Advanced Study on Neuropathic Pain & It's Screening Models

Shital S.Bhure[1], Irshad A.Shaikh[2], Nandkishor B. Bavage[3], Vidyasagar Gali[4], Shyamlila B. Bavage[5]

[1]B.Pharmacy Final Year, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India

[2, 3,4]Department of Pharmaceutical Analysis, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India

[5]Department of Pharmacognosy, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India

Abstract- **The international association for the study of pain (IASP 2011) defines neuropathic pain, as pain caused by lesions or disease of the somatosensory nervous system. Central neuropathic pain and peripheral neuropathic pain is caused by a lesion or disease of central somatosensory and peripheral somatosensory nervous system respectively Clinical lecture on lead Neuropathy published in 1924,the word Neuropathy was used for first time by gordon the history of pain management is explained by tracking the ancient time , nerve tissue is route of transfer the pain to the brain through invisible psychic pnema Diagnostic test aimed at assessing somatosensory afferent Pathway damage are therefore useful for diagnosing neuropathic pain these is manifest with renge of different symptoms such as ongoing burning pain, squeezing or pressure pain paraoxymal electric shock like sensations, stabbing pain or mechanical dynamic allodynia, The various types of neuropathic pain are associated with different underlying nerve abnormalities. Purpose and rationale, procedure, evaluation, modification of the method are studied in experimental neuropathy. Study of the pharmacology of central sensitisation may open the door for novel analgesics effective in neuropathic pain Ideal models should produce just sensory deficits , such as allodynia ,hyperalgesia & spontaneous pain for short period of time ,there are different animal models to evaluate different neuropathic pain etiologies and manifestation, some models study peripheral Np mechanisms This article summarizes types, causes, nature, mechanisms, screening tools and treatments, pain management**

Index terms- **neuropathic pain, mechanism, animal models, treatments**

INTRODUCTION

A limited understanding of underlying pathophysiology, and recent changes in terminology have led to some confusion. The International Association for the Study of Pain (IASP) defines NP as "pains resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system". Originally, NP was used to describe only pain related to peripheral neuropathies, and central pain (CP)to lesions of the central nervous system associated with pain. Neurogenic pain embraced all causes, both peripheral and central.

The addition of a category of "dysfunction" in the definition of NP allows the inclusion of organic pain states which share the clinical features of NP, but which are not initiated by an identifiable lesion of any part of the nervous system. However, this is a contentious issue; some argue that the "dysfunctional" category should be excluded, on the grounds that there is no initiating neural injury. While it is true that including dysfunctional pain causes difficulties in recognising the limits of NP, exclusion of this important type of pain ignores the clinical reality of the existence of similar pain states, one provoked by neurological damage and the other by damage to non-neural tissues. Creation of a separately defined category of dysfunctional pain is acceptable, as long as it is recognised that there may be pathophysiological mechanisms common to both NP and dysfunctional pain.

The debate continues, but from a practical point of view, the current approach to treatment is broadly similar for NP and dysfunctional pain. The most important of the dysfunctional pain states is Complex

Regional Pain Syndrome (CRPS, formerly known as Reflex Sympathetic Dystrophy, RSD)

PHYSIOLOGY OF PAIN PERCEPTION

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior

Endogenous opioid and cannabinoid systems

It is generally accepted that opioids are less effective in relieving neuropathic pain than inflammatory pain. Although, the exact extent of this is controversial, the balance of evidence supports the view of an unfavourable (right) shift in the dose response function for opioids in neuropathy. There are a number of plausible explanations for this observation, including a loss of peripheral opioid effects, loss of spinal opioid receptors and increased activity in physiological opioid antagonists systems (Fig. 6).

