MANAGEMENT OF NEUROPATHIC PAIN: CHALLENGES AND OPPORTUNITIES

Anil Kumar*, Deeksha Pahwa and Puneet Rinwa
Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, INDIA

*Corresponding Author: Email kumaruiips@yahoo.com
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ABSTRACT
Neuropathic pain may result from a wide spectrum of insults to the peripheral or central nervous system. This may include nutritional deficiencies, systemic diseases, chemotherapy, cerebrovascular accident, surgery or trauma. The hallmark of neuropathic pain is abnormal neural activity in peripheral nerve(s) or the central nervous system. This is often accompanied by disordered sensory processing both in the peripheral or central nervous system. Treating neuropathic pain is a major clinical challenge, and the underlying mechanisms of neuropathic pain remain elusive. The present review highlights pathophysiology of neuropathic pain and difficulty in treating the symptoms associated with it. This reflects our poor understanding of the pathophysiological processes which lead to neuropathic pain as well as the limited usefulness of many of our pharmacologic agents. An improved understanding of the pathophysiology of neuropathic pain as a result of laboratory research as well as novel means of delivering currently available drugs have provided us with an improved ability to treat certain types of neuropathic pain. Despite these advances, neuropathic pain remains extremely challenging to treat in the best of hands.

Keywords: Neuropathic pain, pathophysiology, pharmacologic agents, symptoms, chemotherapy.

INTRODUCTION
Neuropathic pain is a type of chronic pain that is caused by damage to the neurons (due to disease, infection, trauma, certain medications or metabolic insults) that affects the somatosensory system. Neuropathic pain may result from disorders of the peripheral nervous system or the central nervous system (brain and spinal cord) without peripheral nociception stimulation [1]. Neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain. Neuropathic pain serves no protective purpose for the body as it is not just a symptom of a disease process but is a disease in itself. Instead, the nervous system gets dysfunctional and becomes the cause of the pain. Neuropathic pain can continue for months or years. It may be continuous or episodic and is often described as “burning,” “electric,” “tingling,” or “shooting” pain. Allodynia (pain produced by normally non-painful stimuli) is a common component of neuropathic pain. Other dyesthetic sensations include coldness, numbness, “pins and needles” and itching. Many common diseases such as postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, spinal cord injury, reflex sympathetic dystrophy, cancer, stroke, HIV, fibromyalgia and degenerative neurological diseases may produce neuropathic pain. Multiple mechanisms, including changes in the peripheral nervous system, spinal cord, brainstem or brain, may contribute to the neuropathic pain. It is undeniably challenging to treat patients with neuropathic pain particularly because of its diverse clinical presentation [2] and dynamic nature leading to resistance to many medications. A number of drugs are used to manage neuropathic pain, including antidepressants, anti-epileptic (anticonvulsant) drugs, opioids and topical treatments such as...
capsaicin and lidocaine [3]. Many people require treatment with more than one drug, but the correct choice of drugs and the optimal sequence for their use, has been unclear.

Mechanisms of neuropathic pain

Ectopic impulse generation and Central sensitization: Pain is a physiological defense mechanism to prevent further injury to a living organism. The defense mechanisms include the pain signal transduction from the nociceptors- peripheral nervous system-spinal dorsal horns-thalamus-cortex and the pain control system from the cortex-periaqueductal grey matter-nucleus raphe magnus-spinal dorsal horn. In healthy situations, the pain signal transduction and the pain control system reach a balance and the subject recovers from the pain. However, any imbalance between the pain signal transduction and the pain control system produces neuropathic pain [1]. This imbalance might manifest in form of a nerve lesion or damage, following which regenerative nerve fibres, develop the characteristics of spontaneous erratic impulse generation; such ectopic impulses are conducted along the primary afferents to the CNS without activation of the nociceptors and are perceived as various dysesthetic sensations [1, 6]. Spontaneous firing or losing inhibitory input can also take place within the dorsal horn of the spinal cord and the altered pain processing can, alternatively, be due to a decreased inhibition from the central structures. These processes can persist without ongoing signals from the nociceptors. This abnormal sensitized state of the nervous system is known as "central sensitization" and is a cardinal feature of neuropathic pain [6].

