Neuropathic Pain: Mechanisms and Treatments

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Neuropathic pain is caused by functional abnormalities of structural lesions in the peripheral or central nervous system, and occurs without peripheral nociceptor stimulation. Many common diseases, such as postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, spinal cord injury, cancer, stroke, and degenerative neurological diseases may produce neuropathic pain. Recently, theories have been proposed that state there are specific cellular and molecular changes that affect membrane excitability and induce new gene expression after nerve injury, thereby allowing for enhanced responses to future stimulation. In addition, the ectopic impulses of neuroma, changes of sodium and calcium channels in injured nerves, sympathetic activation, and deficient central inhibitory pathway contribute to the mechanisms of neuropathic pain. Currently, treatment of neuropathic pain is still a challenge. Pharmacotherapies (antidepressants, antiepileptics) remain the basis of neuropathic pain management. However, patient satisfaction in the results of the treatment of neuropathic pain is still disappointing. Since it has been established that intense noxious stimulation produces a sensitization of central nervous neurons, it may be possible to direct treatments not only at the site of peripheral nerve injury, but also at the target of central changes. In order to provide better pain control, the mechanism-based approach in treating neuropathic pain should be familiar to physicians. In the future, it is hoped that a combination of new pharmacotherapeutic developments, careful clinical trials, and an increased understanding of the contribution and mechanisms of neuroplasticity will lead to an improvement in the results of clinical treatments and prevention of neuropathic pain. *(Chang Gung Med J 2005;28:597-605)*

Key words: pain, neuropathic pain, central plasticity.

Neuropathic pain can be defined as abnormal pain sensation in the peripheral or central nervous system after injuries. It is caused by dysfunctions in the peripheral or central nervous system without peripheral nociceptor stimulation. The prevalence of neuropathic pain is around 1.5% of the general population in the United States.[1] Many common diseases, such as postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, spinal cord injury, cancer, stroke, and degenerative neurological diseases may produce neuropathic pain. Multiple mechanisms, including changes in the peripheral nervous system, spinal cord, brainstem or brain, may contribute to the neuropathic pain.

Treatment of neuropathic pain is known as a challenge. Symptoms vary among patients and may be resistant to common analgesics. However, most patients will experience satisfactory pain relief and

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improved quality of life after appropriate therapy. The main rationales of failed treatment for neuropathic pain include: lack of understanding of the mechanisms, incorrect selection of treatments, inadequate diagnosis, and inappropriate management of comorbid conditions. In this review, we addresses the multi-level pathophysiological mechanisms of the nervous system in neuropathic pain and options in the current management of neuropathic pain.

Mechanisms of neuropathic pain

Pain is a physiological defense mechanism to prevent further injury to a living organism. The defense mechanisms include the pain signal transduction from the nociceptors-peripheral nervous system-spinal dorsal horns-thalamus-cortex and the pain control system from the cortex-periaqueductal grey matter-nucleus raphe magnus-spinal dorsal horn (Fig. 1, 2). In healthy situations, the pain signal transduction and the pain control system reach a balance and the subject recovers from the pain. However, any imbalance between the pain signal transduction and the pain control system produces neuropathic pain. Multiple mechanisms may coexist as the causes of neuropathic pain.[1] A temporal evolution may occur from one mechanism to another during the course of a disease. The factors for driving the mechanisms are not disease-specific. The unifying feature of neuropathic pain is pain caused by damages to some component of the primary sensory neurons. The lesion can be located in a peripheral nerve, a dorsal root ganglion or a dorsal root, and may be the results of compression, inflammation, ischemia, trauma, tumor invasion, nutritional deficits, or degenerative disorders. Loss of primary sensory neurons as well as interruptions of the conduction of these neurons and its peripheral target may result in a loss of sensory input and some detectable sensory impairment.