Inflammation	Nerve injury
• Increased potency	• Decreased potency
• Additional peripheral site of action	• No peripheral effects
• No increase in CCK expression	• Loss of spinal receptors
	• Increased expression of CCK mRNA and CCK_b receptor

Fig 6 Mechanisms of opioid resistance in neuropathic pain: comparison of the effects of inflammation and nerve injury on features of the opioid system
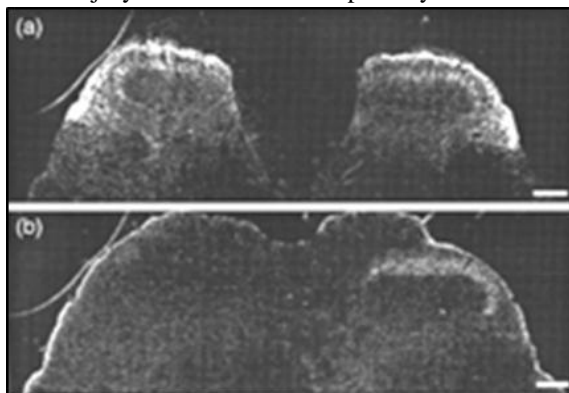

Fig 7 Preservation of cannabinoid CB1 receptors in the dorsal horn after dorsal rhizotomy: sections A and B are transverse sections of rat lumbar spinal cord taken from animals which had undergone dorsal rhizotomy. Section A was immunostained for cannabinoid CB1 receptors and there is no significant effect of dorsal rhizotomy. Section B was immunostained for the lectin IB4 (a marker of the GDNF dependent class of primary afferent nociceptor), the loss of IB4 staining ipsilateral to the dorsal rhizotomy indicates adequate degeneration of primary afferent nociceptors. After similar nerve injury, there is a considerable loss of μ-opioid receptor binding (scale bar 100 μm). Adapted from Farquhar-Smith and colleagues.[40]

EXPERIMENTAL NEUROPATHY

Purpose and Rationale

Partial injury to somatosensory nerves sometimes causes causalgia in humans. Causalgia is characterized by spontaneous burning pain combined with hyperalgesia and allodynia and usually follows an incomplete peripheral nerve injury. Allodynia, a pain sensation due to normally innocuous stimulation, is a particularly troublesome symptom in patients. Bennet and Xie (1988) described a peripheral neuropathy due to nerve constriction in the rat that produces disorders of pain sensation like those seen in man. This method with slight modifications was used by Davar et al. (1991), Mao et al. (1992), Munger et al. (1992), Yamamoto and Yaksh (1992), Tal and Bennet (1993) and reviewed by Bennett (1993).

Procedure

Anesthesia is induced in male Sprague-Dawley rats by inhalation with halothane 4% and maintained at a concentration of 2–3% as needed. After a local incision, the biceps femoralis of each leg is bluntly dissected at midtigh to expose the sciatic nerve. Each nerve is then mobilized with care taken to avoid undue stretching. Four 4-0 chromic gut sutures are each tied

The maximum hyperesthesia occurs between 7 and 14 days after nerve ligation. Before intrathecal injection of the drug or vehicle, the hind paws are tested 3 times alternatively with 5-min intervals as the baseline data. The left and right test sequence is carried out at 5, 15, 30, 60 and 90 min after injection.

Evaluation

The mean ±SEM of the paw withdrawal latency (PWL) is plotted. To analyze the magnitude of

hyperesthesia, the difference score (DS) is calculated by subtraction the maximum PWL of the control side (left side) from the maximum PWL of the affected side (right side). Maximum PWL is defined as the PWL which was the maximum during the first 30 min after injection. To analyze the drug effects in hyperesthetic rats, the dose is plotted against the change in DS (post-drug difference score minus pre-drug difference score).

Modifications of the Method

The first animal model of painful neuropathy was reported by Wall et al. (1979a,b).The sciatic nerve of rats or mice was sectioned and either tied or implanted in a polyethylene tube sealed at its far end. Moreover, in one modification also the saphenous nerve was cut, such that the hind paw was completely denervated. This procedure which is known as the neuroma model is believed to replicate the human syndromes seen after amputation (phantom pain) or after nerve transaction in an intact limb (anesthesia dolorosa). Within several days, the animals begin to self-mutilate the hindpaw on the side of the nerve transection: a behavior named 'autotomy'. Seltzer et al. (1990) ligated only one half of the sciatic nerve in rats unilaterally. The withdrawal thresholds to repetitive von Frey hair stimulation at the plantar side were decreased bilaterally as were the withdrawal thresholds to CO_2 laser heat pulses. The contralateral phenomena resemble the 'mirror image' pains in humans with causalgia. DeLeo et al. (1994) performed cryoneurolysis of the sciatic nerve in the rat using a cryoprobe cooled to –60 °C in a 30/5/30 s freeze-thaw-freeze sequence. Autotomy was observed after 4 to 14 daysKim and Chung (1992) described an experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Either both the L5 and L6 spinal nerves and the L5 spinal nerve alone of one side of the rat were tightly ligated. Zochodne et al. (1994) induced a segmental chronic pain syndrome by lumbar intrathecal NMDA infusion.

