PATHOPHYSIOLOGY OF NEUROPATHIC PAIN: A SYSTEMIC REVIEW

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ABSTRACT

Neuropathic pain is considered as an inappropriate response caused by a lesion or dysfunction in the PNS or CNS. Neuropathic pain can manifest itself as either without a stimulus (stimulus-independent pain) and/or as pain hypersensitivity elicited after a stimulus (stimulus-evoked pain). Stimulus-independent pain includes symptoms described by the patient such as (a) continuous, burning pain (b) intermittent shooting, lancinating pain (c) some dysaesthesias. Conversely, stimulus-evoked pain describes signs the physician induces after mechanical, thermal or chemical stimulation, and usually involves hyperalgesia or allodynia. The mechanism(s) underlying neuropathic pain are not completely understood but are considered to be complex, multifactorial and to evolve over time. Neuropathic pain can be trauma (surgical and non-surgical), accidents, and exposure to toxins, infection, viruses, metabolic diseases, nutritional deficiency, ischemia, and stroke. Current research studies indicate that both peripheral and central mechanisms have been involved in pathogenesis of neuropathic pain.

INTRODUCTION: On the basis of pathological condition, pain may be classified as nociceptive pain and NP. Nociceptive pain is an appropriate physiological response to a painful stimulus and various modulatory mechanisms are involved, which can usually be controlled with standard analgesics. Conversely, NP occurs as a consequence of primary lesion or dysfunction in the nervous system either the central nervous (CNS) or the peripheral nervous system (PNS).

NP is considered as an inappropriate response caused by a lesion or dysfunction in the PNS or CNS. NP can manifest itself as either without a stimulus (stimulus-independent pain) and/or as pain hypersensitivity elicited after a stimulus (stimulus-evoked pain). Stimulus-independent pain includes symptoms described by the patient such as (a) continuous, burning pain (b) intermittent shooting, lancinating pain (c) some dysaesthesias. Conversely, stimulus-evoked pain describes signs the physician induces after mechanical, thermal or chemical stimulation, and usually involves hyperalgesia or allodynia. Normally, non-noxious stimuli such as brushing against clothing, or a puff of air might now elicit pain (tactile allodynia), however stimuli with sharp features, such as a stiff bristle, or the rough surface of sandpaper, will elicit considerable pain that outlasts the stimulus (mechanical hyperalgesia). In addition to chronic, spontaneous NP, the mechanical dyseaesthesia of allodynia and hyperesthesia are most troublesome because of our daily need to interact with objects in our environment.

Keywords: Allodynia, Hyperalgesia, Neuropathic pain, Sensitization, Peripheral, Central

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Classification of Neuropathic Pain: The type of damage or related pathophysiology causing a painful neuropathic disorder can be classified as the following

1. Mechanical nerve injury, e.g. carpal tunnel syndrome, vertebral disk herniation;
2. Metabolic disease, e.g. diabetic poly-neuropathy;
3. Neurotropic viral disease, e.g. herpes zoster, human immunodeficient virus (HIV) disease;
4. Neurotoxicity, e.g. by chemotherapy to treat cancer or tuberculosis;
5. Inflammatory and/or immunologic mechanisms, e.g. multiple sclerosis;
6. Nervous system focal ischemia. e.g. thalamic syndrome (anesthesia dolorosa);
7. Multiple neurotransmitter system dysfunction, e.g. complex regional pain syndrome (CGRP).

The large range of etiologies involved indicate that prevalence of NP may be high in the general population. However, epidemiological studies do not allow estimation of the overall prevalence of NP in the general population, but crude estimation in 1-3 % range have been proposed. Recent research studies indicate that both peripheral and central mechanisms have been involved in pathogenesis of neuropathic pain. Peripheral Sensitization: Peripheral nerve injury is associated with a local inflammatory reaction of the nerve trunk and the released inflammatory mediators sensitize the axotomized nerve fibers.
It is well reported that peripheral or perineural inflammation as measured by plasma extravasation or increased capillary permeability which causes inflammatory cell infiltrate leading to the release of various pronociceptive and pro-inflammatory mediators. Most importantly, neurogenic inflammation has also been reported in experimental models of nerve injury that implicates increased capillary permeability, leading to plasma leakage of proinflammatory and pronociceptive mediators at the local as well as adjacent sites to tissue injury.

