance tends to diminish as time progresses[44]. In the study, scientists conducted in vivo teased fiber recordings to track ectopic discharges for 14 days following spinal nerve ligation (SNL) and investigated their correlation with tactile allodynia, a condition where normally non-painful touch or light pressure causes pain. With teased fiber recordings in vivo, the study revealed that ectopic discharges exhibited three dynamic firing patterns—tonic, bursting, and irregular—with tonic and bursting patterns predominantly observed within the first 24 hours, while by day 14, the irregular pattern became the sole type detected. Over time, the average frequencies of ectopic discharges and the percentage of active filaments exhibited changes, reaching a peak at 24 hours post-ligation before gradually declining. In other words, ectopic discharges showed a strong association with tactile allodynia in the early stages but weakened over time.

Collateral sprouting

Following peripheral nerve injury, both afferent and post-ganglionic neurons undergo degenerative and regenerative alterations. In addition, unlesioned neurons have the potential to undergo collateral sprouting, which is a process where neighboring sensory neurons send out new branches or sprouts in response to nerve damage or injury, in both the peripheral region and the dorsal root ganglion. This reorganization of peripheral neurons can result in the establishment of chemical connections between sympathetic and afferent neurons, which play a crucial role in sensitizing and activating primary afferent neurons through the influence of sympathetic neurons[45]. In the case of neuropathic pain, collateral sprouting of primary afferent neurons can contribute to the development and maintenance of pain signals because of aberrant synaptic connectivity, increased sensitivity and hyperexcitability. This phenomenon has also been observed in the chronic constriction injury (CCI) model, specifically from the saphenous nerve. Interestingly, although sprouting usually starts about 10 days after surgery, its degree does not directly correspond to the intensity of hyperalgesia observed in chronic sciatic section cases. The outcomes suggest that in this specific model, the observed pain behavior may not be significantly influenced by collateral sprouting[40]. However, it is worth noting that the administration of anti-NGF (nerve growth factor) effectively blocked the sprouting, indicating that local release of NGF from skin sources such as keratinocytes and immune cells may be responsible for axon sprouting in these circumstances. Although collateral sprouting likely doesn't make a substantial contribution, early increasing-intensity treadmill exercise effectively diminishes neuropathic pain. This mechanism operates by averting nociceptor collateral sprouting and the disturbance of chloride cotransporters' homeostasis following peripheral nerve injury[46].

Sympathetic-sensory coupling

Various animal models of neuropathic pain have revealed the potential interplay between sensory afferent neurons and sympathetic fibers, which holds significance in the development of sympathetically maintained pain[45][47]. This coupling of sympathetic and sensory functions can manifest either centrally or peripherally[48]. It entails the discharge of noradrenaline by sympathetic fibers, triggering primary afferent neurons, thus influencing the onset or modulation of neuropathic pain. Following peripheral nerve injury, there's substantial sprouting observed in sympathetic efferent fibers within both the dorsal root ganglia (DRG) and spinal nerves. In certain instances, these sprouting fibers create unique structures resembling basket-like webs, known as sympathetic "baskets," or they form rings of tyrosine hydroxylase [TH]-immunoreactivity [IR] encircling medium and large DRG neurons[48]. These aberrant connections allow sympathetic signals to directly influence sensory neurons, leading to altered pain processing and increased pain sensitivity. Observations indicate that activity within the sympathetic nervous system triggers abnormal impulse transmission in sensory neurons, resulting in the perception of pain. Moreover, the abnormal contact may underlie the heightened responsiveness to catecholamines observed in certain cases of neuropathic pain[49][50]. The fundamental inquiry pertains to the manner and location at which the sympathetic nervous system links with the sensory nervous system, thereby generating pain experienced in clinical scenarios. Proposed mechanisms such as direct chemical coupling at peripheral effector sites between noradrenergic and sensory neuron terminals, ephaptic nerve coupling, indirect coupling through peripheral sensitizing mechanisms involving the discharge of inflammatory mediators from sympathetic terminals and the sensitization of primary sensory neuron axons, as well as direct coupling between the sympathetic and sensory nervous systems in the dorsal root ganglion, have been identified as significant contributors, supported by experimental evidence[51]. Understanding these complex interactions is crucial for developing targeted therapies aimed at disrupting sympathetic-sensory coupling and alleviating neuropathic pain symptoms.

