IJPSR (2012), Vol. 3, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 June, 2012; received in revised form 18 September, 2012; accepted 28 September, 2012

PATHOPHYSIOLOGY OF NEUROPATHIC PAIN: A SYSTEMIC REVIEW

Gurudev Singh Raina*, Rajeev Taliyan and P.L. Sharma

Neurobiology Division, Department of Pharmacology, ISF College of Pharmacy, Moga-142001, Punjab, India

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

Correspondence to Author:

Gurudev Singh Raina

Neurobiology Division, Department of Pharmacology, ISF College of Pharmacy, Moga-142001, Punjab, India

E-mail: nickykhalsa84@gmail.com

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 dysaesthesia of allodynia and hyperesthesia are most troublesome because of our daily need to interact with objects in our environment.

QUICK RESPONSE CODE

IJPSR:
ICV- 4.57

Website:
www.ijpsr.com

Classification of Neuropathic Pain: The type of damage or related pathophysiology causing a painful neuropathic disorder can be classified as the following [1, 2, 3] (**fig. 1**);

a) Mechanical nerve injury, e.g. carpal tunnel syndrome, vertebral disk herniation;

b) Metabolic disease, e.g. diabetic poly-neuropathy;

c) Neurotropic viral disease, e.g. herpes zoster, human immunodeficient virus (HIV) disease;

d) Neurotoxicity, e.g. by chemotherapy to treat cancer or tuberculosis;

e) Inflammatory and/or immunologic mechanisms, e.g. multiple sclerosis;

f) Nervous system focal ischemia. e.g. thalamic syndrome (anesthesia dolorosa);

g) Multiple neurotransmitter system dysfunction, e.g. complex regional pain syndrome (CGRP).

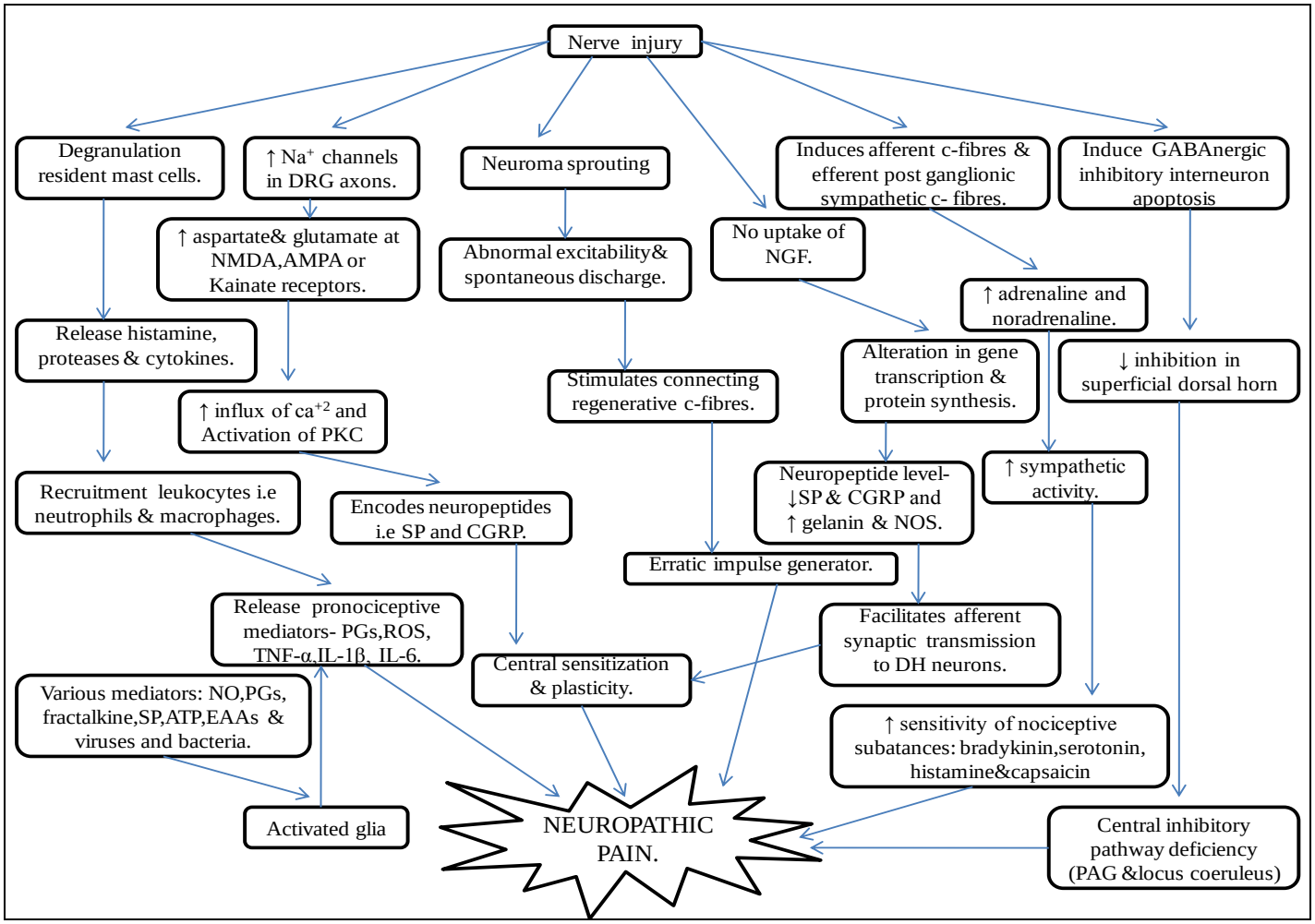

FIG. 1: SUMMARY OF VARIOUS MECHANISM INVOLVED IN THE PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

ATP: Adenosine triphosphate; CGRP- Calcitonin gene-related peptide; DRG:Dorsal root ganglia; EAA: excitatory amino acids; IL: Interleukin; NGF:Nerve growth factor; NMDA:N-methyl-D-aspartate; NO: Nitric oxide; PK: Protein kinase; PG: Prostaglandin; ROS: Reactive oxygen species; TNF: Tumor necrosis factor

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 [4, 5, 6]. Recent research studies indicate that both peripheral and central mechanisms have been involved in pathogenesis of neuropathic pain [7, 8, 9] (**table 1**).

