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Review Article

NEUROPATHIC PAIN: A NEUROLOGICAL DISORDER

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ABSTRACT

Involvement of oxidative damage and mast cell has been reported in the pathophysiology of neuropathic pain. It has been demonstrated that mast cells are degranulated at the site of a nerve lesion releasing mediators such as histamine, serotonin, proteases, prostaglandins and cytokines and all of these mediators cause sensitization of nociceptors leading to neuropathic pain. Mast cell stabilizer (Ketotifen) inhibits the release of mediators such as histamine, leukotrienes and PAF (platelet aggregating factor) thus it benefits in neuropathic pain. Alternatively lycopene works synergistically to neutralize free radicals. So, the aim of this review is to focus on pathophysiology and recent pharmacological mechanism of neuropathic pain.

Keywords: Ketotifen, Lycopene, Neuropathic Pain.

1. INTRODUCTION

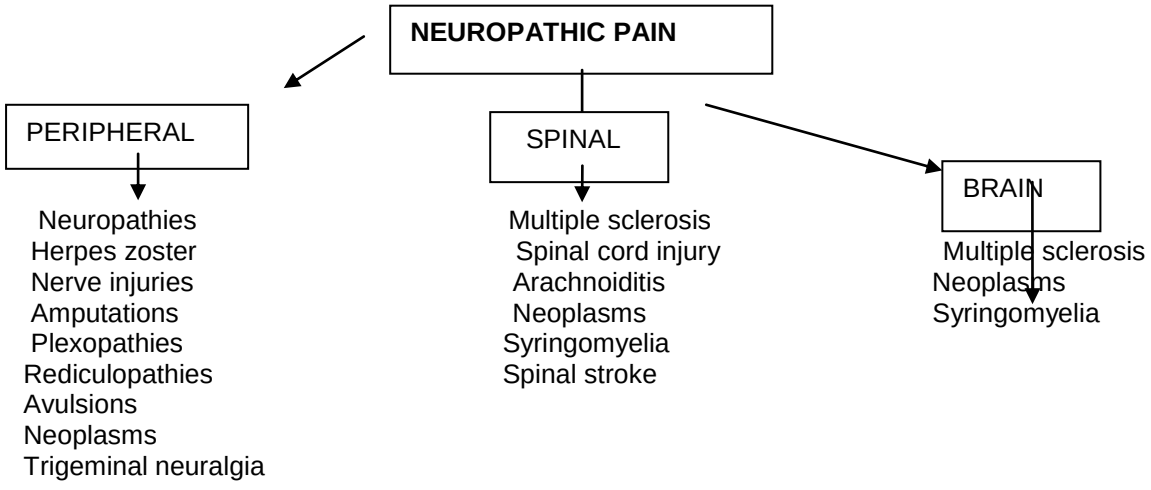
Pain has arisen from the Latin word “poena” or penalty which means unpleasant sensory and emotional experience associated with actual and potential tissue damage (Scadding J., 2003). Pain can be divided into two broad categories:

a) Adaptive
It contributes to survival by protecting the organism from injury or promoting healing when injury has occurred.

b) Maladaptive
It is an expression of the pathologic operation of the nervous system; it is pain as disease (Woolf C J. 2004).

‘Neuropathic pain is group of heterogeneous disease such as diabetes, immune deficiencies, malignant diseases, traumatic and ischemic disorders’ (Sindrup and Jensen, 1999; Woolf and
Mannion, 1999).
“or”
Neuropathic Pain associated with disease or injury of the peripheral or central nervous system. It is caused from abnormal physiology of central or peripheral nervous system and it is not related to the ongoing tissue damage or inflammation. Main symptoms of neuropathic pain are sensory abnormalities including paresthesias, dysesthesias, hyperesthesia, hyperalgesia, hyperpathia and allodynia (Ulugol A. *et al,* 2006).

1.1 Classification of neuropathic pain according to disease and anatomical site (Ashbury and Fields, 1984; Fields,1990, Sindrup and Jensen, 1999, 2000)



1.2 Symptoms

Table 1: Depicting positive-negative sensory symptoms often seen in neuropathic pain patients (Garrone B. *et al*, 2007)

Sensory Symptoms In Neuropathic Pain	
Paresthesias	Numbness or Tingling
Dysesthesias	Electric Shock Phenomenon
Hyperesthesia	Increased sensitivity To Mild Painful Stimuli
Hyperalgesia	Increased sensitivity To Normally Painful Stimuli
Hyperpathia	Pain Produced By Sub threshold Stimuli
Allodynia	Pain Produced By Normally Non painful Of Stimuli
Pall-hypo aesthesia	Reduced sensation to vibration
Thermal Hypoaesthesia	Reduced sensation to cold or warm stimuli
Heat Hyperalgesia	Pain from normally non-painful heat stimuli
Cold Hyperalgesia	Pain from normally non-painful cold stimuli
Hypoalgesia	Reduced sensation to painful stimuli
Hypoaesthesia	Reduced sensation to non-painful stimuli

2. Epidemiology

A review of the epidemiology of chronic pain found that still no accurate data is available for neuropathic pain. It is estimated that 3% of the population suffers from it and about 25% of patients will have neuropathic pain. The dominance of neuropathic pain has been estimated at between 1% and 2% in UK, 0.6% in US.

