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A REVIEW ON NEUROPATHIC PAIN: AN APPROACH TOWARDS TREATMENT

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ABSTRACT

Neuropathic pain is characterized by a primary lesion or dysfunction in the central or peripheral nervous system in which peripheral nerve injury is associated with the presence of abnormal and unpleasant sensory symptoms, such as hyperalgesia (an increased response to a normally painful stimulus) and allodynia (pain in response to a stimulus which does not normally provoke pain; patients with allodynia do not feel pain in the absence of stimulus). Importantly, many of these mechanisms do not depend on the cause of the disease: the same mechanism can be found in different diseases (e.g., in postherpetic neuralgia and in painful polyneuropathy). The mechanism of neuropathic pain is complex, therefore the current treatments are causing a variety of adverse effects. The widely used drug for the treatment of chronic to moderate pain is morphine but the therapeutic value of the same is still controversial because in some patients with neuropathic pain opioids are reported to be ineffective In this review, we will focus on the mechanism of neuropathic pain, the animal models and possible treatments of neuropathic pain.

Keywords: hyperalgesia, allodynia, ectopic, transient receptor potential vanilloid, ephaptic.

INTRODUCTION

Neuropathic pain is defined as a form of chronic pain which is initiated or stimulated by a primary lesion or dysfunction in the central or peripheral nervous system [1, 2]. Neuropathic pain caused by the peripheral nerve injury is associated with the presence of abnormal and unpleasant sensory symptoms, such as hyperalgesia (an increased response to a normally painful stimulus) and allodynia (pain in response to a stimulus which does not normally provoke pain; patients with allodynia do not feel pain in the absence of stimulus) [3]. The severity of chronic pain varies from person to person, between old and young and even with sex. Sometimes lesions similar in appearance may cause pain in one person but no pain in another [4]. The mechanism of neuropathic pain is complicated, therefore the current treatments such as use of tricyclic anti-depressants and anti-convulsants are proved to be ineffective or produce severe side effects [5]. Among opioids, the widely used drug for the treatment of chronic to moderate pain is morphine. But its therapeutic value is still controversial because in some patients with neuropathic pain opioids are reported to be ineffective [6].

PATHOPHYSIOLOGICAL MECHANISM OF NEUROPATHIC PAIN

The underlying mechanisms of neuropathic pain are not completely understood. Neuropathic pain arises through multiple and complex pathophysiological mechanisms. Importantly, many of these mechanisms do not depend on the cause of the disease: the same mechanism can be found in different diseases (eg, in postherpetic neuralgia and in painful polyneuropathy). In one individual patient, different mechanisms might be involved and different mechanisms could lead to the same symptom. Neuropathic pain can be caused by trauma (surgical and non-surgical), accidents, and exposure to toxins, infections, viruses, metabolic diseases, nutritional deficiency, ischemia, and stroke [7, 8, 9]. Current research studies indicate that both peripheral and central mechanisms have been involved in pathogenesis of neuropathic pain [10, 11, 12, 13] (Table 1).

1. Peripheral mechanisms

1.1 Ectopic and spontaneous discharge

The propagation of pain is initiated with the activation of physiological receptors, called nociceptors, which are free nerve endings and represents the most distal part of the afferent neuron14. The afferent fibers within the peripheral nerves can be classified into three groups i.e. heavily myelinated Aβ fibers, thinly myelinated Aδ fibers and unmyelinated C fibers. Pain sensations are normally elicited by activation of unmyelinated (C-) and thinly

myelinated (Aδ-) primary afferent neurons. These nociceptors are usually silent in the absence of stimulation, and respond best to stimuli that are potentially noxious. Following the nerve injury, it has been demonstrated that there is a large increase in the level of spontaneous firing in both injured and neighboring uninjured nociceptive afferents [15, 16, 17]. This has been termed ectopic discharge and has also been demonstrated in humans suffering from neuropathic pain [18].