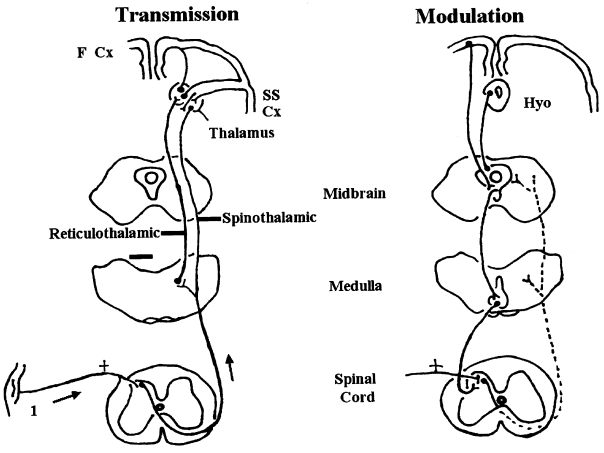

Fig. 1 Pain excitability in dorsal horn neurons is determined by the balance between excitatory inputs from the nociceptors- primary afferents-dorsal horns-thalamus-cortex and inhibitory inputs from the cortex- periaqueductal grey matter-raphe magnus-spinal dorsal horn. F Cx: frontal cortex; SS Cx: somatosensory cortex; Hyo: hypothalamus.

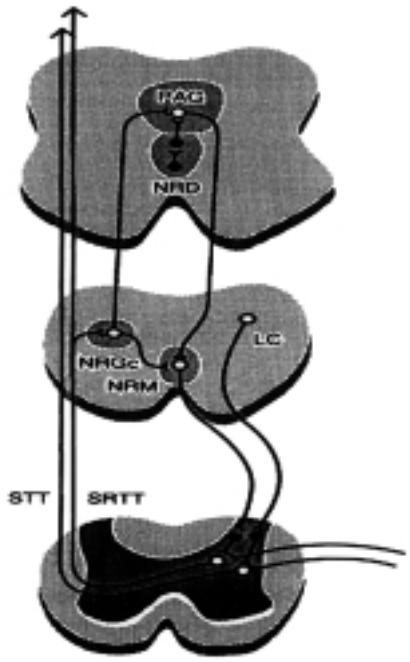

Fig. 2 The pain control system including the descending pathway (PAG: noradrenalin and NRD: serotonin) and local inhibitory interneurons (local: enkephalin). PAG: periaqueductal grey; NRD: nucleus raphe dorsalis; NRGc: nucleus reticularis gigantocellularis; NRM: nucleus raphe magnus; STT: spinothalamic tract; SRTT: spinoreticulothalamic tract; LC: locus ceruleus.

Local nerve injuries

Following nerve transection, regenerative nerve sprouts grow a neuroma at the proximal nerve stump. Abnormal excitability and spontaneous discharges develop in a few days at neuroma sprouts.[2] These tonic discharges stimulate the connecting regenera-

tive C-fibers. After a period of longitudinal growth of regenerating nerve fibers, characteristics of the erratic impulse generator will develop.[2] These abnormal discharges transmit impulse back to the central nervous system and presumably induce dysesthesia, such as tingling, itching or electrifying sensation, in patients with neuropathic problems.

Sodium channels in injured axons

At sites proximal to the nerve transection, up-regulation and increased density of membrane sodium channels have been detected in injured dorsal root ganglian (DRG) axons.[3] Six subtypes of sodium channels have been identified in DRG neurons.[4] Some kinds of these sodium channels are sensory neuron specific and have not been found in other parts of the nervous system.[4] In these sensory neuron specific sodium channels, subtypes SNS/PN3 and SNS/NaN accrued at sites of nerve injury in neuropathic humans and animals.[4] The expression of subtype A-III sodium channels was also elevated after axotomy.[4] These channels, undetectable in normal DRG neurons, showed faster recovery following inactivation.[4] Thus, the repetitive firing of injured neurons was facilitated at low threshold, which has been considered as a mechanism of ectopic impulse generation. Blockage of these sodium channel subtypes may be an important issue in treating patients with neuropathic pain.

Calcium channels in injured nerve endings

It is known that entry of calcium ions into the nerve endings through calcium channels regulates growth-related proteins. Recently N and L-type calcium channels have been found to contribute to calcitonin gene-related peptide (CGRP) release from injured nerve endings in vitro.[5] Blockade of N-, T- and P-type calcium channels has been found to block experimental neuropathic pain.[6,7] These results suggest that calcium channels may play a role in the expression of the neuropathic state. Selective calcium channel blockers, such as gabapentin, oxcabazepine, lamotrigine and ethosuximide, may have significant potential in the treatment of neuropathic pain.