Up-regulation and increased density of voltage gated sodium channels: Proximal to the nerve lesion, there is an up-regulation and increase in the number of voltage gated sodium channels (VGSCs), especially the sodium channel isoforms: Na(v)1.3 in rodent models and Na(v)1.7, Na(v)1.8 in humans [7,8]. Na(v)1.9 is also considered to play an important role in pain. Thus, the repetitive firing of injured neurons gets facilitated at low threshold, which has been considered as a mechanism of ectopic impulse generation. Interestingly, these specific isoforms of VGSCs, are preferentially expressed in the peripheral neurons (all three in dorsal root ganglion and Na(v)1.7 in sympathetic neurons), thus presenting the possibility of targeting sodium channels that do not have any roles in the central nervous system (CNS) or heart. Accordingly, selective modulation of the channels involved in the pathology of the disease, while sparing the channels that are essential for normal nociception, offers promising opportunities for therapeutic intervention.

Calcium channels in nerve injuries: Native calcium channels have been classified by both their electrophysiological and pharmacological properties and are generally divided into low-threshold (T-types) and high threshold (L-, N-, P/ Q- and R-types). N-type calcium channels play a critical role in pain signal transmission. These are distributed across the presynapses of the dorsal horn of the spinal cord. Incoming pain signals activate these channels allowing the influx of calcium into the neuron which then mobilize the synaptic vesicles to release the neurotransmitters passing the signal to the next neuron. The signal thus gets delivered to the brain where it is interpreted as pain. In both the spinal cord and periphery, T-type calcium channels (mainly the Cav3.2 subtype) are implicated in pro-nociceptive mechanisms of somatic pain. By contrast, a recent study has implicated a novel anti-nociceptive role of thalamic Cav3.1 T-type channels in visceral pain mechanisms [13]. The voltage-gated calcium channel subunit α(2δ)1 plays a fundamental role in propagation of excitatory signals associated with release of glutamate and neuropeptides substance P (SP) and calcitonin gene-related protein (CGRP) during nerve injury [1]. The subunit α(2δ)1 can be selectively inhibited by gabapentinoids [15].

Sympathetic-afferent interactions: The neuroma at the nerve injury has both afferent C fibers and efferent post-ganglionic sympathetic C fibers. The afferent fibers release adrenaline and noradrenaline in close proximity to the afferent C fibers. This leads to up-regulation of nociceptive receptors on the regenerating nerve sprout, near the adrenergic nerve terminals. Thus, excessive sensitization of the regenerating sprout to nociceptive substances such as bradykinin, serotonin, histamine, and capsaicin is induced-accounting for ectopic/ spontaneous firing.

Neuroinflammation and Neuropathic pain:
Matrix metalloproteases (MMPs) consist of a large family of endopeptidases that require Zn2+ for their enzyme activity.
MMPs play a critical role in inflammation through the deactivation of the extracellular matrix proteins, cytokines, and chemokines. Nerve injury causes the release of MMP-9 and pro-IL-1β into the extracellular matrix. MMP-9 then deactivates pro-IL-1β to active-IL-1β, with simultaneous activation of dorsal horn microglia. Neuropathic pain development in the late phase requires MMP-2 for activation of pro-IL-1β and astrocytes. Thus, inhibition of MMP-9 or MMP-2 may provide a new approach for the prevention and treatment of neuropathic pain [16]. MMP-9 has been associated with the establishment of aberrant synaptic connections; however, whether this contributes to development of neuropathic pain is not yet clearly understood [19, 20].

Following nerve injury, proinflammatory cytokines such as IL-1β, IL-6, and TNF-α are induced in the nerve and dorsal root ganglion (DRG) [17]. TNF-α and IL-1β have been shown to activate the TTX-resistant sodium channels Nav1.8 [18]. TNF-α enhances excitatory synaptic transmission in superficial dorsal horn neurons whereas IL-6 suppresses inhibitory synaptic transmission in these neurons. IL-1β increases excitation and also decreases inhibition. Thus, proinflammatory cytokines play an important role in central sensitization TNF-α, IL-1β, and IL-6 can further produce long-term effects on synaptic plasticity by inducing gene transcription [16].