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 [10, 11, 12].

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 [13, 14].

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 [13, 15, 16].

TABLE 1: DIFFERENT MECHANISMS OF NEUROPATHIC PAIN [17, 18]

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 sensitizition
Peripheral terminals	**Superspinal mechanisms**
Peripheral Sensitizition	• 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 [13, 16]. 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 [19].

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 antihyperalgesic effects [20]. The PGs including PGE2 and PGI2 (also known as prostacyclin) are also rapidly produced following tissue injury and are major contributors to peripheral sensitization [21, 22, 23, 24]. 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 [21, 22, 23, 24].

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 [25]. 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 [17, 26]. The second one is transcription-dependent form that takes some hours to be induced but outlast the initiating stimulus for prolonged periods [27].

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 [28].

The activity dependent form of central sensitization is responsible for generating secondary pinprick hyperalgesia and dynamic tactile allodynia [29]. 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 [30].

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 [25, 31]. Inflammation may release or generate a variety of pro-inflammatory [32] and/or pronociceptive mediators which may produce pain, hyperalgesia, or allodynia that develop as an acute response to a local inflammatory insult [33]. Inflammation leads to increased capillary permeability, perivascular leakage of plasma protein, infiltration and/or migration of neurophils to the site of injury [31, 34]. 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 [35] (**Fig. 2**).

A. Peripheral inflammatory cells:

1. **Mast Cells:** Mast cells are crucial players in allergic reactions and important initiators of innate immunity [36]. 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 [37]. They release proinflammatory mediators, including histamine, serotonin, cytokines and proteases [36, 38]. Histamine seems to be a key mast cell mediator, having sensitizing effects on nociceptors [39], and is capable of inducing severe burning pain when applied to the skin of patients suffering from postherpetic neuralgia [40]. In addition, neuronal histamine receptors are upregulated after a crush injury to the sciatic nerve [41]. 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 [42, 43]. 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 no tably macrophages [42, 43]. 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 [37], sciatic nerve crush [44], and chronic constriction injury [45] (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 [46]. 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 [43, 47].

   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 [48]. Macrophage function has been examined in various models of neuropathic pain, including CCI [49], PNL [50] and spinal nerve ligation [51] (SNL).

   A reduction in neuropathic pain behaviors correlating with an attenuation of macrophage recruitment into the damaged nerve [52]. 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-1 α) and the IL-1β

[53], the latter two are released by neutrophils. Macrophages secrete prostaglandins, including PGE2 and PGI2 [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 identifition 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 correalated 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 macropages. 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].

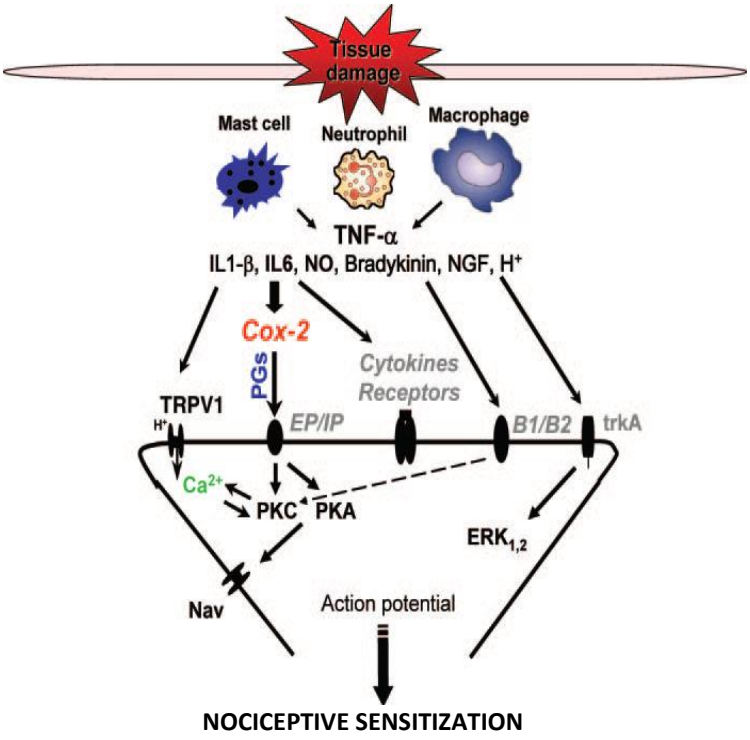

FIG. 2: VARIOUS MEDIATORS OF NEUROPATHIC PAIN

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-_, tumor necrosis factor _, IL-1_; interleukin-1_; IL-6, interlekin-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 [70]. Glial cells usually represent 70% of the cells in the CNS under normal conditions, and microglia represents 5-10% of glia [71]. The most characteristic feature of microglia is their rapid activation in the CNS in response to pathological events, including trauma, ischemia, inflammation, hypoxia, neuro-degeneration and viral or bacterial infection. After activation, microglial cells change morphology from a resting, ramified shape into an active, amoeboid shape [72].

Numerous studies in the recent years suggest an important role of microglial activation observed during NP [73]. However, the role glia in the cellular mechanisms underlying the symptoms of neuropathic pain, such as hyperalgesia or allodynia, is not clear [74]. Microglial cells secrete a large variety of substances, including growth factors, cytokines, complement components, lipid mediators, extra-cellular matrix components, enzymes, free radicals, neurotoxins, NO, and PGs [75,76]. Furthermore, a transient neuropathic state in naïve rats can be induced by intrathecal injection of ATP-stimulated microglia [77].