Sympathetic-related pain

The neuroma has both afferent C-fibers and efferent post-ganglionic sympathetic C-fibers which release noradrenaline and adrenaline. In situations of increased sympathetic activity, a raised sensitivity of the regenerating sprout towards the detection of nociceptive substances, such as bradykinin, serotonin, histamine, and capsaicin, is induced.[8] This finding shows that nociceptive receptors up-regulate at regenerating nerve terminals close to adrenoceptors (Fig. 3). This response to sympathetic neurotransmitters may contribute to causalgia. However, the influence of sympathetic nervous injury is far beyond the peripheral responsiveness of sympathetico-afferent interactions. The excitatory effects on nociceptive receptors of sympathetic nervous system are also caused by hypophysical-adrenocortical system, neuro-immune interactions, neuropeptides, chronic inflammation, psychosomatically mediated mental and emotional reactions.[9]

Cytokines in neuropathic pain

In spite of the complexity of the cytokine network, specific actions between special cytokines and endogenous control systems about neuropathic pain have been identified. Recently, researchers have focused on the roles of interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α).[10,11] Inflammatory hyperalgesia was prevented by experimental administration of endogenous IL-1 receptor antagonist.[12] Neutralizing antibodies to IL-1 receptors reduced pain-associated behavior in mice with experimental neuropathy.[13] Combined epineurial therapy with neutralizing antibodies to TNF- α and IL-1 receptors had additive effects in reducing neuropathic pain in mice.[10] Nerve biopsies from patients with neuropathies revealed higher TNF- α immunoreactivi-

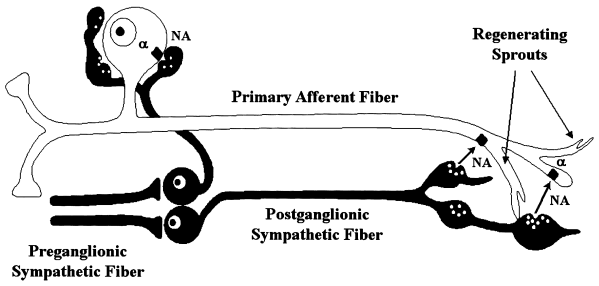

Fig. 3 Sympathetic-sensory coupling. Noradrenaline (NA) released from nearby sympathetic efferent fibers binds to α-adrenoreceptors on the injured afferent evoking depolarization and ectopic firing.

ties in myelinating Schwann cells when the neuropathy was painful, and serum soluble TNF-α-receptor 1 levels were higher in patients with central-mediated allodynia.[14] The central and peripheral changes of underlying cytokines may play important roles in the mechanism of neuropathic pain.

Central sensitization and plasticity

Healthy nerve terminals uptake signal substances, including Nerve Growth Factor (NGF) and other growth factors from their target cells, are transmitted by axonal transport to the DRG neurons.[15,16] After nerve transection, sprouts can no longer take up these growth factors to the DRG neurons.[17] The gene transcription and protein synthesis are altered. At the level of transcription control in the DRG neurons, the *c-jun* gene can be inducted 1 day after axotomy.[18] It is well known that c-Jun expression in the DRG neurons after nerve transection is associated with changes in neuropeptide levels: substance P and CGRP decrease; galanin and NO synthase (NOS) increase dramatically during the weeks and months following axotomy.[19] NOS and galanin are colocalized with c-Jun in the same DRG neurons.[20] This finding strongly suggests that c-Jun is also a transcription controlling protein for the NOS and galanin genes. The increased release and production of NOS at the intraspinal presynaptic terminal may facilitate afferent synaptic transmission to the dorsal horn neurons. Therefore, the pathophysiological processes following nerve injury are carried from the peripheral to the central nervous system.[21] This phenomenon may contribute to spinal neuronal sensitization and hyperalgesia.

Repetitive noxious stimulation leads to the increased activities of aspartate and glutamate at N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5- methylisoxazole-4-propionicacid (AMPA)/kainite receptors, which produce an influx of extracellular Ca^{2+} and activation of protein kinase C (PKC) in dorsal horn neurons.[22] The increased intracellular Ca^{2+} induces the expression of *c-fos* (Fig. 4).[21] Fos protein is believed to be involved in the transcriptional control of genes that encode a variety of neuropeptides, including enkephalin and dynorphin (Fig. 5).[23] Enkephalin typically produces antinociceptive effects.[24] Dynorphin has direct excitatory effects on spinal projection neurons and may also produce inhibition via a negative feedback