Central inhibitory deficiency: Central sensitization in spinal cord dorsal horn neurons can be induced both by an increase in excitatory synaptic transmission mediated via the glutamate NMDA and AMPA receptors and a decrease in loss of inhibitory synaptic transmission (disinhibition) mediated via GABA and glycine receptors [16]. The spinal pain transmission system is under continuous inhibitory control, which originates from brainstem centers located at the periaqueductal gray and the locus ceruleus. Although descending inhibitory controls are still functioning, the inhibitory effects might become weaker in patients with neuropathic pain. Partial nerve injury also induces GABAergic inhibitory interneuron apoptosis and reduces inhibition in the superficial dorsal horn. This transynaptic neural degeneration also contributes to abnormal pain sensitivity [1].

Summarizing, at a molecular level, the lesion of a peripheral nerve causes several changes, including the release of chemical mediators, the upregulation of ion channel receptors and the induction of new genes, resulting in decreased thresholds or spontaneous nociceptor activity, change of cell phenotype and recruitment of silent nociceptors. This hyperexcitability then spreads centrally with the phosphorylation of N-methyl-D-aspartate (NMDA) receptors, the upregulation of the specific dorsal horn sodium channels and an altered gene expression. In addition, the nerve injury produces neuroimmunological change and immune and glial cells perpetuate the pain processing within the CNS.

Strategies targeting neuropathic pain

Treatment of painful sensory neuropathy is a major challenge, and current therapies are often inadequate. Therapeutic approaches for neuropathic pain are largely symptomatic. However, multiple symptoms (and mechanisms) may be present at the same time in neuropathic pain with divergent features that change over time. This complex etiology to symptom relationship in neuropathic pain poses clinical challenges and drug targeting opportunities. The major cellular mechanisms include ectopic or spontaneous nerve activity and peripheral and central hyperexcitability, phenotypic changes in pain conducting pathways, secondary neurodegeneration and morphological reorganization. Further, episodic inflammation and chronic inflammatory conditions also cause nerve injury. There are emerging data that implicate host defense mechanisms and powerful neuroimmune modulation involving peripheral and central immune cell activation in the initiation and maintenance of neuropathic pain [4, 5].

Non-invasive therapies: Current therapeutic strategies for neuropathic pain aim to reduce the excitability of neurons in the peripheral nervous system or the CNS by modulating the activity of ion channels (gabapentin, pregabalin, carbamazepine, lidocaine and capsaicin) or by mimicking and enhancing endogenous inhibitory mechanism (triyclic antidepressants, duloxetine and opioids) [21]. In general, neuropathic pain may be partially or completely unresponsive to primary analgesic treatment. Adjuvant analgesics such as antidepressants and antiepileptic drugs (AEDs), tend to be the mainstay of medical therapies for treating patients with neuropathic pain. Antidepressants have been proved to alleviate pain in some patients with neuropathic pain, although the pain relief may be
The most effective antidepressants in treating neuropathic pain are tricyclic antidepressants (TCAs). However, TCAs are often associated with adverse effects, which limit the tolerance of the patients to the treatments. The newer antidepressants, such as the serotonin selective reuptake inhibitors (SSRIs), have fewer adverse effects but seem to be less effective than the TCAs [1].

There is now abundant evidence not only for a role of voltage-gated sodium channels in pain but also pointing toward specific sodium channel isoforms as major contributors to chronic pain. Till date, relatively nonspecific sodium channel blockers, e.g., lidocaine and carbamazepine, have shown a significant degree of efficacy in terms of treatment of chronic pain. However, the partial nature of the pain relief afforded by these existing medications sets a goal for greater selectivity in therapeutics. The identification of specific sodium channel isoforms, some of which are expressed preferentially within primary sensory neurons, opens up the possibility of targeted therapies aimed at ameliorating hyperexcitability in pain signaling neurons without CNS or cardiovascular side effects. Antiepileptic drugs (AEDs) such as phenytoin, carbamazepine and lamotrigine have been used for the treatment of trigeminal neuralgia for a long time. Resembling the antidepressants, the main problem with using AEDs is their tolerability. Common adverse reactions, including dizziness, ataxia and sedation, tend to reduce the effects of the old generation of AEDs. In most cases, multi-drug therapy may be necessary to obtain good pain relief. The intrathecal administration of methylprednisolone along with 5% lidocaine patch as an add-on therapy is effective in reducing allodynia and pain in patients with post-herpetic neuralgia.