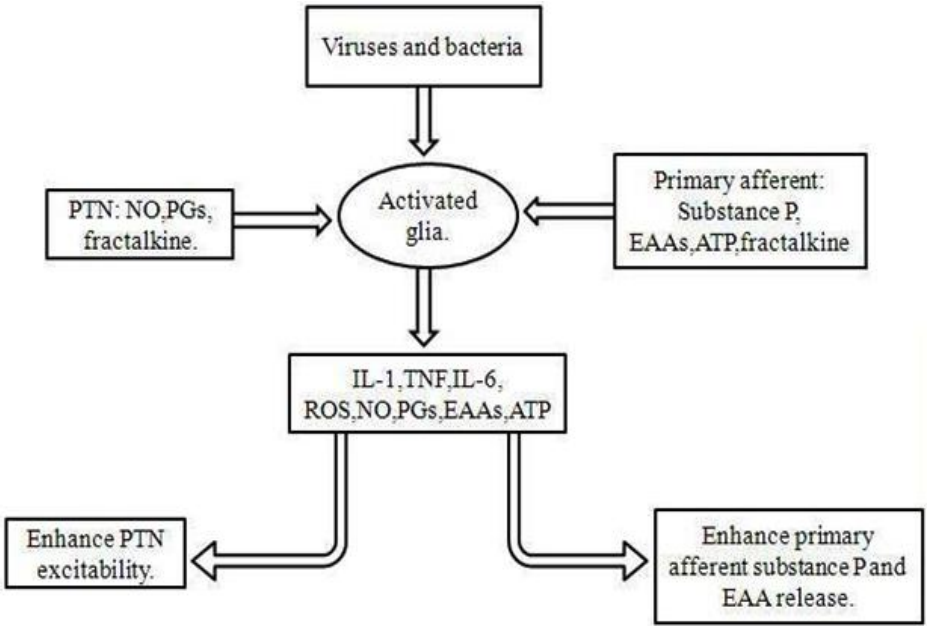

FIG. 3: SPINAL CORD GLIA REGULATION IN THE DEVELOPMENT OF EXAGGERATED PAIN

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)

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 [78].

   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 [79] and can be reduced by glial modulators [80] (e.g., propentofylline and minocycline). Most studies demonstrate that spinal microglial activation precedes astrocyte activation [81], but when established the level of astrocyte activation appears to be closely correlated with pain behaviors in different neuropathic pain models [82].

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 [83].

Cytokines are small regulatory protein that mediate interactions between cells over relatively short distances. They are mostly involved in responses to disease or infection [84]. 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 [85, 86]. These cytokines are also induced in the CNS [87]. 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 [51, 86].

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 stess. 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 [88], intraperitoneal [89] and intrathecal [90] 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 IL1-RI on the cell surface initiates several signaling events, such as translocation of NF-κB into the nucleus. NF-κB then upregulates transcription of several genes, including COX-2, iNOS, TNF-α, IL-1β and IL-6 [91, 92]. 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 [93] and also in spinal cord [94].

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)[95].

   TNFR1 is linked to pathways for cell death, whereas TNFR2 is not [96]. However, activation of either receptor results in p38 MAP kinase signaling [97], translocation of NF-κB to the nucleus and activation of COX-2-dependent prostanoids release [98]. TNF is constitutively expressed in cutaneous mast cell [99], but, in injury or inflammation, it may be released by other cell including neutrophils and macrophages. Injury of the sciatic nerve leads to upregulation of TNF-α and its receptors in the nerve [100], this upregulation is found mainly in Schwann cell and endothelial cell [101].

   Nerve injury also leads to increased TNF-α expression in the dorsal horn of the spinal cord and in the locus coeruleus and hippocampus [102]. Inhibiting TNF-α synthesis with thalidomide or treatment with anti-TNF-α neutralizing antibodies at the time of nerve injury blocked the development of hyperalgesia and allodynia in the these animal models [103, 104]. Furthermore, treatment with etanercept, a recombinant TNF-α receptor (p75)-Fc fusion protein that acts as a TNF-α antagonist, reversed established hyperalgesia in mice with a chronic constriction injury of the sciatic nerve [103].

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 [105] 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 [106]. 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

receptors and ion channels, including TRPV [1107] and tetrodotoxin-resistant N^{a+} channels [108]. 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 [109]. 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 [110], and SNL [111]

5. **Chemokines**: Chemokines are considered a large family of secreted proteins that are found to be chemotactic for leukocytes [112]. Evidences exist that, CCL2 is upregulated exclusively in neurons of the DRG following peripheral nerve injury [113], while it is expressed by neurons and microglia in the spinal cord [114]. A spatial and temporal relationship between CCL2 expression and spinal glial activation following nerve injury is evident [114], suggesting that neuronal CCL2 may serve as a trigger for spinal microglia activation [115].

6. **Prostanoids:** It has been established that the PGs also contribute to nociception at the level of the spinal cord [116]. Various studies have shown that mechanical hyperalgesia in nerve-injured rats was alleviated for up to 10 days by subcutaneous injection of indomethocin (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 [117]. This shows that there is increased expression of PGs in the region of the nerve lesion that contributes to neuropathic pain [118].

   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 [119] 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 [120]. They are released by a number of cell types, including neutrophils (Zuo *et al*., 2003) and macrophages [121] as well as astrocytes [122] and microglia [123].

   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 [124]. It causes pain when injected into the skin of human subjects [125] and contributes to peripheral hyperalgesia in the skin and joints, probably by contributing to PGE2-induced sensitization of primary afferents [126].