ANIMAL MODELS OF NEUROPATHIC PAIN

Whereas the distinction between nociceptive and neuropathicpain has utility, in the actual clinical setting, the mechanisms are often intertwined (e.g., back pain with radiculopathy). Fortunately, however,

this need not be the case with regard to animal models. A great advance in the study of neuropathic pain emanated from the discovery that placement of loose chromic ligatures on the sciatic nerve in rat brought about behavior that appeared analogous to human neuropathic pain conditions (Bennett and Xie, 1988). The rats engaged in protective behavior and had lowered thresholds to heat, cooling, and mechanical stimuli.

Subsequent work indicated that an idiosyncratic immune-mediated response to the chromic suture played a major role in the development of the model (Maves et al., 1993). The nerve swelled, leading to nerve compression and axotomy. But can an axotomy by itself induce pain? The answer is unequivocally yes. Chung and colleagues (Kim and Chung, 1992) devised a now frequently used model in rat whereby one or more spinal nerves that innervates the foot is cut (SNL model in Figure 1A). A substantial innervation of the foot remains, reflecting input from the adjacent spinal nerves. This remaining innervation allows tests for hyperalgesia to be undertaken. A simple axotomy provides a foundation by which to study mechanism in diseases where axotomy is part of the disease process. Some of the common traumatic nerve injury models are illustrated in Figure 1A. These injuries lead to hyperalgesia (Figures 1B and 1C).
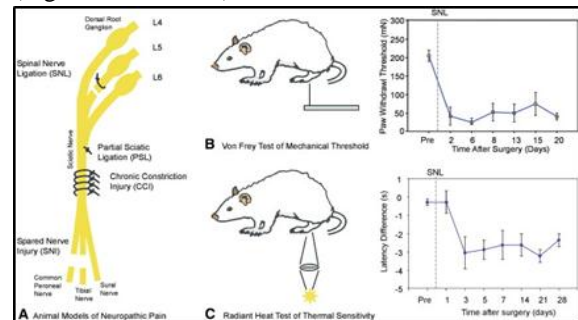

Figure 1. Animal Models of NeuropathicPain(A) Four different nerve injury models are shown. In the spinal nerve ligation (SNL) model, one or more spinal nerves going to the foot are ligated and cut (Kim and Chung, 1992). In the partial sciatic ligation (PSL) model, a portion of the sciatic nerve is tightly ligated (Seltzer et al., 1990). The chronic constriction injury (CCI) model involves placement of four loose chromic-gut ligatures on the sciatic nerve. An immune response to the sutures leads to nerve swelling and nerve constriction. In the spared nerve injury (SNI) model, the common peroneal and tibial

nerves are cut, sparing the sural nerve (Decosterd and Woolf, 2000). In each model, only a portion of the afferents going to the foot are lesioned.(B and C) Each of these nerve injury models leads to hyperalgesia, which is manifest by enhanced responses to mechanical, heat, and/or cooling stimuli. (B) To test for mechanical hyperalgesia, Von Frey monofilaments with different bending forces are applied to the plantar surface of the foot. The threshold force for paw withdrawal decreases dramatically after the nerve injury (adapted with permission [Li et al., 2000]). (C) To test for heat hyperalgesia, a radiant heat source is focused onto the plantar surface of the foot, and the reaction time for paw withdrawal is measured. The difference in reaction time between the ipsilateral and contralateral foot is calculated. After the SNL, the withdrawal of the ipsilateral foot is faster than the contralateral foot (negative latency difference), indicating the presence of heat hyperalgesia (adapted from Kim and Chung [1992] reprinted from Pain, pp. 355–363, copyright 1992, with permission from the International Association for the Study of Pain).Data are presented as mean ± SEM.