Inflamed nerve trunks

Inducing inflammation along a nerve trunk using substances like complete Freund's adjuvant (CFA) or Carrageenan, without causing evident axonal nerve damage, is recognized as a cause of painful peripheral neuropathy. In a study[52], it was demonstrated that perineural inflammation, achieved through the application of CFA around the nerve trunk without causing axonal nerve damage, resulted in elevated spontaneous activity and induced mechanosensitivity in myelinated axons. When nerve trunks are inflamed, they release various pro-inflammatory substances, such as cytokines and chemokines, which can sensitize nearby sensory neurons, amplify pain signals and lead

to the development and maintenance of neuropathic pain. The release of cytokines and chemokines by nociceptors promptly influences resident immune cells and attracts circulating cells to the area of local inflammation, involving primary afferents and cell bodies in both the nerve and dorsal root ganglion (DRG). An example of this is seen with the nociceptor-produced chemokine CCL2, which regulates the activation of local macrophages in the DRG after chemotherapy through Toll-like receptor (TLR) signaling, thus contributing to neuropathic pain. Furthermore, the connective tissue enveloping nerves, termed nervi nervorum, is itself innervated and harbors nociceptors with numerous fields and branches[53,54]; pathologies affecting the nerves such as inflammation, compression or ischemia initiate heightened nerve mechanosensitivity by the stimulation of nervi nervorum. The condition is then described as nociceptive, however, if subsequently nerve damage occurs, it can coexist with neuropathic pain[55].

Central mechanisms

Central sensitization refers to an enhanced responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input[37,56]. With repeated or intense stimulation, spinal and supraspinal nociceptive pathways undergo sensitization, resulting in an exaggerated pain response. The heightened sensitivity stems from alterations at the synapse of second-order neurons in the spinal area, including modifications in calcium permeability, overexpression of receptors, and shifts in synapse positioning. Additionally, microglia, the immune cells residing in the central nervous system, have also been implicated in chronic pain.

Central sensitization (Spinal cord hyperexcitability)

Glial cells and neuroinflammation in promoting central sensitization.

More than half of the cells in the central nervous system are glial cells, also known as neuroglia or simply glia[57]. They are non-neuronal cells that provide support and essential functions for neurons in the nervous system. There are three main types of glial cells: astrocytes, microglia, and oligodendrocytes in the CNS and satellite glial cells (SGCs) in the dorsal root ganglia (DRGs) and trigeminal ganglia (TGs) and Schwann cells in the peripheral nerves of PNS. Only the role of microglia, astrocytes, and SGCs will be reviewed, as their contribution to pain regulation has been thoroughly researched - it has been concluded that these cells are crucial to the development and maintenance of neuropathic pain[58]. Neuroinflammation is a complex process involving the activation of those immune cells in response to injury or disease in the nervous system which leads to the release of pro-inflammatory molecules that contribute to the development of neuropathic pain. In other words, this neuroinflammation can lead to sensitization of nociceptors and altered processing of sensory signals, resulting in chronic pain.

Microglia are macrophage-like cells in the CNS that regulate homeostasis in the brain and spinal cord[6,59]. Though they were thought to derive from the bone marrow, recent fate mapping studies reveal that microglia are in fact derived from erythromyeloid progenitors in the yolk sac and develop together with the forming CNS[60,61]. During development, microglia interact with synapses and induce synaptic pruning (elimination of extra synapses)[62]. They are known to be involved in the maintenance of normal CNS function as well as in the pathogenesis of several neurological disorders. In neuropathic pain, microglia are thought to play a key role in the development and maintenance of chronic pain states through neuroinflammatory mechanisms.