Table 1: Different mechanisms which have been observed in the central and peripheral nervous system after experimental peripheral nerve injury, which may contribute to neuropathic pain

Peripheral Mechanisms	Central Mechanisms
Ectopic and spontaneous discharge Ephaptic conduction Alteration in ion channel expression Collateral sprouting of primary afferent neurones Sprouting of sympathetic neurones into the DRG Nociceptor sensitization	Sprouting of Aβ afferent terminal Spinal reorganization Central sensitization Changes in inhibitory pathways

Some studies revealed that some ectopic discharge could also originate from dorsal root ganglion (DRG) and other points along with nerves [19.]

The ectopic discharge is a massive increase in the level of normal firing in the primary afferent neurons (A- and C-fibers) and the efferent neurons close to the site of the injury, this is due to 'cross excitation' [18.] Since the Dorsal root ganglion (DRG) neurons are all isolated from each other so ephapsis and cross excitation do not normally occur in DRG following the nerve injury [19]. However, it has been reported that chemically mediated cross-excitability occur in DRG [15.] Following the peripheral nerve injury, many DRG neurons alter their membrane potential to bring it closer to the firing threshold. Therefore, it may be possible that the cross-excitation is sufficient enough to evoke ectopic firing.

The increase in the expression of mRNA for voltage-gated sodium ion channel in primary afferent neuron is responsible for the ectopic discharge. There is alteration in the expression of sodium ion channel in fact there is clustering of sodium ion channel at sites of ectopic

impulse generation which leads to lowering of action potential threshold and consequent hyperactivity [20, 21, 22].

Nerve injury also leads to the upregulation of various receptor proteins such as TRPV1 (transient receptor potential vanilloid 1). TRPV1 is mainly present in the peripheral nerve endings and as it is temperature sensitive so gets activated by noxious heat at about 41°C [23]. After a nerve lesion, TRPV1 gets downregulated on injured nerve fibres but upregulated on uninjured C fibres. Recent studies also provide evidence for an upregulation of TRPV1 in injured DRG cells [24]. A patient with such underlying pain mechanism can be characterized by the presence of heat hyperalgesia or cold allodynia in addition to burning pain [25].

It has been reported that hyperalgesia and allodynia may also be elected by calcium ion channels. It has been demonstrated that there is alteration in Ca^{2+} currents after peripheral nerve injury. More specifically, after nerve injury the N-type current in DRG decreases, with no significant changes in P- or Q- type currents [26, 27]. This suggests that the loss of N-type Ca^{2+} channels in response to peripheral nerve injury, increases the excitability of the neurons which in turn leads to increase in ectopic firing and spontaneous pain.

These observations suggest that the ectopic discharge is important for the development of hyperalgesia and allodynia. The ectopic discharge is responsible for the development of ongoing neuropathic pain [28].

1.2 Collateral sprouting

Collateral fibres from sensory axons in the skin show sprouting into the denervated areas following the nerve injury [29]. Sprouting was also observed from saphenous nerve in the CCI model [30]. This sprouting occurs at around 10 days post-operation, but the degree of sprouting is not directly proportional to the degree of hyperalgesia after chronic constriction injury [31]. These results show that collateral sprouting is unlikely to contribute to the pain behavior seen in this model. Collateral sprouting basically is a process of repair in which a neurite sprouts off the axon of an intact motor unit and innervates denervated muscle fibers of an injured motor unit. The sprouts connect with smaller terminal branches, thinner myelin, and weaker neuromuscular junctions.