   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 [127]. 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 [128].

   Treatment with a non-specfic 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 [129].

   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 [130].

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, norepinephine, 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**).

Anticonvilsant drug such as carbamazapine (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, anti-depressants 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 neuropathicpain 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.

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,	Tremors, ataxia
	Topical lidocaine	Local erythema, rashes
Analgesics		
Peripheral	NSAIDs	GI 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.

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.

REFERENCES:

1. Paice JA. Clinical challenges: chemotherapy-induced peripheral neuropathy. Semin Oncol Nurs 2009; 25(2 Suppl 1): S8-S19.

2. Yamashiro E, Asato Y, Taira K, Awazawa R, Yamamoto Y, Hagiwara K, Tamaki H, Uezato H. Necrotizing fasciitis caused by Streptococcus pneumoniae. J.Dermatol 2009; 36: 298-305.
3. Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol 2001; 429: 23-37.
4. Irving GA. Contemporary assessment and management of neuropathic pain. Neurology 2005; 64: S21-S27.
5. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003; 60: 1524-1534.
6. Bowsher D. Neurogenic pain syndromes and their management. Br Med Bull 1991; 47: 644-66.
7. Beggs S and Salter M. Neuropathic pain: Symptoms, model, and mechanisms. Drug Dev. Res. 2006; 67: 287-301.
8. Campbell N and Meyer R. Mechanisms of neuropathic pain. Neuron 2006; 52: 77-92.
9. Truini A and Cruccu G. Pathophysiological mechanisms of neuropathic pain. Neuro. Sci. 2006; 27: 179-182.
10. Planells-Cases R, Garcìa-Sanz N, Morenilla-Palao C, Ferrer-Montiel A. Functional aspects and mechanisms of TRPV1 involvement in neurogenic inflammation that leads to thermal hyperalgesia. Pflugers Arch. 2005; 451: 151-159.
11. Shaw SK, Owolabi SA, Bagley J, Morin N, Cheng E, LeBlanc BW, Kim M, Harty P, Waxman SG, Saab CY. Activated polymorphonuclear cells promote injury and excitability of dorsal root ganglia neurons. Exp Neurol 2008; 210: 286-294.
12. Wang JG, Strong JA, Xie W, Zhang JM. Local inflammation in rat dorsal root ganglion alters excitability and ion currents in small-diameter sensory neurons. Anesthesiology. 2007; 107: 322-332.
13. La Rana G, Russo R, D'Agostino G, Sasso O, Raso GM, Iacono A, Meli R, Piomelli D, Calignano A. AM404, an anandamide transport inhibitor, reduces plasma extravasation in a model of neuropathic pain in rat:role for cannabinoid receptors. Neuropharmacology 2008; 54: 521-529
14. Trevisani M, Siemens J, Serena Materazzi S, Bautista DM, Nassini R, Campi B, Imamachi N, Andrè E, Patacchini R, Cottrell GS, Gatti R, Basbaum A, Bunnett N, Julius D and Geppetti P. 4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. Proc.Natl. Acad. Sci. U.S.A. 2007; 104: 13519-13524.
15. Russo R, Loverme J, La Rana G, Compton TR, Parrott J, Duranti A, Tontini A, Mor M, Tarzia G, Calignano A, Piomelli D. The fatty acid amide hydrolase inhibitor URB597 (cyclohexylcarbamic acid 3'-carbamoylbiphenyl-3-yl ester) reduces neuropathic pain after oral administration in mice. J Pharmacol Exp Ther. 2007; 322: 236-42.
16. Yonehara N, Yoshimura M. Influence of painful chronic neuropathy on neurogenic inflammation. Pain 2001; 92: 259-265.
17. Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci. 2004; 74: 2605–2610.