Secondary Hyperalgesia and Central Sensitization

A starting place in understanding neuropathicpain is to consider what happens with injury to nonneural tissues. Skin injury produces ongoing pain and two types of hyperalgesia: primary and secondary (Meyer et al., 2006). Primary hyperalgesia occurs at the site of tissue injury and is mediated in part by sensitization of primary afferent nociceptors. This is reflected by increased responses to heat stimuli, for example. Secondary hyperalgesia occurs in the uninjured tissue surrounding the site of injury and is thought to be due to sensitization in the central nervous system. Secondary hyperalgesia is characterized by hyperalgesia to mechanical, but not heat, stimuli. This mechanical hyperalgesia is comparable to the hyperalgesia seen in patients with neuropathicpain. Two types of mechanical hyperalgesia are observed: pain to light-stroking stimuli (i.e., allodynia) and enhanced pain to punctate stimuli.

In the second study, a fine electrode was placed into the superficial peroneal nerve (Torebjörk et al., 1992). Electrical intraneural microstimulation produced a nonpainful tactile percept that was referred to a small zone on the top of the foot. Capsaicin was injected adjacent to this area so that the zone of secondary hyperalgesia overlapped the area of referred sensation. Microstimulation after the injection produced a painful percept. Because this stimulation bypasses any peripheral sensitization processes at the cutaneous receptor, this experiment also provides evidence for altered central processing of mechanoreceptor input. Additional studies have shown that the tactile pain arises from central sensitization to the inputs of Aβ fibers, whereas the punctate hyperalgesia is due to a central sensitization to the inputs of capsaicin-insensitive Aδ nociceptors (Magerl et al., 2001).

The tactile fibers have known convergence onto dorsal horn cells that in addition receive inputs from nociceptive primary afferents. The inputs from the nociceptors in the injury zone are presumed to sensitize these so-called wide-dynamic range neurons and thereby enhance the synaptic efficacy of the tactile fibers. Nociceptive-specific neurons (dorsal horn neurons in lamina I) may be sensitized in similar fashion.

Where Do the Abnormal Signals in NeuropathicPainOriginate?

As shown in Figure 2, multiple sites along the neural axis are altered after nerve injury. Abnormalities occur in the injured and uninjured afferents supplying the affected region. Central sensitization, similar to that discussed above following tissue injury, is observed. In addition, changes in descending control systems have been reported. Finally, an immune response, both peripherally and centrally, is observed.
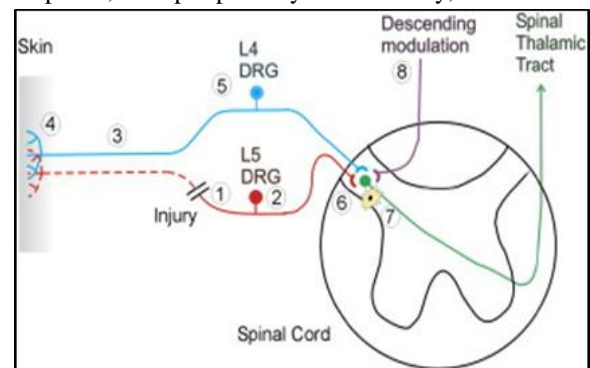

Figure 2. A Spinal Nerve Injury Leads to Alterations at Many Sites along the Neural Axis for PainEight different sites of pathophysiological changes are shown.

1. Spontaneous neural activity and ectopic sensitivity to mechanical stimuli develops at the site of nerve injury.
2. The expression of different molecules in the dorsal root ganglion of the injured nerve is up- or downregulated, reflecting the loss of trophic support from the periphery. Spontaneous neural activity develops in the dorsal root ganglia.
3. The distal part of the injured nerve undergoes Wallerian degeneration, exposing the surviving nerve fibers from uninjured portions of the nerve to a milieu of cytokines and growth factors.
4. Partial denervation of the peripheral tissues leads to an excess of trophic factors from the partly denervated tissue that can lead to sensitization of primary afferent nociceptors.
5. The expression of different molecules in the dorsal root ganglion of the uninjured nerve is up- or downregulated, reflecting the enhanced trophic support from the periphery.
6. Sensitization of the postsynaptic dorsal horn cell develops, leading to an augmentation of the response to cutaneous stimuli.
7. Activated microglial cells contribute to the development of this dorsal horn sensitization.
8. Changes in descending modulation of dorsal horn neurons also may contribute to the enhanced responsiveness of dorsal horn neurons.