**TABLE 1: DIFFERENT MECHANISMS OF NEUROPATHIC PAIN**

| Peripheral Mechanisms                        | Central Mechanisms                                      |
|----------------------------------------------|---------------------------------------------------------|
| Ectopic and spontaneous discharge            | Spinal mechanism:                                       |
| Alteration in ion channel expression         | • Sprouting of Aβ afferent terminal                      |
| Changes in neuropeptides expression          | • Phenotypic changes in the spinal cord                  |
| Sympatheic sprouting                         | • (Phenotypic switch)                                    |
| Collateral sprouting of primary afferent      | • Central sensitization                                  |
| Peripheral terminals                         |                                                         |
| Peripheral Sensitization                     |                                                         |
|                                             | **Superspinal mechanisms**                              |
|                                             | • Reduction of descending inhibitory tone                |
|                                             | • Increase in descending facilitatory tone.              |

This is accompanied by enhanced release of substance P(SP) and calcitonin gene-related peptide (CGRP) in the control of vascular tone following nerve injury. Thus, the pro-inflammatory mediators might be involved in the development and maintenance of neuropathic hyperalgesia. The role of the bradykinin receptors is particularly interesting in this regard. Bradykinin is released as a result of tissue damage, and has been mainly associated with the inflammatory hyperalgesia.

However, recent finding also suggest its role in neuropathic pain. In a recent study, peripheral nerve injury caused a, de novo, expression of the B1 receptor, which is normally absent in neuronal cell. Moreover, the antagonists of bradykinin receptors had anti-hyperalgesic effects. The PGs including PGE2 and PGI2 (also known as prostacyclin) are also rapidly produced following tissue injury and are major contributors to peripheral sensitization. It has been reported that COX inhibitors, which inhibit the production of PGs, attenuate the thermal and mechanical hyperalgesia in animal model of neuropathic pain.

**Central Sensitization:** Central sensitization represents a state of heightened sensitivity of dorsal horn neurons such that their threshold of activation is reduced, and their responsiveness to a synaptic input is augmented. There are two forms of central sensitization.

The first form is an activity-dependent form that is rapidly induced within seconds by afferent activity in nociceptors and which produces changes in synaptic efficacy that last for tens of minutes as a result of the phosphorylation and altered trafficking of voltage- and ligand-gated ion channel receptors. The second one is transcription-dependent form that takes some hours to be induced but outlast the initiating stimulus for prolonged periods.

Under normal conditions the activity-dependent form of central sensitization is produced only following the activation of small caliber Aδ and C fiber afferents by a noxious or tissue damaging stimulus. After peripheral nerve injury, C-fiber input may arise spontaneously and drive central sensitization. In addition, the phenotypic changes that occur in Aβ fibers after nerve injury leads to central sensitization and repeated light touch after nerve injury begin to produce central sensitization.

The activity dependent form of central sensitization is responsible for generating secondary pinprick hyperalgesia and dynamic tactile allodynia. In addition to events such as lowering of activation thresholds of spinal neurons, central sensitization is also characterized by the appearance of ‘wind-up’. Wind-up is characterized by an increasing response to repeated C-fiber stimulation, and may contribute to hyperalgesia.
**Inflammation:** Inflammation is the body defensive mechanism against injury to body tissues. Inflammation can be acute or chronic depending upon the severity of the trauma. Inflammation may release or generate a variety of pro-inflammatory and/or pronociceptive mediators which may produce pain, hyperalgesia, or allodynia that develop as an acute response to a local inflammatory insult. Inflammation leads to increased capillary permeability, perivascular leakage of plasma protein, infiltration and/or migration of neutrophils to the site of injury. In general terms, acute inflammation is associated with high levels of polymorphonuclear cells, particularly neutrophils, whereas chronic or adaptive immune inflammation has higher levels of mononuclear cells, macrophages, T- and B-lymphocytes (Fig. 2).

A. Peripheral inflammatory cells:

1. **Mast Cells:** Mast cells are crucial players in allergic reactions and important initiators of innate immunity. After a partial ligation of the sciatic nerve (PNL), the resident population of mast cells in the peripheral nerve are activated and degranulated at the site of nerve damage. They release proinflammatory mediators, including histamine, serotonin, cytokines and proteases. Histamine seems to be a key mast cell mediator, having sensitizing effects on nociceptors, and is capable of inducing severe burning pain when applied to the skin of patients suffering from postherpetic neuralgia. In addition, neuronal histamine receptors are upregulated after a crush injury to the sciatic nerve. These studies suggest that activated mast cells contribute directly to neuropathic pain by releasing algogenic mediators after degranulation. Mast cells may also contribute indirectly by enhancing the recruitment of other key immune cell types which, in turn, release pronociceptive mediators (Fig. 2).