The results of a recent study suggested that mutations leading to the gain-of-function or loss-of-function of a particular sodium channel isoform Nav1.7 leads to painful disorders and loss of ability to experience pain in humans [9, 10]. Thus, translational efforts involving gene therapy could certainly lead to development of new and more specific molecules. However, whether these agents will in fact provide more effective clinical therapies for pain remains to be determined. NMDA receptor antagonists, such as Ketamine, may have a particular role in patients that are poorly responsive to traditional analgesics. Topical capsaicin cream decreases diabetic and postsurgical neuropathic pain. In mice, the administration of anti-NGF antibodies produced a profound reduction in bone cancer pain-evoked behaviors in the mouse model. N-type calcium channels have been recognized as key targets in controlling pain through modulation of the entry of calcium into neurons. Morphine and other related drugs control pain by affecting these calcium channels but indirectly by attaching to the opioid receptors that are present upstream of the calcium channels. However, morphine not only inhibits the N-type calcium channels; it also affects the higher cognitive functions, gastrointestinal and respiratory systems. Brief application of capsaicin induces N-type calcium channel internalization. A more preferred drug option, especially for severe intractable pain, is ziconotide (Prialt), a peptide N-type calcium channel blocker that is administered through a surgically implanted spinal pump [12]. It binds directly and selectively to N-type calcium channels. But, while Prialt inhibits the rapidly firing neurons associated with chronic neuropathic pain, it also inhibits other sensory neurons transmitting innocuous information. Zalicus (formerly Neurorned) has developed an orally administered, small molecule N-type (Cav2.2) calcium channel blocker (Z160) that is state dependent, thereby, targeting only those N-type calcium channels involved with transmitting high frequency pain signals in chronic pain [14]. These selective binding agents are expected to provide superior analgesia, thus, reducing the incidence of side effects experienced with Prialt and opioids and increasing the quality of life for patients worldwide.

In general, pharmacological treatments may act preferentially or selectively on some components of the studied etiologic diagnosis, rather than producing global and uniform analgesic effects. To reach satisfying pharmacological selections or combinations, etiology and mechanism-based evaluation of patients with neuropathic pain should be conducted.

Invasive Therapies: In addition to pharmacotherapeutics, transcutaneous electrical nerve stimulation (TENS) is also a useful adjunctive treatment. The mechanism of TENS in pain-relief is based on the gate control theory. While stimulating largeafferent fibers, the input of small pain afferent fibers will be inhibited on the dorsal horn neurons before projecting.
to the spinal cord. TENS is almost free from adverse effects. As with TENS, spinal cord dorsal column stimulation attempts to inhibit nociceptive transmission by stimulating large afferent fibers. It works especially well on patients with ischemic pain.

Neuroimmune modulation approaches: The conventional therapeutic approaches towards neuropathic pain management aim at only ameliorating the symptoms, generally by suppressing the excitability of neurons or by enhancing the endogenous inhibitory mechanisms. However, most analgesic drugs lack selective action, satisfactory efficacy or produce intolerable side effects. According to recent studies, neuropathic pain has many features of a neuroimmune disorder. It involves not only neuronal pathways, but also the non-neuronal components Schwann cells, satellite cells in the dorsal root ganglia, components of the peripheral immune system spinal microglia and astrocytes [21]. Recognition of the role of immune cells and glia in the pathophysiological changes after nerve injury offers a completely new treatment approach. Given the enormous need for therapeutic progress, surprisingly few clinical studies have tested immunosuppressive drugs or drugs interfering with glial functions for neuropathic pain.