A Role for Primary Afferents
The importance of primary afferent inputs in neuropathicpain is strongly suggested by several pharmacological studies. For example, systemic administration of AM1241, a selective CB2 cannabinoid receptor agonist, results in reversal of signs of mechanical and thermal hyperalgesia following an SNL lesion (Ibrahim et al., 2003). Because CB2 is not expressed in the central nervous system, the effects are likely due to a peripheral mechanism.

The Injured Afferent Hypothesis
The above evidence makes a clear case for the role of primary afferents, and one might assume that the culprit is the injured afferent itself. Indeed, much evidence favors this hypothesis. When nerve is injured a neuroma forms. The spontaneous activity and ectopic sensitivity to mechanical, thermal, and chemical stimuli that originate from the traumatic neuroma have been well documented ([Blumberg and Jänig, 1984] and [Devor, 2006a]). Clinical evidence has suggested that local-anesthetic blockade of an injured nerve in patients relieves pain, though no study, surprisingly, has really addressed this issue in a well-designed blinded fashion ([Arner et al., 1990], [Burchiel et al., 1993], [Gracely et al., 1992] and [Koltzenburg et al., 1994]). Additional support for the role of injured afferents comes from experiments in the rat L5 SNL model in which anesthetics (Sukhotinsky et al., 2004) or tetrodotoxin (TTX) (Lyu et al., 2000) directed at the L5 ganglia reversed the neuropathic behavior.

The Intact Nociceptor Hypothesis
According to this hypothesis, the intact nociceptors that survive injury and that innervate the region affected by the transected nerve fibers sensitize and have spontaneous activity. These changes in the intact nociceptors may induce ongoing pain and may account for certain aspects of hyperalgesia.
Following peripheral nerve lesions in primate and rodent models, spontaneous activity developed in uninjured, unmyelinated nociceptive afferents that shared the same innervation terrritory of the transectedfibers ([Ali et al., 1999], [Djouhri et al., 2006] and [Wu et al., 2001]). Although the average discharge frequency was low (seven action potentials/5 min), the incidence of spontaneously active fibers was high (50%). Low rates of spontaneous activity may therefore assume importance if this phenomenon is occurring in large numbers of C fibers, in particular given the high convergence of C fiber input in the CNS. Consistent with this hypothesis is the observation that low-frequency electrical stimulation in C fibers can lead to hyperalgesia in humans (Klede et al., 2003) and behavioral signs of hyperalgesia in rats (Wu et al., 2002). The development of spontaneous activity has also been observed in uninjured, myelinated afferents in the L4 dorsal root (Boucher et al., 2000), and this activity originated within the dorsal root ganglion.
CRPS is a striking disorder manifest by severe pain typically in an extremity. Patients typically have edema, hyperalgesia, and may even have a motor disability that is difficult to explain from a purely electrophysiological perspective. In certain of these patients, selective anesthetic blockade of the sympathetic nervous system leads to dramatic relief

of pain (sympathetically maintained pain, or SMP). Blockade of α-adrenergic receptor function with intravenous infusion of the antagonist phentolamine also leads to pain relief (Raja et al., 1991). In patients with SMP, in whom a sympathetic ganglion block was done to relieve pain and block release of norepinephrine, injection of physiological concentrations of norepinephrine evoked substantial pain (Figure 3A).
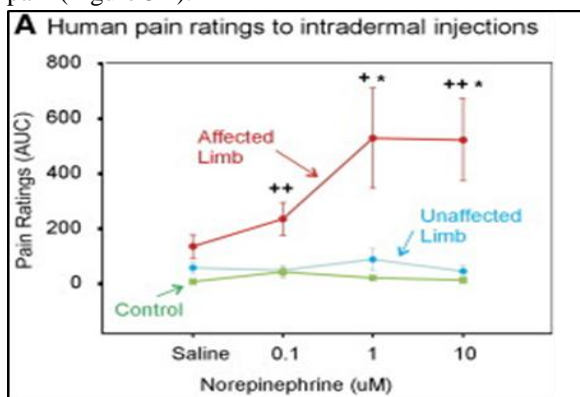