18. Pasero C. Pathophysiology of neuropathic pain. Pain Manag Nurs. 2004; 5: 3-8.
19. Wang S, Dai Y, Fukuoka T, Yamanaka H, Kobayashi K, Obata K, Cui X, Tominaga M and Noguchi K. Phospholipase C and protein kinase A mediate bradykinin sensitization of TRPA1: a molecular mechanism of inflammatory pain Brain 2008; 131: 1241-1251.
20. Porreca F, Vanderah TW, Guo W, Barth M, Dodey P, Peyrou V, Luccarini JM, Junien JL and Pruneau D. Antinociceptive Pharmacology of *N*-[[4-(4,5-Dihydro-1*H*-imidazol-2-yl)phenyl] methyl]-2-[2-[[(4-methoxy-2,6dimethyl- phenyl) sulfonyl]methy lamino]ethoxy]-*N*-methylacetamide, Fumarate (LF22-0542), a Novel Nonpeptidic Bradykinin B_1 Receptor Antagonist . J. Pharmacol. Exp. Ther. 2006; 318: 195-205.
21. Ma W, Eisenach JC. Cyclooxygenase 2 in infiltrating inflammatory cells in injured nerve is universally up-regulated following various types of peripheral nerve injury. Neuroscience 2003a; 121: 691-704.
22. Ma W, Eisenach JC. Four PGE2 EP receptors are up-regulated in injured nerve following partial sciatic nerve ligation. Exp Neurol 2003b; 183: 581-592.
23. Ma W, Quirion R. Does COX2-dependent PGE2 play a role in neuropathic pain? Neurosci Lett 2008; 437: 165-169.
24. Ma W, Quirion R.J. Up-regulation of interleukin-6 induced by prostaglandin E from invading macrophages following nerve injury: an in vivo and in vitro study. Neurochem 2005; 93: 664-673.
25. Julius D and Basbaum A. Molecular mechanisms of nociception. Nature 2001; 413: 203-210.
26. Azkue JJ, Liu XG, Zmmermann M, and Sandkuhler J. Induction of long-term potentiation of C fibre-evoked spinal field potentials requires recruitment of group I, but not group II/III metabotropic glutamate receptors. Pain. 2003; 106: 373-379.
27. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci 2003; 26: 696-705.
28. Dray A. Neuropathic pain: emerging treatment. Bri. J. Anaesth. 2008; 101: 48-58.
29. Sycha T, Anzenhofer S, Lehr S, Schmetterer L, Chizh B, Eichler HG, Gustorff B. Rofecoxib attenuates both primary and secondary inflammatory hyperalgesia: a randomized, double blinded, placebo controlled crossover trial in the UV-B pain model. Pain. 2005; 113: 316-322.
30. Curros-Criado MM and Herrero JF. The antinociceptive effect of systemic gabapentin is related to the type of sensitization-induced hyperalgesia. J. Neuroinflamm. 2007; 4: 15-24.
31. Schmid-Schonbein GM. Analysis of inflammation. Ann. Rev. Biomed. Engg. 2006; 8: 93-151.
32. Gilroy DW, Lawrence T, Perretti M and Rossi AG. Inflammatory resolution: new opportunities for drug discovery. Nat. Rev. Drug Discov 2004; 3: 401-416.
33. Bueno L and Fioramonti J. Visceeral perception: inflammatory and non-inflammatory mediators. Gut 2002; 51 (Suppl 1): 19-23.
34. Torres-Dueñas D, M R N Celes MRN, Freitas A, Alves-Filho JC, Spiller F, DalSecco D, Dalto VF, Rossi MA, Ferreira SH and Cunha FQ. Peroxynitrite mediates the failure of neutrophil migration in severe polymicrobial sepsis in mice Br J Pharmacol. 2007; 152: 341-352.
35. Trivedi A, Olivas AD and Linda J. Noble-Haeusslein Inflammation and Spinal Cord Injury: Infiltrating Leukocytes as Determinants of Injury and Repair. Processes Clin Neurosci Res. 2006; 6: 283-292.
36. Galli SJ, Nakae S, Tsai M. Mast cells in the development of adaptive immune responses. Nat Immunol 2005; 6: 135–142.
37. Zuo Y, Perkins NM, Tracey DJ, Geczy CL. Inflammation and hyperalgesia induced by nerve injury in the rat: a key role of mast cells. Pain 2003; 105: 467–479.
38. Metcalfe DD, Baram D, Mekori YA. Mast cells. Physiol Rev 1997; 77: 1033–1079.