2. **Neutrophils:** Neutrophils (or polymorpho-nuclear leukocytes) are normally the earliest inflammatory cells to infiltrate damaged tissue and dominate the acute inflammatory stage. As well as being capable of phagocytosis, they release a variety of proinflammatory factors, including cytokines and chemokines, which, in turn, activate and attract other inflammatory cell types, most notably macrophages. Neutrophils are almost absent in the intact, uninjured nerve. Significant infiltration of neutrophils has been observed at the site of nerve lesion in a number of rodent neuropathy models, including PNL, sciatic nerve crush, and chronic constriction injury (CCI). Perkins and Tracey have demonstrated that preventive, rather than curative, depletion of circulating neutrophils, after systemic administration of a selective cytotoxic antibody, reduced the development of thermal hyperalgesia. Thus, neutrophils may be important during the early stages of neuropathic pain development, releasing mediators such as chemokines at the injury site that initiate macrophage infiltration and activation. It is likely that other leukocyte populations (i.e. eosinophils and basophils) are involved in the early events after nerve injury, but little is known about their potential role in the production of neuropathic pain.

3. **Macrophages:** Macrophages are the key immune and phagocytic cell in the peripheral nerve. They are recruited in response to peripheral nerve injury, such as inflammation of and/or loss of axons, myelin, or both. Their main function is to phagocytose foreign material, microbes, and other leukocytes as well as to play a critical role in removing injured and dying tissue debris during Wallerian degeneration.

The recruitment and activation of macrophages within the peripheral nerve is an extremely specific and well-modulated mechanism, involving several proinflammatory mediators and other cell types. Macrophage function has been examined in various models of neuropathic pain, including CCI, PNL, and spinal nerve ligation (SNL).

A reduction in neuropathic pain behaviors correlating with an attenuation of macrophage recruitment into the damaged nerve. It is likely that they contribute through several mechanisms, including the release of pronociceptive mediators. Macrophages are recruited by monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α) and the IL-1β
53, the latter two are released by neutrophils. Macrophages secrete prostaglandins, including PGE2 and PG12 54, 55, which sensitize primary afferent directly. Prostaglandin release by macrophages is strongly implicated in neuropathic pain since inhibition of COX, an enzyme responsible for PGs synthesis, relieves hyperalgesia in nerve-injured rats 56 and COX-2 is up-regulated in macrophages in the injured nerve 21, 22, 23.

4. **T-lymphocytes**: Lymphocytes are divided into two subpopulation: B lymphocytes, responsible for antibody production, and T lymphocytes, which are mediators of cellular immunity (T cells), or natural killer cells. After the identification of both T Cells and natural killer cells at the site of nerve injury in several rodent models, the involvement of T cells in NP was proposed 57. Further, after transection of a spinal nerve, both cell types appear in the adjacent, uninjured DRG, although in lower numbers 58. The invasion of DRG is apparently triggered by retrograde signals from the peripheral nerve. Finally, sural nerve biopsies taken from neuropathic pain patients suggest that T-cell infiltration may be temporally correlated to hyperalgesia 59.

5. **Schwann cells**: Following peripheral nerve injury, Wallerian degeneration distal to the injury site results in the production of cytokines, such as TNF-α 60. Schwann cells produce TNF-α expression in injured and non-injured nerves, IL-1β and neurotrophins, e.g., NGF. IL-1β regulates synthesis of NGF in non-neuronal cells of the rat sciatic nerve, by Schwann cell and macrophages. There have been reports where TNF-receptors immunoreactivity is also observed in Schwann cells and macrophages 61.

The compelling evidence that Schwann cells are involved in the production of neuropathic pain comes from a series of studies which demonstrate neuroprotective and anti-nociceptive effects of erythropoietin after both CCI and crush-induced lesions 62. Furthermore, they were able to correlate these findings with a reduction in levels of TNF-α immunoreactivity in Schwann cells 63.