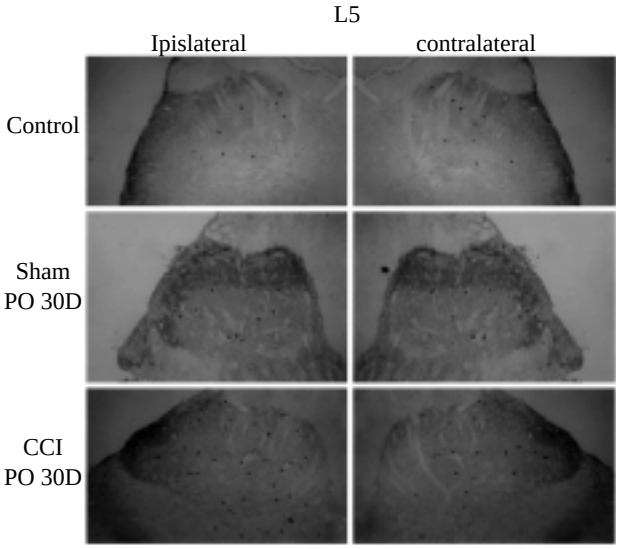

Fig. 4 Photomicrographs display the temporal and spatial changes in the number of Fos-like immunoreactive (Fos-LI) neurons in the location of the spinal dorsal horn at L5 segments in normal control, sham-operated and chronic constriction injury (CCI) rats. Each dot represents one Fos-LI neuron. Note that CCI rats increased Fos-LI neurons ipsilaterally and contralaterally to the sciatic nerve injury occurs at 30d in contrast to the control and sham-operated rats. The Fos-LI neurons increase significantly more ipsilaterally than contralaterally in laminae I-IV at the L1 and L5 segments. The findings suggest that a strong pain signal will induce central sensitization via a wide dynamic change in the spinal dorsal horn, not only in the ipsilateral side but also in the contralateral side.

mechanism on dynorphin-containing neurons.[25] The net effect of these changes may have complex modulations in the development of central plasticity.[26]

Electrophysiologically, there is plenty evidence for sensitization of dorsal horn cells and enhancement of spinal reflexes by a repetitive or prolonged noxious stimulation. This enhanced synaptic transmission is manifested by long-term potentiation (LTP) following a short train of stimulation at C-fiber.[27] The transition of LTP between spinal interneurons involves glutamate and neurokinin 1 receptors. Thus, blocking the LTP spreading with the NMDA and/or neurokinin 1 receptor antagonists which may be a potential treatment of neuropathic pain.[27]

Central inhibitory pathway deficiency

Recently, researchers have suggested that part of

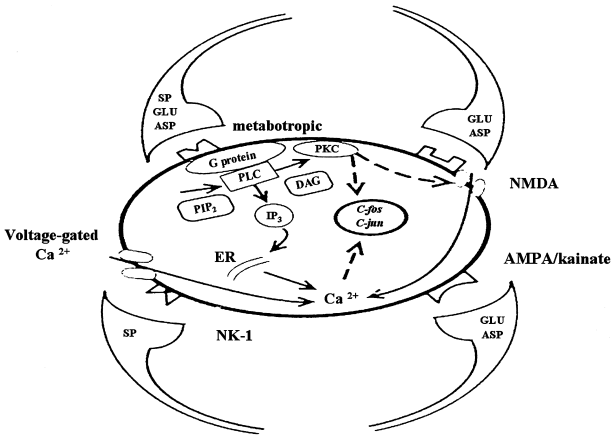

Fig. 5 Noxious stimulation leads to central sensitization of dorsal horn neurons. Repetitive activation of AMPA/kainate and NMDA receptors by aspartate, glutamate and substance P produces a membrane depolarization which enhances influx of extracellular Ca^{2+}. Increased intracellular Ca2+ concentration leads to the expression of *c-fos*, which participates in the regulation of mRNA encoding dynorphin and enkephalin in spinal cord and can influence long-term changes in cellular function. PKC: protein kinase C; PLC: phospholipase C; DAG: diacylglycerol; PIP_2: phosphatidylinositol 4,5-biphosphate; IP3: inositol trisphosphate; ER: endoplasmic retineculum; SP: substance P; GLU: glutamate; ASP: aspartate; NMDA: N-methyl-D-aspartate receptor; AMPA: alpha-amino-3-hydroxy-5- methylisoxazole-4-propionicacid receptor.

neuropathic pain is due to the inefficiency of endogenous inhibitory systems. The spinal pain transmission system is under continuous inhibitory control, which originates from brainstem centers located at the periaqueductal gray and the locus ceruleus (Fig. 2).[18] Although descending inhibitory controls are still functioning, the inhibitory effects might become weaker in patient with neuropathic pain.[18] Partial nerve injury also induces GABAergic inhibitory interneuron apoptosis and reduces inhibition in the superficial dorsal horn.[28] This transynaptic neural degeneration also contributes to abnormal pain sensitivity.