Research has delved into how microglia contribute to structural changes in the dorsal horn and hippocampus concerning neuropathic pain. It has been suggested that microglia-mediated neuroinflammation and synaptic remodeling in the dorsal horn of the spinal cord contribute to the development and maintenance of neuropathic pain[63–67]. Consequently, it is often investigated within the framework of particular nerve injuries that induce hyperalgesia, allodynia, and heighten dorsal horn excitability. While essential for the immune reaction to infection or trauma, microglia also play a role in pathological neuroinflammation by releasing cytokines and neurotoxic proteins. They can induce the formation of neurotoxic reactive astrocytes, culminating in the establishment of a chronic pain condition[68]. In addition, microglia can phagocytose and remove inhibitory synapses onto pain-sensing neurons, which can further enhance their excitability and contribute to the development of chronic pain[59].

Research studies suggest that microglia play a role in neurodegenerative and psychiatric disease states by remodeling neuron structure. There is also evidence indicating the potential involvement of microglia in pain memory formation after nerve injury, which contributes to the chronicity of neuropathic pain[69]. Additionally, in models of Alzheimer's disease and other neurodegenerative conditions, microglia have been observed to play a role in both the loss and dysfunction of synapses[70].

In addition to abundant evidence demonstrating the participation of microglia in various pain conditions, there is also documentation indicating the involvement of astrocytes, at times appearing to assume a more prominent role than microglia[71]. Typically dormant under normal circumstances, astrocytes undergo a shift to a reactive state in response to nerve injuries like spinal nerve ligation (SNL), chronic constriction injury (CCI), and spinal cord injury (CCI). This reactive state is characterized by the upregulation and hypertrophy of glial fibrillary acidic protein (GFAP), enabling astrocytes to participate in the progression of neurological disorders[72]. Neuronal activity is promoted by the astrocyte activation via the increasing d-serine secretion, which potentiates NMDA receptor function on spinal neurons,

thereby promoting central sensitization[73,74]. Reactive astrocytes exhibit temporal-dependent functional variations in response to injury and unlike the microglia, astrocytes do not always react immediately to a stimulus[6]. Some reactive states, such as a change in the phosphorylation of signaling molecules or an increase in intracellular Ca2+, happen within minutes, while others, like the astrocyte hypertrophy or translational regulation, occur after hours or days. Moreover, astrocyte hypertrophy occurs 3 days after the peripheral injury and lasts for several months[75].

Spinal cord reorganization (Neuroplasticity)

Spinal cord reorganization refers to structural and functional changes that occur within the neural circuits of the spinal cord in response to injury, chronic pain, or prolonged nociceptive input, and it is still not clear if spinal cord reorganization is a cause or a consequence of chronic pain. It was suggested that the development of pain-associated plasticity resembles memory trace formation, which makes the pain perception more affective than somatic in nature[76,77]. In other words, structural spinal and supraspinal reorganization is thought to maintain the chronicity of pain with representational shifting towards emotional than nociceptive circuits; however, it is still worth noting that these reorganizations are not present in every clinical case.