**FIG. 2: VARIOUS MEDIATORS OF NEUROPATHIC PAIN**

After tissue damage, mast cells and macrophages are activated and some blood-born immune cells including neutrophils are recruited. A variety of immune mediators are released, which exert algesic actions by acting directly on nociceptors, or indirectly via the release of other mediators, most notably prostanoids. TNF-α, tumor necrosis factor IL-1β, interleukin-1β; IL-6, interleukin-6; NO, nitric oxide; PGs, prostaglandins; NGF, nerve growth factor; Cox-2, cyclooxygenase 2. (Thacker et al., 2007)

**B. Central inflammatory cells (Non-neuronal cells):**

1. **Microglia**: Among the non-neuronal cells, microglia are generally considered the immune cells of the CNS. They are known for their response to any kind of pathological insult for which the reaction is termed microglial activation 64, 65. Microglia is, however, known to play a crucial role in the maintenance of neuronal homeostasis in the CNS, and the microglia production of immune factors is believed to play an important role in nociceptive transmission 66. There is increasing evidence that uncontrolled activation of microglial cells under NP conditions induces the release of proinflammatory cytokines 67, 68, 69 (IL-1β, IL-6, TNF-α), complement components (C1q, C3, C4, C5, C5a) and other substances that facilitate pain transmission (fig. 3).
Pharmacological attenuation of glial activation represents a novel approach for controlling NP. Glial cells usually represent 70% of the cells in the CNS under normal conditions, and microglia represents 5-10% of glia. The most characteristic feature of microglia is their rapid activation in the CNS in response to pathological events, including trauma, ischemia, inflammation, hypoxia, neurodegeneration and viral or bacterial infection. After activation, microglial cells change morphology from a resting, ramified shape into an active, amoeboid shape.

Numerous studies in the recent years suggest an important role of microglial activation observed during NP. However, the role glia in the cellular mechanisms underlying the symptoms of neuropathic pain, such as hyperalgesia or allodynia, is not clear. Microglial cells secrete a large variety of substances, including growth factors, cytokines, complement components, lipid mediators, extracellular matrix components, enzymes, free radicals, neurotoxins, NO, and PGs. Furthermore, a transient neuropathic state in naïve rats can be induced by intrathecal injection of ATP-stimulated microglia.

2. Astrocytes: Astrocytes, developmentally derived from the neuroectoderm, are the most abundant glial cell type in the CNS. In addition to their neuron-supportive functions, astrocytes also directly alter neuronal communication because they completely encapsulate synapses and are in close contact with neuronal somas.

There are large number of studies which explore that astrocytic responses are more consistent with the maintenance of pain behavior in neuropathic pain models is delayed and can be reduced by glial modulators (e.g., propentofylline and minocycline). Most studies demonstrate that spinal microglial activation precedes astrocyte activation, but when established the level of astrocyte activation appears to be closely correlated with pain behaviors in different neuropathic pain models.

C. Immune factors in neuropathic pain conditions:

1. Cytokines: The mediators released by inflammatory and immune cells may act directly to sensitize or activate neurons (nociceptors in the periphery or dorsal horn neurons in the spinal cord). Alternatively, they may act on a non-neuronal cell, which on activation releases another mediator that does act directly on the neuron. There mediators form a long and increasing list that includes bradykinin, eicosanoids, cytokines, neurotrophins and reactive oxygen species.

FIG. 3: SPINAL CORD GLIA REGULATION IN THE DEVELOPMENT OF EXAGGERATED PAIN

ATP: Adenosine triphosphate; EAA: excitatory amino acids; IL: Interleukin; NO: Nitric oxide; PTN: Pain transmission neurons; PG:Prostaglandin; ROS: Reactive oxygen species; TNF: Tumor necrosis factor (Watkins and Maier, 2002)
Cytokines are small regulatory protein that mediate interactions between cells over relatively short distances. They are mostly involved in responses to disease or infection. Many of them are known as interleukins, a mediator released by one leukocyte and acting on another, but they are synthesized by most cell types. Several are pro-inflammatory, such as IL-1β, IL-6 and TNF, while others such as IL-10 are anti-inflammatory. These pro-inflammatory cytokines contribute to the mechanism of neuropathic pain. These cytokines are also induced in the CNS. The algesic effects of pro-inflammatory cytokines are often indirect, so that they may not act directly on the nociceptor but they induce the expression of agents (such as PGE2) that themselves sensitize nociceptors.

2. Interleukin-1β: IL-1β is the one of many pluripotent pro-inflammatory cytokines. It is produced and secreted by immune cells including macrophages, monocytes, and microglia under conditions of stress. IL-1β has been identified as one of many algogenic agents that may play a role in neuropathic pain. In the periphery, IL-1β itself results in prolonged hyperalgesia and allodynia after intraplantar intraperitoneal and intrathecal administration.