Inhibitors of glial metabolism such as fluorocitrate [22], propentofylline [23,24], minocycline [25, 26] and teriflunomide [27] reduce cytokine release and attenuate pain-responsive behavior in several animal models of neuropathic pain. Fluorocitrate, with preferential action on the glial cells, inhibits aconitase, which leads to blockade of the citric acid cycle. However, toxicity issues prevent its clinical use. Propentofylline, another investigational drug, reduces proliferation and activity of both microglia and astrocytes by inhibiting extracellular adenosine transporters and phosphodiesterases, which results in an increase in cyclic nucleotides, including cyclic AMP [28]. Minocycline is a member of the tetracycline class of broad-spectrum antibiotics that diffuses into the central nervous system. Apart from its antibiotic properties, minocycline inhibits matrix metalloproteases, reduces microglial activity by suppressing the expression of inducible nitric oxide synthase (iNOS) and the phosphorylation of p38 MAP kinase, and has neuroprotective function as an inhibitor of neuronal necrosis and apoptosis [29]. Teriflunomide blocks the de novo synthesis of pyrididines in rapidly dividing cells such as lymphocytes by binding to dihydroorotate dehydrogenase. It also inhibits antigen presentation. Prolonged treatment is, however, associated with an increased risk of sensory and motor neuropathy [34], thus, limiting its use for immunomodulation in neuropathic pain.

Recent interventions have been targeted at purinoceptors, cannabinoid receptors, MAP kinases, TNF and interleukins. Purinoceptors (P2RX and P2Y) are present on the immune cells and the sensory neurons. These get activated by the passive ATP influx from the damaged sensory neurons into the extracellular fluid [21]. Activation of purinoceptors induces various signaling pathways that lead to prolonged nociceptor activity and sensitivity. Novel selective antagonists of P2RX2 and P2RX3 heteromultimers and inhibitors of P2RX3 [30] and P2RX7 [31] reduce spontaneous discharges and evoked responses of primary sensory neurons, decrease cytokine release and attenuate mechanical hypersensitivity after nerve injury.

Type 2 cannabinoid receptors (CB2) are primarily expressed by peripheral immune cells, including macrophages and lymphocytes, and by microglia and astrocytes in the central nervous system [32]. CB2-selective agonists reduce pain-like behavior in animal models of peripheral nerve injury [33]. The role of p38, JNK and ERK in the activation of microglia and astrocytes makes MAP kinases promising targets [35]. However, to specifically block spinal microglial activation, a p38 inhibitor would have to be directed against the b isoform of this MAP kinase, sparing the a isoform that is present in dorsal horn neurons [21]. Furthermore, MAP kinases are important in many cellular processes, such as proliferation and differentiation, stress response, and apoptosis. They are involved in the development, learning and memory, so that systemic application of such inhibitors poses significant risk of interference with physiological functions.

Etanercept, a soluble TNF receptor fusion protein, and Anakinra, a recombinant form of human IL-1 receptor antagonist, have been tested in animal models of peripheral nerve injury and reduce neuropathic pain-like behavior [36]. Induced expression of anti-inflammatory IL-10 in the dorsal root ganglion and spinal meninges provides a prolonged analgesic effect. Thalidomide, an inhibitor of TNF synthesis,
also modulates the expression of other cytokines, including IL-10 [21]. It decreases mechanical and thermal hypersensitivity in rats after nerve injury when the treatment starts at the time of the injury; thalidomide however, has no analgesic effect once neuropathic pain hypersensitivity is established [21]. Similarly, minocycline does not reverse existing hypersensitivity after nerve injury [37]. In contrast, propentofylline, which inhibits microglial and astrocyte activation, attenuates pain responsive behavior when administered early after nerve injury and also decreases established hypersensitivity [38]. Thus, immunosuppression and subsequent blockade of the pathological signaling pathways between immune cells, peripheral glia and primary sensory neurons sets new opportunities for disease modification by reducing the neurobiological alterations that support the development of persistent pain and providing more successful management of pain.

Challenges in the management of neuropathic pain

Neuropathic pain is a cause of significant disability, decreases productivity and quality of life, and increases the cost of health care many folds. Current pharmacological and interventional modalities available for the treatment of chronic neuropathic pain have variable efficacy. In addition, other problems with current therapy include partial target selectivity for sodium and calcium channel blockers, low bioavailability of oral drugs and intolerable adverse effects which are an issue for greater concern in cases of refractory pain. The aforementioned attractive targets for pain intervention if more selective in their approach have still a long way to go before they reach clinical realization.

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