NMDA receptor changes

Dysfunction of N-methyl-D-aspartate receptors (NMDARs) within the nucleus accumbens (NAc), situated in the ventral striatum and pivotal in numerous behavioral and sensory processes, holds significant sway over various neurological and psychiatric disorders like chronic pain, drug addiction, and depression[78]. NMDARs are heterotetrameric complexes typically composed of two obligatory NR1 subunits and two NR2 (NR2A-D) or NR3 (NR3A-B) subunits. While much research has focused on the involvement of NR2A and NR2B-containing NMDARs in different neurological conditions, the role of NR2C/2D subunits in the NAc concerning chronic pain remains unexplored[78]. NMDARs stand as one of the principal glutamate receptors in both the spinal cord and brain. Neurodegenerative processes may ensue from even a modest increase in glutamate, triggered by the activation of extrasynaptic NMDA receptors[79,80]. The functional properties of NMDARs, which are predominantly determined by the specific combinations of subunits, particularly the NR2 subunits, have been widely studied[81]. Accumulating evidence suggests that alterations in the expression and function of NR2B or NR2A subunits in various regions of the central nervous system, including the spinal cord, anterior cingulate cortex, periaqueductal grey, hippocampus, and insular cortex, play a crucial role in the development and maintenance of chronic pain[78,81–84]. Recent investigations have specifically highlighted the involvement of enhanced NR2B subunits in medium spiny neurons (MSNs) within the nucleus accumbens (NAc) in pain hypersensitivity and the associated negative emotional states[85,86]. The role of NR2C/2D subunit-containing NMDARs in modulating neuropathic pain within the NAc has yet to be elucidated, as current evidence in this context is still limited. Nevertheless, an examination of neuropathic pain and depression induced by nerve injury in mice following SNL surgery revealed that the enhancement of NR2C/2D subunit-containing NMDAR function at synapses of NAc shell MSNs is indeed implicated in neuropathic pain and associated depressive-like behaviors[78].

NMDAR activation plays an essential role in synaptic plasticity, the ability of neurons to change their strength and connectivity[87,88]. In the context of neuropathic pain, the increased NMDAR activity contributes to abnormal synaptic plasticity, leading to the potentiation and amplification of pain signals along pain pathways. Specifically, the trafficking and activity of NMDA receptors (NMDARs) are controlled by protein tyrosine kinases, Src-family kinases (SFKs). The phosphorylation of NMDARs by SFKs has been strongly associated with plasticity in the spinal dorsal horn (SDH) and the development of inflammatory and neuropathic pain, and despite that previous research has primarily concentrated on the modulation of NMDARs at postsynaptic locations, SFKs have also been implicated in the regulation of presynaptic NMDARs in primary afferent neurons.

Until recently, the significance of presynaptic NMDARs in spinal cord function has received limited attention, despite their existence being known for many years89. However, recent studies have highlighted the critical role of preNMDARs in modulating the release of glutamate from related primary neurons[89]. This modulation can occur through direct entry of calcium ions into the presynaptic terminal and/or via metabotropic signaling mechanisms. While progress has been made in unraveling the involvement of preNMDARs in the spinal dorsal horn (SDH), there are still several important obstacles to overcome. It is necessary to explore potential differences in preNMDARs based on sex and developmental stages, and to integrate this knowledge into the constantly evolving understanding of molecular and cellular circuitry of the SDH.

Treatment

Primary pharmacological treatments for neuropathic pain include serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and gabapentinoids[90]. Carbamazepine and oxcarbazepine are the first-choice medications for trigeminal neuralgia[91,92]. If medications prove ineffective, alternative options such as interventional procedures, physical therapy, and psychological therapies are available for managing refractory cases.

Anticonvulsants

Drugs prescribed to manage epileptic seizures are referred to as anti-seizure medications, or anticonvulsants. The precise mechanisms through which anticonvulsant drugs provide relief from neuropathic pain remain uncertain[93], however, these medications are thought to hinder the neuron's ability to generate high-frequency firing, possibly by enhancing gamma-aminobutyric acid (GABA) inhibition or by stabilizing neuronal cell membranes. Moreover, another possible mechanism involves the action on N-methyl-D-aspartate (NMDA) receptor sites. Typically, anticonvulsants can disrupt the hyperactive transmission of pain signals originating from injured or hypersensitive nerves, such as in fibromyalgia. Thirteen studies were identified that investigated the effectiveness of anticonvulsants for alleviating pain after spinal cord injury (SCI). Among these, gabapentin and pregabalin, which are recommended as first-line treatments in clinical practice guidelines, were the most frequently studied anticonvulsants. However, there is comparatively less research evidence available for the remaining anticonvulsants, namely valproate, lamotrigine, levetiracetam, and carbamazepine. Typical adverse effects of anticonvulsant drugs include chest pain, constipation, confusion, drowsiness, nausea, heart issues like cardiac arrhythmias, and severe allergic reactions. Moreover, it's generally cautioned for pregnant women to avoid these medications.