39. Koda H, Mizumura K. Sensitization to mechanical stimulation by inflammatory mediators and by mild burn in canine visceral nociceptors in vitro. J. Neurophysiol 2002; 87: 2043–2051.
40. Baron R, Schwarz K, Kleinert A, Schattschneider J and Wasner G. Histamine-induced itch converts into pain in neuropathic hyperalgesia. Neuro. Report 2001; 12: 3475-3478.
41. Kashiba H, Fukui H, Morikawa Y, Senba E. Gene expression of histamine H1 receptor in guinea pig primary sensory neurons: a relationship between H1 receptor mRNA-expressing neuronsand peptidergic neurons. Brain Res Mol Brain Res 1999; 66: 24–34.
42. Faurschou M, Borregaard N. Neutrophil granules and secretory vesicles in inflammation. Microbes Infect 2003; 5: 1317-1327.
43. Witko-Sarsat V, Rieu P, Descamps-Latscha B, Lesavre P, Halbwachs-Mecarelli L. Neutrophils: molecules, functions and pathophysiological aspects. Lab Invest 2000; 80: 617-653.
44. Perry VH, Brown MC, Gordon S. The macrophage response to central and peripheral nerve injury.A possible role for macrophages in regeneration. J Exp Med 1987; 165: 1218-1223.
45. Clatworthy AL, Illich PA, Castro GA, Walters ET. Role of peri-axonal inflammation in the development of thermal hyperalgesia and guarding behavior in a rat model of neuropathic pain. Neurosci Lett 1995; 184: 5–8.
46. Scapini P, Lapinet-Vera JA, Gasperini S, Calzetti F, Bazzoni F, Cassatella MA. The neutrophil as a cellular source of chemokines. Immunol Rev 2000; 177: 195–203.
47. Bruck W. The role of macrophages in Wallerian degeneration. Brain Pathol 1997; 7: 741–752.
48. Griffin JW, George R, Ho T. Macrophage systems in peripheral nerves. A review. J Neuropathol Exp Neurol 1993; 52: 553–560.
49. Cui JG, Holmin S, Mathiesen T, Meyerson BA, Linderoth B. Possible role of inflammatory mediators in tactile hypersensitivity in rat models of mononeuropathy. Pain 2000; 88: 239–248.
50. Liu T, Knight KR, Tracey DJ. Hyperalgesia due to nerve injury-role of peroxynitrite. Neuroscience 2000; 97: 125-131.
51. Rutkowski MD, DeLeo JA. The Role of Cytokines in the Initiation and Maintenance of Chronic Pain. Drug News Perspect. 2002; 15: 626-632.
52. Ramer MS, French GD, Bisby MA. Wallerian degeneration is required for both neuropathic pain and sympathetic sprouting into the DRG.Pain 1997; 72: 71-78.
53. Perrin FE, Lacroix S, Aviles-Trigueros M, David S. Involvement of monocyte chemoattractant protein-1, macrophage inflammatory protein-1{alpha} and interleukin-1 {beta} in Wallerian degeneration. Brain. 2005; 128: 854-866.
54. Nathan CF. Secretory products of macrophages. J. Clin. Invest. 1987; 79: 319–326.
55. Woodham PL, MacDonald RE, Collins SD, Chessell IP and Day NC. Localisation and modulation of prostanoid receptors EP1 and EP4 in the rat chronic constriction injury model of neuropathic pain. Euro.J. Pain 2007; 6: 605-613.
56. Ghilardi JR., Svensson CI, Rogers SD, Yaksh TL and Mantyh PW. Constitutive spinal cyclooxygenase-2 participates in the initiation of tissue injury-induced hyperalgesia. J. Neurosci. Res 2004; 24: 2727-2732.
57. Lisak RP, Benjamins JA, Bealmear B, Nedelkoska L, Studzinski D, Retland E, Yao B, Land S. Differential effects of Th1, monocyte/macrophage and Th2 cytokine mixtures on early gene expression for molecules associated with metabolism, signaling and regulation in central nervous system mixed glial cell cultures. J Neuroinflam 2009; 6: 4-17.
58. Hu P, McLachlan EM. Macrophage and lymphocyte invasion of dorsal root ganglia after peripheral nerve lesions in the rat. Neuroscience 2002; 112: 23-38.
59. Kleinschnitz C, Hofstetter HH, Meuth SG, Braeuninger S, Sommer C, Stoll G. T cell infiltration after chronic constriction injury of mouse sciatic nerve is associated with interleukin-17 expression. Exp Neurol 2006; 200: 480-485.
60. Wagner R and Myers RR. Schwann cells produce tumor necrosis factor alpha: expression in injured and non-injured nerves. Neuroscience 1998; 73: 625-629.
61. Tofaris GK, Patterson PH, Jessen KR and Mirsky R. Denervated Schwann Cells Attract Macrophages by Secretion of Leukemia Inhibitory Factor (LIF) and Monocyte Chemoattractant Protein-1 in a Process Regulated by Interleukin-6 and LIF. J. Neurosci. 2002; 22: 6696-6703.
62. Sekiguchi Y, Kikuchi S, Myers RR, Campana WM. Erythropoietin inhibits spinal neuronal apoptosis and pain following nerve root crush. Spine 2003; 28: 2577-2584.
63. Campana WM, Li X, Shubayev VI, Angert M, Cai K, Myers RR. Erythropoietin reduces Schwann cell TNF-alpha, Wallerian degeneration and pain-related behaviors after peripheral nerve injury. Eur J Neurosci 2006; 23: 617-626.
64. Pietr M, Kozela E, Levy R, Rimmerman N, Lin YH, Stella N, Vogel Z, Juknat A.Differential changes in GPR55 during microglial cell activation. FEBS Lett 2009; 583: 2071-2076.
65. Kim SU, de Vellis J. Microglia in health and disease. J Neurosci Res 2005; 81: 302-313.
66. Inoue K, Tsuda M. Microglia and neuropathic pain. Glia 2009; 11: 145-163..
67. Raghavendra V, Tanga F, DeLeo JA. Inhibition of microglial activation attenuates the development but not existing hypersensitivity in a rat model of neuropathy. J Pharmacol Expt Ther 2003a; 306: 624-630.
68. Raghavendra V, Tanga F, Rutkowski MD, DeLeo JA. Anti-hyperalgesic and morphine-sparing actions of propentofylline following peripheral nerve injury in rats: mechanistic implications of spinal glia and proinflammatory cytokines. Pain 2003b; 104: 655-664.
69. Raghavendra V, Tanga FY, DeLeo JA. Complete Freunds adjuvant-induced peripheral inflammation evokes glial activation and proinflammatory cytokine expression in the CNS. Eur J Neurosci 2004; 20: 467-473.
70. Mika J. Modulation of microglia can attenuate neuropathic pain symptoms and enhance morphine effectiveness. Pharmacol Rep 2008; 60: 297-307.
71. Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. Trends Neurosci 2001; 24: 450-455.
72. Nakajima K, Kohsaka S. Microglia: activation and their significance in the central nervous system. J Biochem 2001; 130: 169-175.
73. Masuda J, Tsuda M, Tozaki-Saitoh H, Inoue K. Intrathecal delivery of PDGF produces tactile allodynia through its receptors in spinal microglia. Mol Pain 2009; 5: 23-34.
74. Fu KY, Light AR, Maixner W. Relationship between nociceptor activity, peripheral edema, spinal microglial activation and long-term hyperalgesia induced by formalin. Neuroscience 2000; 101: 1127-1135.
75. Lin HW, Jain MR, Li H, Levison SW. Ciliary neurotrophic factor (CNTF) plus soluble CNTF receptor alpha increases cyclooxygenase-2 expression, PGE2 release and interferon-gamma-induced CD40 in murine microglia. J Neuroinflam 2009; 6: 7-24.
76. Padi SSV, Kulkarni SK. Minocycline prevents the development of neuropathic pain, but not acute pain: possible anti-