1.3 Coupling between sympathetic and sensory nervous system

The neuropathic pain is dependent on the activity of the sympathetic nervous system. This is referred to as 'sympathetically maintained pain'. For example, some patients suffering from complex regional pain syndrome type 1 (CRPS 1) can be classified as having sympathetically maintained pain [32]. It has been reported that, following nerve injury, an abnormal contact develops between the sympathetic nervous system and the sensory nervous system which ultimately leads to neuropathic pain [33]. So it can be concluded that sympathetic nervous system and sensory nervous system together are responsible for pain perception. A number of coupling sites between sympathetic and sensory nervous system are reported such as a direct correlation between sympathetic and sensory nervous system which gets coupled in dorsal root ganglion 34 , direct chemical coupling between the noradrenergic and sensory neurone terminals within peripheral effector sites [35] , ephaptic nerve coupling between sensory nerve fibres in damaged nerves [36] and release of inflammatory mediators following nerve injury leads to peripheral sensitization which causes indirect coupling in sympathetic terminals and sensitization of primary sensory neuron axons [37]. In many patients with neuropathic pain sympathetic sprouting has been found [38]. Cytokines and neurotrophins are mainly responsible for the sympathetic sprouting formation [39, 40]. The sprouted neurones are responsible for the over excitability of the DRG neurons as they transformed their terminals to form structures similar to synapses with cell bodies [34].

1.4 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 [41, 42]. It is well reported that peripheral or perineural inflammation is measured by plasma extravasation or increased capillary permeability which causes increase in the release of various pro-nociceptive and pro-inflammatory mediators [43,44]. Most importantly, neurogenic inflammation has also been reported in experimental models of nerve injury that implicates increased capillary permeability leaving plasma leakage of pro-inflammatory mediators at the local as well as adjacent sites to nerve injury [45, 46]. Inflammation after a nerve lesion induces activation and migration of macrophages into the nerve and dorsal root ganglion, which causes pain hypersensitivity by releasing proinflammatory cytokines, including tumour necrosis factor α (TNF-α). After peripheral and central nerve lesions, activated microglia within the CNS release several immune modulators that also maintain neuropathic pain.This is accompanied by enhanced release of substance P and calcitonin gene related peptide

(CGRP) in the control of vascular tone. Bradykinin also plays an important role in the development of pain hypersensitivity. Bradykinin is released as a result of tissue damage, which has been mainly associated with the inflammatory hyperalgesia. The PGs (prostaglandins) are also rapidly produced following tissue injury and are major contributors to peripheral sensitization [47,48]. These inflammatory processes, as well as other changes in peripheral nerve endings leads to peripheral sensitization (i.e. decreased activation thresholds and increased membrane excitability) [49].

2. Central mechanisms

2.1 Anatomical reorganization of spinal cord

In response to peripheral nerve injury, there is considerable degree of re-organization of spinal cord. Under the normal physiological condition, the primary nociceptive afferent fibers terminate in the laminae of dorsal horn in spinal cord. Small diameter cells with myelinated Aδ-fibres and unmyelinated C-fibres terminate in the lamina I (marginal layer) and in lamina II (substantia gelatinosa) and large diameter neuronal cells with Aβ-fibres terminates in lamina III and IV.

The lamina I neurons are called nociceptive-specific neurons as they respond to noxious stimulation and project to higher brain centers. In the lamina II, both excitatory and inhibitory interneurons are present and only some of them respond to nociceptive input. Laminae III and IV neurons responds to non-noxious stimuli by receiving monosynaptic input from Aβ-fibers. Lamina V is a region of assemblage of inputs. Lamina V neurons receive either nociceptive or non-nociceptive inputs from Aβ, Aδ and C-fibers, project to brain stem and thalamus [50].

It has been demonstrated that after sciatic nerve axotomy, the large myelinated primary afferent fibres (Aβ- fibers) sprout into lamina II of the dorsal horn [51]. This sprouting occurs within 1 week of sciatic nerve axotomy and is at its highest after 2 weeks . The consequence of this synaptic rearrangement is that the second order neurones present in the spinal cord, which normally gets activated on receiving high-threshold sensory inputs, begin to receive low-threshold sensory inputs. This is due to the fact that the sprouted fibres establish synaptic contacts with second-order neurons, causing misinterpretation of information within the spinal cord and leads to the emergence of allodynia after peripheral nerve injury [53].

2.2 Spinal cord hyperexcitability or central sensitization

Peripheral nerve injury is associated with the development of hyperexcitability of DRG neurons, this process is called as ‘central sensitization’ [54, 55]. This hyperexcitability of spinal

cord is characterized by occurrence of 'wind- up' in which C-fibres are frequently stimulated and the response of the neurons of the dorsal horn progressively increases, and cause hyperalgesia [54,56].