• ***Carbamazepine (brand name Tegretol)***

Carbamazepine likely relieves pain by reducing the flow of sodium ions through channels and inhibiting abnormal nerve discharges[94]. In other words, it functions by blocking voltage-sensitive sodium channels, which results in a reduced number of available channels to open[95]. This leads to a decrease in the excitability of brain cells, making them less likely to generate firing signals. Positive results in treating trigeminal neuralgia, painful diabetic neuropathy, and postherpetic neuralgia have been demonstrated in clinical trials, particularly for nerve pain characterized by sensations like burning, shooting, or stabbing. Although carbamazepine has shown to provide noticeable relief for some patients experiencing distressing chronic pain, there is no evidence supporting its effectiveness in managing established acute pain, underscoring the necessity for further research. However, carbamazepine has demonstrated long-standing efficacy in the treatment of neuropathic pain and is often preferred when cost considerations are paramount. Research indicates that, in the short term, at least one out of every two patients treated with carbamazepine for neuropathic pain will experience moderate or greater pain relief, a response that would not have been achieved with a placebo. Overall, approximately 70% of individuals attain some level of pain relief. However, it is important to note that the participant numbers in trials are typically limited, and the duration of the studies is relatively short[95].

• ***Pregabalin (brand name Lyrica) and Gabapentin (brand name Neurontin)***

Considered the primary treatment option for neuropathic pain following spinal cord injury (SCI), both drugs have demonstrated effectiveness in managing pain associated with postherpetic neuralgia and diabetic peripheral neuropathy. Gabapentin used as a standalone treatment has been found to be effective in alleviating pain and improving sleep disturbances caused by diabetic peripheral neuropathy, as well as enhancing mood and overall quality of life[96]. Its mechanism of action involves the inhibition of calcium channels by binding to the $\alpha 2$-δ subunit of the calcium channel complex, thereby reducing the release of neurotransmitters from the presynaptic terminal triggered by action potentials[97].

• ***Oxcarbazepine (brand name Oxtellar XR, and Trileptal)***

Oxcarbazepine, a closely related anticonvulsant to carbamazepine, has been found to be effective in managing neuropathic pain. However, there is conflicting evidence from randomized controlled trials (RCTs). Compared to carbamazepine, oxcarbazepine is reported to have better tolerability, however, the research results on its efficacy vary a lot[98]. For example, one review discovered a scarcity of evidence supporting the effectiveness of oxcarbazepine in treating painful diabetic neuropathy, radiculopathy-induced neuropathic pain, and mixed neuropathies of different origins[99]. When it comes to blocking the pain associated with trigeminal neuralgia—a facial nerve disorder characterized by intense, sudden, and brief pain—carbamazepine and oxcarbazepine are usually more effective than other medications.

• ***Topiramate, Topamax (brand name Qudexy XR, Topamax, and Trokendi XR)***

Topiramate, an antiepileptic drug, has demonstrated efficacy in the treatment of neuropathic pain. It achieves pain relief through multiple mechanisms, including the blockade of sodium and calcium channels, inhibition of glutamate receptors, enhancement of the inhibitory effect of gamma-aminobutyric acid (GABA), and inhibition of carbonic anhydrase[100]. In cases where other drugs have failed to provide relief, topiramate has shown positive effects in the treatment of neuropathic pain. A study demonstrated the efficacy of topiramate in treating neuropathic pain, with no significant difference compared to gabapentin[101]. However, it's important to note that none of these drugs achieve complete pain relief, and thus combining them is suggested for better outcomes.

Antidepressants

Excessive expression of sodium channels in the peripheral nervous system can lead to spontaneous pain and hyperexcitability, which tricyclic antidepressants (TCAs) help mitigate by blocking these sodium channels[102]. Similarly, serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine are effective in managing neuropathic pain by

inhibiting the reuptake of serotonin and norepinephrine[103]. Increased blood pressure, insomnia, dry mouth, dizziness, sexual dysfunction, and nausea are common side effects of SNRIs. However, their dual action is beneficial for individuals with both chronic pain and comorbid depression. Additionally, atypical antidepressants like bupropion and trazodone may be prescribed for neuropathic pain, potentially relieving pain by modulating neurotransmitters.