inflammatory and antioxidant mechanisms. Eur J Pharmacol 2008; 601: 79-87.
77. Coull JA, Beggs S, Boudreau D, Boivin D, Tsuda M, Inoue K, Gravel C, Salter MW, De Koninck Y. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. Nature 2005; 438: 1017-1021.
78. Haydon PG. GLIA: listening and talking to the synapse. Nat Rev Neurosci 2001; 2: 185-93.
79. Winkelstein BA, DeLeo JA. Nerve root injury severity differentially modulates spinal glial activation in a rat lumbar radiculopathy model: considerations for persistent pain. Brain Res2002; 956: 294-301
80. Tanga FY, Raghavendra V, DeLeo JA.Quantitative real-time RT-PCR assessment of spinal microglial and astrocytic activation markers in a rat model of neuropathic pain. Neurochem Int 2004; 45: 397-407.
81. Colburn RW, Rickman AJ, DeLeo JA. The effect of site and type of nerve injury on spinal glial activation and neuropathic pain behavior. Exp Neurol 1999; 157: 289-304.
82. Coyle DE. Partial peripheral nerve injury leads to activation of astroglia and microglia which parallels the development of allodynic behavior. Glia 1998; 23: 75-83.
83. Thacker MA, Clark AK, Marchand F, McMahon SB. Pathophysiology of Peripheral Neuropathic Pain: Immune Cells and Molecules .Anesth Analg 2007; 105: 838–847.
84. Dinarello C. Proinflammatory cytokines. Chest 2000; 118: 503-508.
85. Valko M, Leibfritz D, Moncol J, Cronin M, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem. Cell Biol 2007; 39: 44–84.
86. Verri WA Jr, Cunha TM, Parada CA, Poole S, Cunha FQ, Ferreira SH. Hypernociceptive role of cytokines and chemokines: targets for analgesic drug development? Pharmacol Ther 2006; 112: 116-138.
87. Wieseler-Frank J, Maier SF, Watkins LR. Central proinflammatory cytokines and pain enhancement. Neurosignals 2005; 14: 166-174.
88. Ferreira SH, Cunha FQ, Lorenzetti BB, Michelin MA, Perretti M, Flower RJ and Poole S. Role of lipocortin-1 in the anti-hyperalgesic actions of dexamethasone Br. J. Pharmacol. 1997; 121: 883–888.
89. Watkins LR, Wiertelak EP, Goehler LE, Smith KP, Martin D, Maier SF. Characterization of cytokine-induced hyperalgesia. Brain Res 1994; 654: 15–26.
90. Zelenka M, Schafers M, Sommer C. Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. Pain 2005; 116: 257–263.
91. Pahl HL. Activators and target genes of Rel/NF-kappaB transcription factors. Oncogene 1999; 18: 6853–6866.
92. Tegeder I, Niederberger E, Schmidt R, Kunz S, Guhring H, Ritzeler O, Michaelis M, Geisslinger G. Specific inhibition of I{kappa}B kinase reduces hyperalgesia in inflammatory and neuropathic pain models in rats. J Neurosci 2004; 24: 1637–1645.
93. Zhang JH, Huang YG. The immune system: a new look at pain. Chin Med J (Engl). 2006; 119: 930-938.
94. Apkarian AV, Laverello S, Randolf A, Berra HH, Chialvo DR, Besedovsky HO and Del Rey A. Expression of IL-1beta in superaspinal brain regions in rats with neuropathic pain. Neurosci. Lett. 2006; 407: 176-181.
95. Locksley RM, Killeen N, Lenardo M. The TNF and TNF receptor superfamilies: integrating mammalian biology. J.Cell 2001; 104: 487-501.
96. Aggarwal BB. Signalling pathways of the TNF superfamily: a double edged sword. Nat Rev Immunol 2003; 3: 745–756.
97. Schäfers M, Svensson CI, Sommer C, Sorkin LS. Tumor necrosis factor-alpha induces mechanical allodynia after spinal nerve ligation by activation of p38 MAPK in primary sensory neurons. J Neurosci 2003c; 23: 2517-2521.
98. Dinarello CA. Cytokines as endogenous pyrogens. J Infect Dis 1999; 179: S294-S304.
99. Walsh LJ, Trinchieri G, Waldorf HA, Whitaker D, Murphy GF. Human dermal mast cells contain and release tumor necrosis factor alpha, which induces endothelial leukocyte adhesion molecule 1. Proc Natl Acad Sci U S A. 1991; 88: 4220-4224.
100. Xu JT, XiWJ, Zang Y, Wu CY, Liu XG.The role of tumor necrosis factor-alpha in the neuropathic pain induced by Lumbar 5 ventral root transection in rat. Pain 2006;1 23: 306-321.
100 Wagner R, Myers RR. Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. Neuroreport 1996; 7: 2897–2901.
101 Ignatowski TA, Covey WC, Knight PR, Severin CM, Nickola TJ, Spengler RN. Brain-derived TNFalpha mediates neuropathic pain. Brain Res. 1999; 841: 70-77.
102 Sommer C, Lindenlaub T, Teuteberg P, Schäfers M, Hartung T, Toyka KV. Anti-TNF-neutralizing antibodies reduce pain-related behavior in two different mouse models of painful mononeuropathy. Brain Res 2001 ; 913: 86-89.
103 Sommer C, Schafers M. Painful mononeuropathy in C57BL/Wld mice with delayed Wallerian degeneration: differential effects of cytokine production and nerve regeneration on thermal and mechanical hypersensitivity. Brain Res 1998; 784: 154–162.
104 Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T, Mitsubuchi H, Tonoki H, Awaya Y, Matsuda I. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet 1996; 13: 485–488.
105 Lewin GR, Ritter AM, Mendell LM. Nerve growth factorinduced hyperalgesia in the neonatal and adult rat. J Neurosci 1993; 13: 2136–2148.
106 Bonnington JK, McNaughton PA. Signalling pathways involved in the sensitisation of mouse nociceptive neurones by nerve growth factor. J Physiol 2003; 551: 433–446.
107 Zhang YH, Vasko MR, Nicol GD. Ceramide, a putative second messenger for nerve growth factor, modulates the TTXresistant Na^+ current and delayed rectifier K^+ current in rat sensory neurons. J Physiol 2002; 544: 385–402.
108 McMahon SB, Bennett DLH, Priestley JV, Shelton D. The biological effects of endogenous NGF on adult sensory neurones revealed by a trkA-IgG fusion molecule. Nature Medicine 1995; 1: 774–780.
109 Gandhi R, Ryals JM, and Douglas E. Wright Neurotrophin-3 Reverses Chronic Mechanical Hyperalgesia Induced by Intramuscular Acid Injection J. Neurosci. 2004; 24: 9405-9413.
110 Ramer MS, Murphy PG, Richardson PM, Bisby MA. Spinal nerve lesion-induced mechanoallodynia and adrenergic sprouting in sensory ganglia are attenuated in interleukin-6 knockout mice. Pain. 1998; 78: 115-121
111 Ryschich E, Kerkadze V, Deduchovas O, Salnikova O, Parseliunas A, Märten A, Hartwig W, Sperandio M, Schmidt J. Intracapillary leukocyte accumulation as a novel antihemorrhagic mechanism in acute pancreatitis in mice. Gut 2009; 23: 243-254.
112 White FA, Wilson NM. Chemokines as pain mediators and modulators. Curr Opin Anaesthesiol 2008; 21: 580-585.
113 Zhang J, De Koninck Y. Spatial and temporal relationship between monocyte chemoattractant protein-1 expression and