The mechanism of action of IL-1β in periphery is still not clear. But several studies have shown that binding of IL-1β to its receptor IL1RI on the cell surface initiates several signaling events, such as translocation of NF-kB into the nucleus. NF-kB then upregulates transcription of several genes, including COX-2, iNOS, TNF-α, IL-1β and IL-6. IL-1β may act directly as well indirectly on nociceptors. IL-1 is implicated in neuropathic pain since IL-1α and IL-1β are both upregulated in injured peripheral nerve and also in spinal cord.

3. Tumor Necrosis Factor-α: Tumor Necrosis Factor (TNF, TNFSF2, formerly and TNF-α) is a member of a large super family of protein, which have an unusual trifold symmetry. There is an equally large super family of receptors; the receptors activated by TNF-α are the constitutively expressed TNFR1 (TNFRSF1A, p22-R) and the inducible TNFR2 (p75-R).

4. Nerve Growth Factor: Neurotrophic factors regulate the long-term survival, growth or differentiated function of discrete populations of neurons. The prototypical neurotrophin is NGF. Critical evidence for a role of NGF in pain production was the identification of a mutation in the gene encoding trkA, the high-affinity receptor for NGF. This mutation in trkA leads to congenital insensitivity to pain by disrupting NGF signaling and demonstrates its importance for normal nociceptive functioning.

The role of NGF in pain signaling is now well understood. Small doses of NGF produce pain and hyperalgesia in adult animals and humans. In rodents, thermal and mechanical hyperalgesia develop after systemic NGF administration. NGF produces sensitization of nociceptors both directly (after activation of trkA on nociceptors) and indirectly, mediated via other peripheral cell types. The direct mechanisms involve both altered gene expression and posttranslational regulation of

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receptors and ion channels, including TRPV and tetrodotoxin-resistant N channels. Indeed, NGF over expressing mice display a marked hypersensitivity to both mechanical and thermal stimuli after CCI, suggesting that excess NGF may enhance neuropathic pain behaviors. Several groups have therefore tested the use of anti-NGF treatment in models of neuropathic pain. Anti-NGF antibodies are able to delay the development of neuropathic pain behaviors after both CCI, and SNL.

5. Chemokines: Chemokines are considered a large family of secreted proteins that are found to be chemotactic for leukocytes. Evidences exist that, CCL2 is upregulated exclusively in neurons of the DRG following peripheral nerve injury, while it is expressed by neurons and microglia in the spinal cord. A spatial and temporal relationship between CCL2 expression and spinal glial activation following nerve injury is evident, suggesting that neuronal CCL2 may serve as a trigger for spinal microglia activation.

6. Prostanoids: It has been established that the PGs also contribute to nociception at the level of the spinal cord. Various studies have shown that mechanical hyperalgesia in nerve-injured rats was alleviated for up to 10 days by subcutaneous injection of indomethacin (a classic inhibitor of COX-1/2) into the affected hind paw. Subcutaneous injection of selective COX-2 inhibitors or an EP1 receptor blocker relieved thermal as well as mechanical hyperalgesia, but with a shorter time course. This shows that there is increased expression of PGs in the region of the nerve lesion that contributes to neuropathic pain.

Several animal models of neuropathic pain showed that the number of COX-2 immunoreactive cells was dramatically increased in the region of the nerve lesion and increased levels of PGE2 are found in the injured nerves. Furthermore, cells immunoreactive for EP receptors are found in the injured nerve, but not in normal intact nerve. Observation, based on several animal models of sciatic nerve injury, support the idea that upregulation of COX-2 and EP receptors in the injured nerve contribute to neuropathic pain.

7. Nitric Oxide(NO) and Reactive Oxygen Species (ROS): Reactive oxygen species such as NO and superoxide play important roles in inflammatory and immune responses, including defense mechanisms against invading microbes. They are released by a number of cell types, including neutrophils (Zuo et al., 2003) and macrophages as well as astrocytes and microglia.

NO is a diffusible free radical that is synthesized by three distinct NO synthases (NOS), neuronal and endothelial forms (nNOS and eNOS) are constitutive, while the inducible form (iNOS) is upregulated in immune cells. Once released, NO can react with superoxide radicals to form peroxynitrite, which is toxic and may cause tissue damage.

NO play important role in nociception. It causes pain when injected into the skin of human subjects and contributes to peripheral hyperalgesia in the skin and joints, probably by contributing to PGE2-induced sensitization of primary afferents.