Figure 3. A Model for Sympathetically Maintained Pain

(A) After acutely relieving pain by performing a sympathetic block, norepinephrine in physiological concentrations was injected intradermally in a
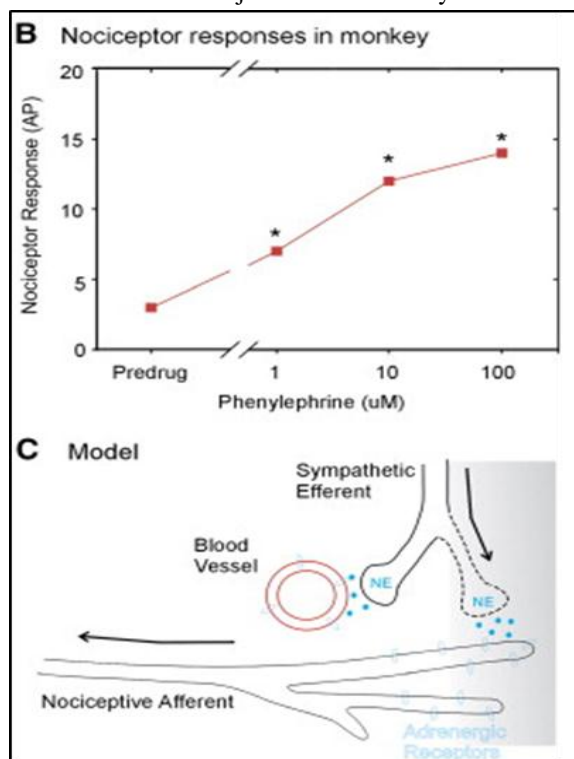

Figure 3. A Model for Sympathetically Maintained Pain

blinded fashion into the previously hyperalgesic area. The norepinephrine injections into the affected, but not the unaffected, extremity produced pain. Norepinephrine does not induce pain in control subjects. These data suggest that the nociceptors are sensitized to catechols in patients with SMP (adapted with permission [Ali et al., 2000]). ACUC, area under curve.

(B) In primates, normal nociceptors do not respond to catechol administration. However, in a monkey-spinal nerve ligation model, nociceptors developed a response to the α1 adrenergic agonist phenylephrine administered topically to their receptive field (adapted and used with permission [Ali et al., 1999]). AP, action potentials.

(C) A model to account for SMP. After a partial nerve lesion, some afferent fibers still remain in the skin. Factors released in the skin induce the sympathetic efferents to sprout into more superficial areas of the skin (Yen et al., 2006). These factors also lead the nociceptors to express α1 adrenergic receptors. Now, the release of norepinephrine from the sympathetic terminals leads to activation of the nociceptive terminals, which accounts for the coupling of sympathetic activity with nociceptor responses.Data are presented as mean ± SEM.

In a primate model of neuropathicpain, an L6 SNL leads to hyperalgesia just as it does in rodent models (Carlton et al., 1994). About one-half of the afferents to the top of the foot are lost, and the other half reach the foot from the adjoining and putatively normal spinal nerves (Ali et al., 1999). More than 60% of the intact nociceptors had spontaneous activity (normally infrequently seen), and more than 50% had sensitivity to the select α-adrenergic agonist phenylephrine (Figure 3B). These studies indicate that the mechanisms of SMP relate to an adrenergic sensitization of nociceptors (Figure 3C). Moreover, this chemical sensitization occurs in the intact nociceptors that survive a proximal nerve injury. Thus, SMP is a specific example of the importance of the intact nociceptors in the pathogenesis of a particular neuropathicpain disorder.

The Role of Growth Factors
Trophic factors in the target tissue have an ongoing influence on sensory and motor fibers. Nerve injury

induces changes in growth-factor expression (Griffin, 2006). The change in expression occurs in the tissue deprived of innervation (e.g., the skin), the Schwann cells affected by Wallerian degeneration (denervated Schwann cells), the DRG, and the dorsal horn. Of note, in the SNL model, the L5 root is lesioned, but the L4 root shares the innervation territory, the same Schwann cells, and has convergent input to dorsal horn cells served by the L5 afferents. Nerve injury leads to increased levels of NGF in the skin supplied by L4. The binding of this NGF to the Trk-A receptors on the L4 fibers leads to transport of NGF back to the L4 DRG. Evidence suggests that this increased level of NGF in the L4 DRG affects factors such as BDNF. Indeed, the changes in gene expression in the intact L4 DRG and the lesioned L5 DRG are quite different.