Non-pharmacological therapies

• ***Interventional therapies***

For intractable neuropathic pain, the effectiveness of interventional therapies like sympathetic nerve/ganglion treatment, transcutaneous electrical nerve stimulation (TENS), epidural motor cortex stimulation, repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex, transcranial direct current stimulation (tDCS) of the primary motor cortex, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex, and transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex varies. Among these, the outcomes of DBS, rTMS, and tDCS are inconclusive[104].

DRG neurons in neuropathic pain can exhibit spontaneous firing due to their lower action potential thresholds[105]- another highly effective interventional therapy is dorsal root ganglion stimulation (DRGS), a safe and effective neuromodulatory technique used for treating neuropathic pain syndromes in various types of NP[106]. Compared to standard spinal cord stimulation (SCS), DRGS offers more precise targeting and pain inhibition even at sub-dermatomal levels. In a recent experiment, DRGS and SCS exhibited comparable wash-in effects, but DRGS demonstrated a faster washout course[107] . In contrast, the implantation of a dorsal root ganglion stimulation (DRGS) device is considered to be more complex compared to spinal cord stimulation (SCS) implantation. However, further research involving animal studies is necessary to explore the long-term effectiveness of this technique, as well as its cost-effectiveness and implications for neuropathic pain treatment. Despite these uncertainties, DRGS holds promise as a potential method for managing drug-resistant neuropathic pain.

Effects of physical therapies like heat and cold applications, fluidotherapy, whirlpool, massage, ultrasound, short-wave diathermy, low-frequency currents (e.g., TENS, diadynamic currents and interferential currents), high-voltage galvanic stimulation, laser are inconclusive[108], rehabilitation techniques (relaxation techniques, acupuncture, mirror therapy, graded motor imagery, visual illusion) are not well-established[109]a, while exercise training have been found to be beneficial for all types of NP[110]; also, exercise therapy combined with psychological therapy have been found to have moderate contribution to the neuropathic pain relief[111].

• ***Psychological therapy***

Psychological therapies offer an approach to enhance coping skills and foster acceptance of chronic pain. The concept of coping in the pain literature lacks a clear definition, but it encompasses behaviors exhibited in response to pain, successful strategies to mitigate pain's impact, and intentional efforts to adapt or manage the negative response to pain[112]. Acceptance of chronic pain is another option that can be defined as living with pain without negative reaction or attempts to avoid it[113]. It involves a realistic outlook on the pain. A comparison study was conducted regarding the efficiency of both coping and acceptance methods. It was identified that acceptance correlated with reduced pain, depression, disability and pain-related anxiety - common features of this technique were recognizing that a cure for the pain is improbable, redirecting attention from the pain to other areas of life, and rejecting the notion that experiencing pain signifies personal weakness. However, it is not clear if these findings would be similar for neuropathic pain, as its unpredictable nature might cause patients encounter challenges when attempting to shift their focus away from the pain.

Overall, there is limited evidence available on the effectiveness and safety of psychological interventions for individuals with neuropathic pain. There has been conducted a research analysis of two studies of small groups, enrolling a total of 105 participants. One study examined a standard cognitive behavioral treatment (CBT) program for 61 individuals with spinal cord injury-related pain, followed them for three months and compared their outcomes to those on a waiting list. The other study involved weekly group psychotherapy for 44 individuals with burning mouth syndrome, which was compared to a daily placebo tablet. However, both trials had significant risk of bias. While both the treatment and control groups showed improvement, there was no significant difference in improvement between the two groups for any of the measured outcomes, either immediately after treatment or during the follow-up period[114].