Central sensitization is initiated and maintained by activity in pathologically sensitized C-fibers. These fibers sensitize spinal cord dorsal horn neurons by releasing glutamate and substance P. Glutamate is the major excitatory amino acid neurotransmitter which is released from the central terminals of primary afferent nociceptive neurons after noxious stimulation. Glutamate acts directly on various pre- and post-synaptic receptors, but out of them the inotropic N-methyl-D-aspartate (NMDA) receptor is the one which is involved in the events correlated with the nociception [57] and it is behind the mechanism of central sensitization. The initial NMDA receptor activation is the main cause for elevating the release of glutamate and aspartate, contributes to positive feedback loop that maintains central sensitization. NMDA receptors can increase the concentration of the calcium ions and excitatory amino acids, which could also form a positive feedback loop, through indirect activation of protein kinase C, which is responsible for allodynia [58]. Following nerve injury, the voltage-gated N-calcium channels located at the presynaptic sites on the terminals of primary afferent nociceptors gets overexpressed and facilitates the release of glutamate and substance P which further leads to central sensitization [59].

After peripheral nerve injury, it has been reported that, there are changes in the spinal cord, the peripheral nerve and in the brain. The pathophysiological properties that are responsible for NP can be broadly categorized into two groups i.e. the peripheral effects and the central effects. The peripheral effects are:ectopic impulse generationin damaged primary afferent fibres, sprouting of sympathetic neurons into the DRG, nociceptor sensitization, and alterations in ion channel expression, ectopic and spontaneous discharge.The central effects are: central sensitization, spinal and cortical re-organization, changes in the inhibitory pathways. It is probably a combination of these phenomenon that contributes to the pain symptomatology [8].

ANIMAL MODELS

The animal models of neuropathic pain are the mainstay for developing a treatment schedule and predicting the possible mechanism of the neuropathic pain. But there are many drawbacks of animal models, viz., due to lack of verbal communication it is difficult to understand what is actually perceived by the animal. So it is important to develop such

animal models of neuropathic pain in which the behavioral pain response can be measured. The animal models should be predictable, reproducible and have a relationship to the disease. Ideally, they should be experimentally straight forward and have a reasonable throughput. Neuropathic pain in experimental animal models is measured as allodynia and hyperalgesia, where a non-noxious or mildly noxious stimulus induces nociceptive behavioral response.

Various animal models of neuropathic pain have been developed such as, the simple axotomy model. In this model, the self-mutilation of the injured foot (autotomy) was observed in response to pain. More recently, it has been reported that autotomy occurs because there is a complete motor and sensory denervation of the hind-paw rather than pain.

In the spinal nerve ligation (SNL) model, light ligationand transection of the L5 and L6 spinal nerves are made; in chronicconstriction injury (CCI) of sciatic nerve model, several loose ligations ofthe sciatic nerve are made; in the partial sciatic nerve ligation (PSNL)model, about 1/2 to 1/3 of the sciatic nerve is lightly ligated; in the spared nerve injury (SNI) model, tight ligation of 2 of the 3 terminal branches of the sciatic nerve (common peroneal and tibial nerve) are made leaving the sural intact.

Most of the animal models of neuropathic pain have been produced in rodents (rat or mouse), and the peripheral nerve injury models are most important, widely used and extensively studied models of neuropathic pain [60, 61]. These models are based on procedures near or at sciatic nerve, they differ in the location and form of injury. Such models include the chronic constriction injury (CCI) of sciatic nerve model in which several loose ligations of the sciatic nerve are made, the partial sciatic nerve ligation (PSNL) model in which about 1/2 to 1/3 of the sciatic nerve is lightly ligated, the spinal nerve ligation (SNL) model which includes light ligation and transection of the L5 and L6 spinal nerves and spared nerve injury (SNI) model in which tight ligation of 2 of the 3 terminal branches of the sciatic nerve (common peroneal and tibial nerve) are made[62,63,64, 65,66].