In addition, the endogenous opioid system showed a decrease in efficacy in deafferented animals.[29] The induction of *c-jun* of axotomized neurons has been closely related with inhibitory transsynaptic neuron death or apoptosis by NGF starvation.[30] Thus, a lessened efficacy of the spinal opioid system, which corroborates with attenuation of opiods or other analgesics, has been shown in response to peripheral nerve lesions.

Diagnosis

The International Association for the Study of Pain (IASP) defines various terms of pains, including neuropathic pain (Table 1). Under the application of the IASP definition, the diagnostic work-up in patients with suggested neuropathic pain must include detailed medical history, review of systems, and detailed physical and neurological examination results. The medical history provides information into the onset, distribution, quality of the pain (e.g., burning, aching, electric shooting) and the possible association of the pain with trauma or surgical procedures. Because the diagnosis of neuropathic pain depends heavily on the presentation of sensory abnormalities in the area innervated by the suggested damaged nerve, careful sensory examinations using special instruments (e.g., warm and cold metal rollers for temperature sensation, a camel hair brush for touch sensation, and a pin for pain sensation) should be performed.

Comorbid Conditions

Behavioral and psychiatric complications are very common in patients with neuropathic pain and may lead to a delayed diagnosis or mistreatment. Depression, anxiety, and sleep disorders are more common among patients with chronic neuropathic pain, and may be accompanied by substance abuse, abnormal illness behavior or adaptation to chronic illness. Recognition and treatment of these psychiatric comorbidities can lead to improvements in pain relief and quality of life.[31]

Treatment

Non-Invasive Therapies

Pharmacotherapy remains the basis of neuropathic pain management. In general, neuropathic pain may be partially or completely unresponsive to primary analgesic treatment (Fig. 6). Adjuvant analgesics, such as antidepressants and antiepileptic drugs (AEDs), tend to be the mainstay of medical therapies for treating patients with neuropathic pain. Antidepressants have been proved to alleviate pain in some patients with neuropathic pain, although the pain relief may be incomplete.[32] The most effective

Table 1. Definitions Of Various Pains From The Published International Association For The Study Of Pain (IASP) List

Pain term	Definition
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage
Allodynia	Pain due to a stimulus which does not normally provoke pain
Causalgia	A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Paresthesia	An abnormal sensation, whether spontaneous or evoked
Hyperalgesia	An increased response to a stimulus which is normally painful
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system

antidepressants in treating neuropathic pain are tricyclic antidepressants. However, tricyclic antidepressants are often associated with adverse effects, which limit the tolerance of the patients to the treatments.[33] The newer antidepressants, such as the serotonin selective reuptake inhibitors, have fewer adverse effects but seem to be less effective than the tricyclic antidepressants.[1] AEDs have been used for the treatment of trigeminal neuralgia for a long time. Some AEDs, such as phenytoin, carbamazepine and lamotrigine, have the ability to reduce neuronal membrane hyperexcitability by inhibiting sodium channels. Resembling the antidepressants, the main problem with using AEDs is their tolerability. Common adverse reactions, including dizziness, ataxia and sedation, tend to reduce the effects of the old generation of AEDs. However, recent clinical trials have not shown evidence that the new generation of AEDs are more effective in controlling neuropathic pain than old generation of AEDs.[34] The selection of a particular drug relies on the experience of the clinicians and reactions of the patients. Multi-drug therapy may be necessary to obtain good pain relief. The drug choices of combined treatment are empirical and the principle is to choose drugs based on their added therapeutic effects.