That channel function may strongly affect nociception has been further emphasized by the discovery of the genetic underpinnings of a striking neuropathicpain disorder known as erythromelalgia. Here, patients present with profound heat hyperalgesia and ongoing burning pain typically affecting the feet. The feet may also be intensely red, indicating profound vasodilation. Point mutations in the TTX-sensitive channel Nav1.7 account for the disorder (Figure 4). These mutations lead to a hypoexcitability in sympathetic neurons (accounting for the increased perfusion in the feet) and a hyperexcitability in small-sensory neurons (accounting for the pain and hyperalgesia) (Rush et al., 2006). Release of vasoactive peptides in the skin from the tonically active nociceptors may also contribute to the vasodilatation.
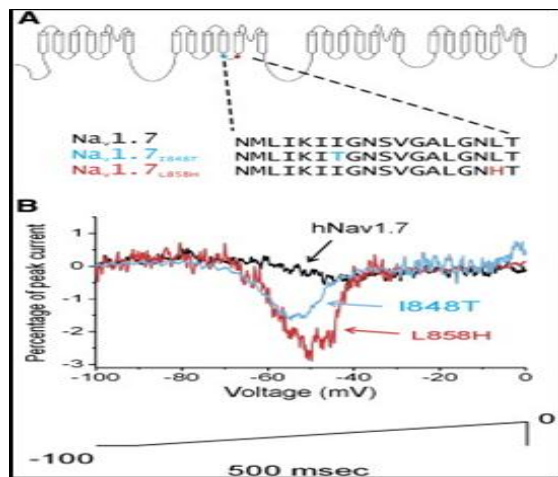
(A) Schematic of the Nav 1.7 voltage-gated sodium channel that is found exclusively in sensory and sympathetic neurons. A number of point mutations have been identified in this sodium channel in families of patients with erythromelalgia (Waxman and Dib-Hajj, 2005). The two mutations shown here produced single amino acid substitutions at the sites indicated.

(B) Whole-cell-patch-clamp recordings in transfected HEK293 cells revealed that these point mutations lead to an augmentation of the response of the channel to a slow depolarizing ramp (100 mV in 500 ms). These mutations would be expected to increase the excitability of the peripheral sensory neuron. (Adapted with permission [Cummins et al., 2004].Copyright 2004 by the Society for Neuroscience.).

The Role of Central Sensitization

Central sensitization refers to the augmented response of central signaling neurons. Though thalamic and cortical levels may be involved, most attention has focused on the dorsal horn and in this review we will concentrate on this area. nociceptive inputs alter synaptic efficacy such that A-β mechanoreceptors acquire the capacity to evoke responses. Electrophysiological evidence for heterosynaptic sensitization has been shown in primate studies of dorsal horn cells where the response to light stroking of the skin was enhanced after capsaicin injection (Simone et al., 1991).
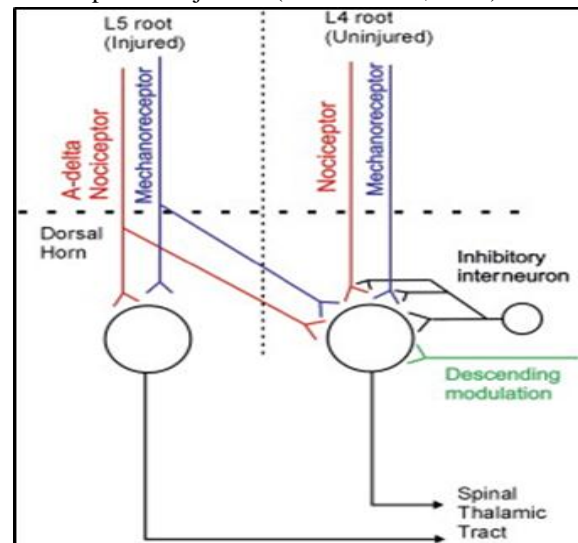

Figure 4. A Genetic Basis for Erythromelalgia

Figure 5. Central Sensitization Mechanisms Involved

in the Spinal Nerve Ligation ModelSpontaneous activity from the injured afferents (L5) and intact nociceptors (L4) may sensitize central pain-signaling neurons. The spontaneous activity in the L5 fibers is restricted to myelinated afferents. Nociceptive C fibers from L4 spontaneously discharge and may themselves be sensitized. The enhanced discharge of the primary afferents leads to augmented response of dorsal horn cells to nociceptor input and increased synaptic efficacy of inputs from mechanoreceptors (mechanism for allodynia). Alterations in descending modulation and inhibitory interneuron function also likely play a role.