3. Mechanism of Neuropathic Pain

The pathophysiology of neuropathic pain is complex and difficult process **(**Manocha A. *et al,* (2011);Nickel T.F. *et al*, 2012**)**. The major pathways are

1. Peripheral /Nociceptor sensitization
2. Central sensitization
3. Sympathetic activation
4. Disinhibition

3.1 Peripheral /Nociceptor sensitization

Nociceptors are respond to mechanical, chemical, thermal noxious stimuli. Two types of nociceptor fibers one is c- fibers and another is Aδ fibers which are involved in transmission of pain from sites to spinal cord. Damage and degradation of axon and myelin sheath leads to the release of proinflammatory cytokines (interleukins, Tumor necrosis factor α), inflammatory mediators (bradykinin and prostaglandin) and growth factors (nerve growth factor) these changes cause allodynia and hyperalgesia.

3.2 Central sensitization

It is start from spinal cord after peripheral injury and release neurotransmitters (glutamate, GABA and calcitonin) and tachykinins (neuropeptides substance P and neurokinins). These neurotransmitters are bind to neural receptors and activate N – methyl D-aspartate (NMDA) receptors which increase intracellular calcium levels through N type of calcium channels and result in hypersensitivity and hyperexcitability of spinal neurons.

3.3 Sympathetic activation

Sympathetic activation is related to complex regional pain syndrome (CRPS) though and its principles are shared by other types of neuropathic pain which are post herpatic neuropathy, phantom limb syndrome, and traumatic neuropathy. The increase in sympathetically mediated vasomotor activity leads impaired oxygen and nutrition this acts as potent nociceptive stimuli. Injury to the nerves can also lead to nascent of sympathetic neurons into dorsal root ganglia of

the injured sensory neurons and into the dermis.

3.4 Disinhibition

This occurs when the control mechanisms along inhibitory pathways disappear or are suppressed. This further triggers abnormal excitability in central neurons. It is believed that central sensitization and disinhibition together with certain peripheral changes lead to allodynia (pain is evoked by a non-painful stimulus such as clothes rubbing against skin).

4. Animal Models Used in Neuropathic Pain

The study of neuropathic pain mechanisms is largely based on animal models but one major drawback is the lack of verbal communication; thus, the evaluation of pain in these models is based on empirical behavioral responses.

5. Pharmacological Management of Neuropathic Pain

The pharmacological treatment of neuropathic pain is generally depending upon the requirement and preference of the individual patient. The drugs mainly used in neuropathic pain include antidepressants, anticonvulsants, local anesthetics, opioid analgesics and some herbal plants.

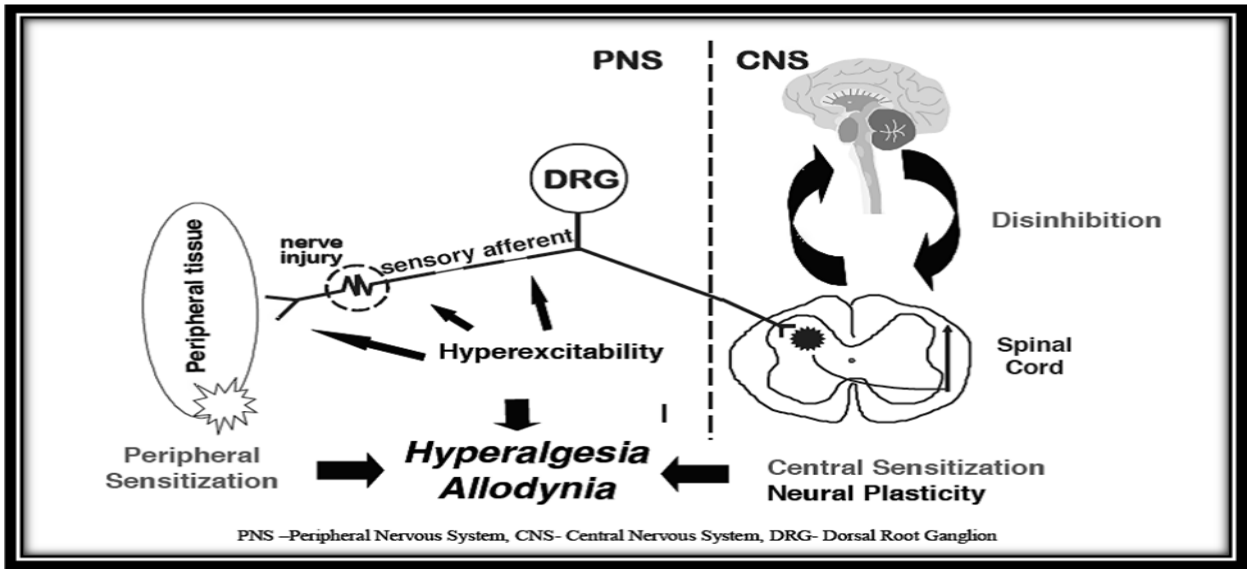


Fig. 1: Showing pathogenesis of Neuropathic Pain (Manocha A. *et al,* 2011)