spinal glial activation following peripheral nerve injury. J Neurochem 2006; 97: 772-783.

114 Thacker MA, Clark AK, Bishop T, Grist J, Yip PK, Moon LD, Thompson SW, Marchand F, McMahon SB. CCL2 is a key mediator of microglia activation in neuropathic pain states. Eur J Pain 2009; 13: 263-272.

115 Yaksh TL, Dirig DM, Conway CM, Svensson C, Luo ZD and Isakson PC. The Acute Antihyperalgesic Action of Nonsteroidal, Anti-Inflammatory Drugs and Release of Spinal Prostaglandin E2 is Mediated by the Inhibition of Constitutive Spinal Cyclooxygenase-2(COX-2) but not COX-1. J. Neurosci. 2001; 21: 5847–5853.

116 LaBuda CJ and Little PJ. Pharmacological evaluation of the selective spinal nerve ligation model of neuropathic pain in the rat. J. Neurosci. Methods 2005; 144: 175-181.

117 O'Rielly DD and Loomis CW. Spinal prostaglandins facilitate exaggerated A- and C-fibre-mediated reflex responses and are critical to the development of allodynia early after L5-L6 spinal nerve ligation. Anesthesiology 2007; 106: 795-805.

118 Zhao Y, Patzer A, Herdegen T, Gohlke P and Culman J. Activation of cerebral peroxisome proliferator-activate receptors gamma promotes neuroprotection by attenuation of neuronal cyclooxygenase-2 overexpression after focal cerebral ischemia in rats FASEB J. 2007; 201: 1162-1175.

119 Siniscalco D, Fuccio C, Giordano C, Ferraraccio F, Palazzo E, Luongo L, Rossi F, Roth KA, Maione S, de Novellis V. Role of reactive oxygen species and spinal cord apoptotic genes in the development of neuropathic pain. Pharmacol Res 2007; 55: 158-166.

120 Billack B. Macrophage activation: role of toll-like receptors, nitric oxide, and nuclear factor kappa B. Am J Pharm Educ 2006; 70: 102-109.

121 Cantoni O, Palomba L, Persichini T, Mariotto S, Suzuki H, Colasanti M. Pivotal role of arachidonic acid in the regulation of neuronal nitric oxide synthase activity and inducible nitric oxide synthase expression in activated astrocytes. Methods Enzymol 2008; 440: 243-252.

122 Vilhardt F. Microglia: phagocyte and glia cell. Int. J. Biochem. Cell Biol. 2005; 37: 17–21.

123 Luo ZD, Cizkova D. The role of nitric oxide in nociception. Curr Rev Pain 2000; 4: 459-466.

124 Holthusen H and Arndt JO. Nitric oxide evokes pain at nociceptors of the paravascular tissue and veins in humans. J. Physiol. 1995; 487: 253-258.

125 Aley KO, McCarter G and Levine JD. Nitric Oxide Signaling in Pain and Nociceptor Sensitization in the Rat. J.Neurosci. 1998; 18: 7008-7014.

126 Kamei J, Tamura N, Saitoh A. Possible involvement of the spinal nitric oxide/cGMP pathway in vincristine-induced painful neuropathy in mice. Pain 2005; 117: 112-120.

127 Naik AK, Tandan SK, Kumar D, Dudhgaonkar SP. Nitric oxide and its modulators in chronic constriction injury-induced neuropathic pain in rats. Eur J Pharmacol 2006 ; 530: 59-69.

128 Dudhgaonkar SP, Tandan SK, Kumar D, Naik AK and Raviprakash V. Ameliorative effect of combined administration of induced nitric oxide synthase inhibitor with cyclooxygenase-2 inhibitors in neuropathic pain in rats. Eur. J. Pain 2007; 11: 528-534.

129 Twining CM, Sloane EM, Milligan ED, Chacur M, Martin D, Poole S, Marsh H, Maier SF, Watkins LR. Peri-sciatic proinflammatory cytokines, reactive oxygen species, and complement induce mirror-image neuropathic pain in rats. Pain 2004; 110: 299-309.

130 Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr. Opin. Anaesthesiol 2007; 20: 456-472.

131 Hendrich J, Van Minh AT, Heblich F, Nieto-Rostro M, Watschinger K, Striessnig J, Wratten J, Daves A and Dolphin AC. Pharmacological disruption of calcium channel trafficking by the alpha2delta ligand gabapentin. Proc. Natl. Acad. Sci. U.S.A 2008; 105: 3628-3633.

132 Eisenberg E, River Y, Shifrin A and Krivoy N. Antiepileptic drugs in the treatment of neuropathic pain. Drugs 2007; 67: 1265-1289.

133 Zin CS, Nissen LM, Smith MT, O'Callaghan JP, Moore BJ. An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. CNS Drugs. 2008; 22: 417-42.

How to cite this article:
Raina GS, Taliyan R and Sharma PL: Pathophysiology of Neuropathic Pain: A Systemic Review. *Int J Pharm Sci Res* 2012; Vol. 3(10): 3530-3542.