NO is also implicated in central mechanisms of hyperalgesia where nNOS and NO form part of a second messenger cascade involving cyclic GMP and may be partly responsible for sensitization of spinal neurons. In rats with a chronic constriction injury of the sciatic nerve, iNOS is induced in macrophages and Schwann cells at the injury site and distal to it.

Treatment with a non-specific NOS inhibitor (L-NAME) alleviated hyperalgesia and blocked ectopic mechanosensitivity of injured A-fibers. NO also plays a role in central mechanisms of neuropathic pain so that, in nerve injured rats, intrathecal delivery of the NOS inhibitor L-NAME produced a dose-dependent reduction of thermal hyperalgesia.

Growing body of evidence indicates that ROS are also implicated in neuropathic pain. ROS also contribute to mechanical allodynia, which is relieved by SOD in an inflammatory model of neuropathic pain.
Treatment of Neuropathic Pain: First line drugs for the treatment of peripheral neuropathic pain includes gabapentin, pregabalin, 5% lidocaine patch, tri-cyclic antidepressants like nortriptyline, desipramine and selective norepinephrine reuptake inhibitors (SSNRI) like duloxetine and venalafaxine. The second line therapy includes opioid analgesics, tramadol hydrochloride, and the third line medication includes other anticonvulsants like carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid and antidepressants such as bupropion, citalopram, paroxetine. Local anesthetics like mexiletine, NMDA receptor antagonists and topical capsaicin etc. 131.

Gabapentin (Neurontin), an anti-epileptic drug was introduced in 1993 and originally it was used for the treatment of partial seizures with or without secondary generalization. It is FDA approved for the treatment of post-herpetic neuralgia (PHN). It binds to α2δ subunit of voltage-gated calcium channel, decreasing the release of glutamate, norepinephrine, and substance P 132. However, the relationship between binding at this site and the antinociceptive property of gabapentin has not been well determined. In addition, the 5% lidocaine patch (Lidoderm®) has been approved by the FDA for the treatment of PHN (table 2).

TABLE 2: LIST OF DRUGS, THEIR MECHANISM OF ACTION AND DRUGS

| Therapeutic Class | Drugs                                      | Dose-limiting ADRs/SEs                          |
|------------------|--------------------------------------------|------------------------------------------------|
| Antiepileptic    | Gabapentin, Pregabalin                    | Sedation, dizziness, Peripheral oedema         |
|                  | Lamotrigine, Carbamazepine                | Hepatotoxicity, CNS toxicity, Teratogenicity   |
| Antidepressants  | Amitriptylline, Paroxetine, Duloxetine, Nortriptyline | Anticholinergic side effects, Sedation and orthostatic, Hypotension |
| Local anesthetics| Mexiletine, Topical lidocaine             | Tremors, ataxia                                |
|                  |                                           | Local erythema, rashes                         |
| Analgesics       | Peripheral NSAIDs                         | Gl ulceration, Renal Failure                   |
|                  | Central Opioids                            | Addiction, dependence, tolerance              |

CONCLUSION: Many studies have provided evidence of a critical role for immune cells and proinflammatory mediators in the generation of neuropathic pain after injury of the peripheral nervous system. Although there is growing evidence for specific actions of individual molecules, the complex interactions of the cells and mediators involved are not fully established. The peripheral immune response may play a pivotal role in nerve injury-induced pain.

Anticonvulsant drug such as carbamazepine (Tegretol®) act through membrane stabilization was also approved by the FDA for the treatment of trigeminal neuralgia 133.

Antidepressant drug duloxetine (Cymbalta®) that act through selective serotonin and nor-epinephrine reuptake inhibition has recently been approved by the FDA for treatment of diabetic neuropathic pain (DNP). Another antiepileptic drug, pregabalin (Lyrica®) was also launched in the treatment of DNP in 2004 134. Other agents includes systemic local anesthetic, anticonvulsants like lamotrigine, tiagabine etc, antidepressants like selective serotonin reuptake inhibitors (SSRI), opioid analgesics, NMDA receptor analgesics are in preclinical and various phases of clinical trials. Despite these many therapeutic options, the treatment of neuropathic pain is not fully effective and often unsatisfactory and severely hampered by dose-limiting side effects which limit the treatment.

Thus, there is unmet need to understand disease pathogenesis, identify and characterize novel targets, and develop newer agents which act at one or more sites in the pathogenesis of neuropathic pain.

Although important, these peripheral processes do not occur in isolation from central neuroinflammation.

Together, these neuroimmune interactions seem essential for the production of neuropathic pain symptoms.

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