Homosynaptic and heterosynaptic sensitization involve many mechanisms, but fundamentally these mechanisms come down to two processes: (1) increased release of excitatory neurotransmitter (e.g., glutamate, substance P) and/or (2) enhanced synaptic efficacy. These changes in turn may relate to several cellular mechanisms (Basbaum, 1999). These mechanisms may be considered in five categories: (1) presynaptic changes, (2) postsynaptic changes, (3) interneuron changes, (4) changes in descending modulation, and (5) immune/microglial mechanisms (discussed in the following section). Evidence suggests a role for each of these mechanisms in neuropathicpain. Long-term potentiation (LTP), a phenomenon that has received intensive study in the hippocampus, appears to apply to the dorsal horn to some degree. However, given the abnormal ongoing input of primary afferents documented after nerve injury, the acute central-sensitizing effects of primary afferents may have an ongoing role. Thus, both short-term sensitization and LTP mechanisms likely apply. A role for long-term depression (LTD) in inhibitory cells is also considered below.

1. Presynaptic Mechanisms
2. Postsynaptic Mechanisms
3. Roleof Disinhibition Mechanisms
4. Descending Modulatory Mechanisms
5. Supraspinal Mechanisms
6. The Immune System and Neuropathic Pain
7. Peripheral Immune Mechanisms
8. Central Immune Mechanisms

TREATMENT FOR NEUROPATHIC PAIN

Treatments include,
- Treating the underlying cause - if possible
- Medicines
- Physical treatments
- Psychological treatments

REFERENCES

[1] Bennett GJ (1993) An animal model of neuropathic pain: a review. Muscle Nerve 16:1040–1048

[2] Bennet GJ, Xie YK (1988) A peripheral neuropathy in the rat that produces disorders of pain sensation like those seen in man. Pain 33:87–108

[3] Davar G, Hama A, Deykin A, Vos B, Maciewicz R (1991) MK- 801 blocks the development of thermal hyperalgesia in a rat model of experimental painful neuropathy. Brain Res 553:327–330

[4] DeLeo JA, Coombs DW, Willenbring S, Colburn RW, Fromm C, Wagner R, Twitchell BB (1994) Characterization of a neuropathic pain model: sciatic cryoneurolysis in the rat. Pain 56:9–16

[5] Gregg JM (1973) A surgical approach to the ophthalmic-maxillary nerve trunks in the rat. J Dent Res 52:392–395

[6] Mao J, Price DD, Mayer DJ, Lu J, Hayes RL (1992) Intrathecal MK-801 and local anesthesia synergistically reduce nociceptive behaviors in rats with experimental peripheral neuropathy. Brain Res 576:254–262

[7] Munger BL, Bennett GJ, Kajander KC (1992) An experimental painful peripheral neuropathy due to nerve constriction. ExperNeurol 118:204–214 Seltzer Z, Dubner R, Shir Y (1990) A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. Pain 43:205–218

[8] Vos BP, Strassman AM, Maciewicz RJ (1994) Behavioral evidence of trigeminal neuropathic pain following chronic constriction injury to the rat's infraorbital nerve. J Neurosci 14:2708–272

[9] Wall PD, Devor M, Inbal R, Scadding JW, Schonfeld D, Seltzer Z, Tomkiewicz MM (1979a) Autotomy following peripheral nerve lesions: experimental anesthesia dolorosa. Pain 7:103–113

[10] Wall PD, Scadding JW, Tomkiewicz MM (1979b) The production and prevention of

experimental anesthesia dolorosa. Pain 6:175–182

[11] Zochodne DW, Murray M, Nag S, Riopelle RJ (1994) A segmental chronic pain syndrome in rats associated with intrathecal infusion of

[12] NMDA: evidence for selective action in the dorsal horn. Can J NeurolSci 21:24–28

[13] Vogel's screening models in pharmacology Page: No: 436-478

[14] http://www.google.co.in

[15] http:// wekipedia.co.in

AUTHOR PROFILE

Shital S. Bhure, Student of B.pharmacy 4th year, Latur College of Pharmacy, Hasegaon.

Irshad A. Shaikh, Assistant Professor, Department of Pharmaceutical Analysis, Latur College of Pharmacy, Hasegaon.