Hypnosis has been recognized as a potential therapeutic approach for managing various conditions, including chronic pain[115,116]. Research suggests that hypnosis can have positive effects on pain perception, symptom reduction, and overall well-being. During hypnosis, individuals enter a focused state of attention and relaxation, allowing them to be more receptive to suggestions and imagery. By guiding patients to redirect their attention and alter their perception of pain, hypnosis can help modulate the intensity and unpleasantness of chronic pain. Studies have shown promising results in the use of hypnosis for conditions such as fibromyalgia, irritable bowel syndrome, and cancer-related pain. However, it is important to note that the effectiveness of hypnosis can vary among individuals, and it may not be a standalone solution for everyone. In a recent study, it was discovered that hypnosis demonstrated a substantial moderate to large effect size when compared to controls, particularly when the treatment consisted of eight sessions or

more (Hedge's g: -0.555; p = 0.034). Conversely, for treatments comprising fewer than eight sessions, the effect size was small and not statistically significant (Hedge's g: -0.299; p = 0.19) 115. These findings indicate that a minimum of eight hypnosis sessions could provide an effective complementary approach to managing chronic musculoskeletal and neuropathic pain.

Limitations and Future Prospects

The limitations of this study on neuropathic pain primarily center on the generalizability of the findings, as the insights derived may be limited by the specificity of the conditions and methodologies employed. Furthermore, despite notable advancements, a complete understanding of the underlying peripheral and central mechanisms remains elusive.

Looking ahead, future research should prioritize longitudinal studies observing the progression of neuropathic pain over time and evaluating the long-term efficacy of both current and emerging treatments. Additionally, integrating artificial intelligence and machine learning for analyzing large-scale datasets would be critical for improving outcomes for patients suffering from neuropathic pain.

Conclusion

Our understanding of neuropathic pain has advanced significantly in the past 20 years, shedding light on its peripheral and central mechanisms, and informing current therapeutic strategies. Neuropathic pain arises from a combination of peripheral nerve damage and maladaptive changes within the central nervous system. Peripheral mechanisms involve structural and functional alterations in peripheral nerves, leading to heightened sensitivity and transmission of pain signals. Inflammatory mediators, immune cell activation, and disrupted nerve signaling contribute to peripheral sensitization, amplifying pain perception. Meanwhile, central mechanisms involve neuroplastic changes in the spinal cord and brain, where persistent pain signals lead to maladaptive alterations in pain processing and amplification of pain signals.

Current therapies target both peripheral and central mechanisms. Pharmacological interventions are key, with medications such as tricyclic antidepressants and selective serotonin-norepinephrine reuptake inhibitors modulating pain processing in the central nervous system. Non-pharmacological approaches, including physical therapies, transcutaneous electrical nerve stimulation, and psychological interventions like cognitive-behavioral therapy, provide complementary support.

Advancements in therapeutic techniques have expanded treatment options. Invasive procedures like spinal cord stimulation and dorsal root ganglion stimulation deliver electrical impulses to modulate pain signals. Intrathecal drug delivery provides targeted pain relief. Ongoing research into gene therapy, stem cell transplantation, and neurostimulation technologies holds promise for future developments. Moreover, gene therapy aims to modify pain-related genes, while stem cell transplantation seeks to regenerate damaged nerves. Neurostimulation technologies, such as closed-loop systems, may offer improved treatment outcomes.

Despite progress, challenges remain due to the heterogeneity of neuropathic pain and individual treatment responses. Personalized approaches, further research, and the identification of novel therapeutic targets are necessary. By refining treatment strategies, individualizing care, and exploring innovative approaches, we strive to achieve effective and personalized management of neuropathic pain.

Methods

This literature review on neuropathic pain was methodically conducted by selecting and analyzing peer-reviewed research articles, reviews, and meta-analyses that focus on the mechanisms, treatment, and pathophysiology of neuropathic pain. The search was filtered to include only peer-reviewed articles published in English within the last 20 years. Articles were initially screened based on abstracts for relevance to neuropathic pain mechanisms and treatments.

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