Other commonly used model of neuropathic pain is streptozotocin (STZ) or alloxan induced diabetic neuropathy. This model is generated by the intravenous (i.v.) or intraperitonial (i.p.) injection of pancreatic β-cell cytotoxic agents such as streptozotocin (STZ) or alloxan in rodents. This model produces functional, biochemical, and structural abnormalities in the sciatic nerve similar to those seen in human diabetic neuropathy. Animal models for diagnosis and treatment of cancer associated pain are also been reported.

NEUROPATHIC PAIN: TREATMENT

First line drugs for the treatment of peripheral neuropathic pain includes gabapentin, pregabalin, 5% lidocaine patch, tri-cyclic antidepressants (TCAs) like nortriptyline, desipramine and selective serotonin norepinephrine reuptake inhibitors (SSNRIs) like duloxetine and venalafaxine. The second line therapy include opioid analgesics, tramadol hydrochloride and the third line medication includes other anticonvulsants like carbamazepine, lamotrigine, oxcarbazepine and antidepressants such as bupropion, citalopram, paroxetine, local anesthetic like mexiletine, NMDA receptor antagonists and topical capsaicin etc. [9, 67] (Table 2).

Gabapentin is FDA approved for the treatment of post herpetic neuralgia (PHN). It bindson α2-δ subunit of voltage gated calcium channel and decreases release of glutamate, norepinephrine and substance P. FDA also approved 5% lidocaine patch for treatment of PHN. Antidepressant drug duloxetine that act through inhibition of both serotonin and norepinephrine reuptake has recently been approved by FDA for treatment of diabetic neuropathic pain. Another antiepileptic drug, pregabalin was also launched for the treatment of DNP in 2004.

Pregabalin is also efficient in relievingthe pain after spinal cord injury. Tricyclic antidepressants (TCAs) such as nortriptyline and desipramine are approved for the treatment of diabetic neuropathy, PHN, pain after spinal cord injury and chronic radiculopathy. TCAs acts by inhibition of reuptake of serotonin and/or norepinephrine and blocks ofsodium channels. Opioid agonists such as morphine, oxycodone, methadone, levorphanol and tramadol acts as μ-receptor agonists and inhibits norepinephrine and serotonin reuptake. These opioids are proved to be effective in treatment of diabetic neuropathy, phantom pain, SCI, and cancer associated neuropathic pain [68].

Table 2: Recommended treatments for neuropathic pain

Therapeutic Class	Drug (s)	Mechanism of action
Antiepileptic	Gabapentin, Pregabalin,	sedation, dizziness and peripheral edema
	Lamotrigine, Carbamazepine	Hepatotoxicity, CNS toxixity
Tricyclic Antidepressants	Nortriptyline, Desipramine	Sedation, anticholinergic effects (e.g., dry mouth or urinary retention, weight gain

SSNRIs	Duloxetine, Venlafaxine	Nausea
Local anesthesics	Topical lidocaine (5% lidocaine patch)	Local erythema, rash
Opiods	Morphine, oxycodone, methadone, levorphanol, Tramadol	Nausea/ vomiting, constipation, dizziness, sedation, renal failure

Despite these many therapeutic options, the treatment of neuropathic pain is not fully effective, 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.

CONCLUSION

The reasons that only some patients with nerve lesions develop neuropathic pain is still unknown. Risk factors such as age, gender, pain intensity before and after the lesion, and emotional and cognitive features indicate that there are multiple factors other than the nerve lesion itself that contribute to manifestation of chronic pain. Differences in the extent of the lesion of certain subgroups of nociceptive afferent pathways might also be a predictor for development of neuropathic pain, as well as genetic determinants.

The prospect for developing a mechanism-based classification and treatment approach seems promising. Although there are still important hurdles, several research groups across the world systematically analyzing sensory profiles that are likely to correspond to underlying mechanisms. Given the diverse mechanisms of action of the drugs, this research provides hope that we will soon be able to target specific drugs to individual patients and improve the outlook for patients with neuropathic pain.

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