Table 2: This current review we classify the model used in following categories

S.No.	Models	Mechanism
1	Nerve injury model	Partially injury to the sciatic nerve is commonly used to induce neuropathic pain behavior and the presence of neuropathic pain is mainly assessed by hyperalgesia to thermal and mechanical stimuli and allodynia to cold and tactile stimuli. (Hogan, 2002; Wang & Wang, 2003) (Attal et al., 1990; Seltzer et al., 1990; Kim & Chung, 1992; Choi et al., 1994; Malmberg & Basbaum, 1998).
2	Cancer Models	Cancer pain is caused by nerve compression and immunoreactive and pronociceptive substances released from tumors, the molecular mechanisms of this pain remain to be studied (Schwei et al., 1999; Wacnik et al., 2001; Shimoyama et al., 2002; Walker et al., 2002)..
3	Chemotherapeutic agent induced model	Paclitaxel is an antineoplastic agent derived from the Pacific yew tree *Taxus brevifolia* that is often used to treat a variety of cancers including ovarian, breast, and non-small cell lung cancer. This neuropathy is characterized by dysesthesia, numbness, and burning pain (Cavaletti et al., 1995a, 1995b; Aley et al., 1996; Tanner et al., 1998; Mimura et al., 2000; Quasthoff & Hartung, 2002; Strumberg et al., 2002).
4	Diabetic Models	Experimental animal models of diabetic neuropathic pain are mainly produced by the injection of a pancreatic h-cell cytotoxic agent such as alloxan or streptozotocin (STZ) in rodents. Intravenous (i.v.) or intraperitoneal (i.p.) injection of STZ is most commonly used. The STZ model of diabetes produces functional, biochemical, and structural abnormalities in the sciatic nerve similar to those seen in human diabetic neuropathy (Sima & Sugimoto, 1999) (Kamei et al., 1991; Courteix et al., 1993; Rashid & Ueda, 2002).

Table 2: Herbal Treatment for Neuropathic Pain (Kaur S. *et al*, 2011)

Drug	Mechanism of action
Ginkgo biloba	Blocks induction of inducible nitric oxide synthase (iNOS) and release of nitric oxide (NO)
Panax ginseng	Inhibits the voltage-gated Na+ (sodium) channels
Ocimum sanctum	Decreases the levels of oxidative stress and calcium
Acorus calamus	Decreases the oxidative stress and calcium levels
Emblica officinalis	Inhibits lipid peroxidation and restores the level of antioxidant enzymes
Combination of *Psidium guajava, Momordica charantia* and *Coccinia indica*	Inhibits protein kinase C and acts as an antioxidant

Table 3: Showing different drugs with their mechanism of action and major side effects (Garrone B. *et al*, 2007)

Category	DRUG	Mechanism Of Action	Major Side-effects
TCA (Tricyclic Antidepressants)	Nortriptyline, Desipramine	Inhibits Reuptake Of Serotonin, Norepinephrine (NE), Blocks Sodium ($Na^{+)}$ Channels, Anticholinergic	Sedation, Anticholinergic Effects
SNRI (Serotonin Norepinephrine Reuptake Inhibitors)	Duloexitine, Venlafaxine	Inhibition Of Both Serotonin And NE	Nausea
Anticonvulsants	Gabapentin, Lamotrigine	Decreases The Release Of Glutamate, NE And Substance P, With Ligands On A2-Δ Subunit Of Voltage Gated Calcium Channel	Sedation, Dizziness, Peripheral Oedema
Local Anesthetic	Lidocaine Patch/iv	Blockade Of Sodium Channels	Local Erythema, Rash
Opioid Analgesics	Morphine, Fentanyl, oxycodone, Methadone	μ-Receptor Agonism (Oxycodone Also Causes κ-Receptor Antagonism)	Nausea/ Vomiting, Constipation, Sedation, Dizziness

6. CONCLUSION

Neuropathic pain has been described as 'the most horrifying of all pains and sufferings, which a nerve lesion could inflict' (Mitchell S.W *et al,* 1872). The pharmacotherapy for neuropathic pain has had an incomplete success with little or no response to normally used pain decreasing drugs, such as NSAIDS (Woolf C.J *et al*, 1999). Therefore, there has been an extensive requirement to investigate novel treatment modalities. The assessment of neuropathic pain in humans is extremely multifaceted because most of the stimuli required to induce neuropathic pain may cause irreversible damage. Furthermore, it is also very difficult to recruit large number of humans for such type of testing.

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