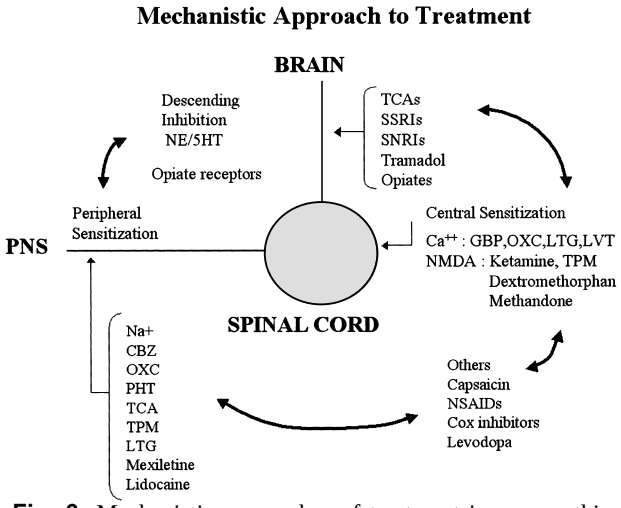

Fig. 6 Mechanistic approaches of treatment in neuropathic pain. CBZ: carbamazepine; Cox: cyclooxygenase; 5HT: 5-hydroxytryptamine; GBP: gabapentin; LTG: lamotrigine; LVT: levitiracetam; NE: norepinephrin; NMDA: N-methyl-D-aspartate; NSAID: non-steroid anti-inflammatory drug; OXC: oxcabazepine; PHT: phenytoin; PNS: peripheral nervous system; SNRI: selective serotonin norepinephrin reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TPM: topiramate.

Additionally, the present study revealed that the 5% lidocaine patch, as a add-on therapy, was clearly effective in reducing allodynia and pain in patients with postherpetic neuralgia.[35] The intrathecal administration of methylprednisolone has also been proved to be an effective treatment for postherpetic neuralgia.[36] NMDA receptor antagonists, such as Ketamine, may have a particular role in patients that are poorly responsive to traditional analgesics.[37] Topical capsaicin cream decreases diabetic and postsurgical neuropathic pain.[38,39] In mice, the administration of anti-NGF antibodies produced a profound reduction in bone cancer pain-evoked behaviors in the mouse model.[40] In general, pharmacological treatments may act preferentially or selectively on some components of the studied etiologic diagnosis, rather than producing global and uniform analgesic effects. To reach satisfying pharmacological selections or combinations, etiology and mechanism-

based evaluation of patients with neuropathic pain should be conducted.

Invasive Therapies

In addition to pharmocotherapeutics, transcutaneous electrical nerve stimulation (TENS) is also a useful adjunctive treatment. The mechanism of TENS in pain-relief is based on the gate control theory. While stimulating large afferent fibers, the input of small pain afferent fibers will be inhibited on the dorsal horn neurons before projecting to the spinal cord.[41] TENS is almost free from adverse effects. As with TENS, spinal cord dorsal column stimulation attempts to inhibit nociceptive transmission by stimulating large afferent fibers. It works especially well on patients with ischemic pain.[42]

Clinical evidence demonstrated microvascular that decompression provided good long-standing outcomes for trigeminal neuralgia.[43] Temporary nerve blocks carried out by local anesthetic injection are controversial in controlling neuropathic pain.[44] Other applications of neurosurgical management include spinothalamic tractotomies, thalamotomies, cingulotomy, frontal lobotomy, dorsal rhizotomy, dorsal root entry zone lesioning, as well as neural ablation. None of these surgical techniques has been found to be consistently successful in treating patients with neuropathic pain. In general, these treatments are not recommended because damage to the nervous system may intensify the neuropathic pain.[45]

Conclusions

Despite the significant advancements in our understanding of neuropathic pain during recent decades, clinical management of patients with this disease remains challenging. The satisfaction of the patients in the treatment of neuropathic pain is still disappointing. In order to provide better pain control for patients, clinicians should focus on the mechanisms underlying the symptoms of neuropathic pain. Treatment strategies should address the multifactorial nature of neuropathic pain, including the multiple levels of the mechanisms and the presence of comorbid conditions. This mechanism-based approach to the treatment of neuropathic pain is beneficial for improving the quality of life of patients with neuropathic pain. In the future, it is hoped that a combination of new pharmacotherapeutic developments, careful clinical trials, and an increased understanding of the contribution and mechanisms of neuroplasticity will lead to improved of clinical treatment and prevention of neuropathic pain.

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病態性神經疼痛：機轉與治療

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病態性神經疼痛是由於中樞或周邊神經系統的損害所造成，發生時並沒有直接的疼痛性刺激。常見造成病態性神經疼痛的原因包括帶狀皰疹後神經痛、三叉神經痛、糖尿病神經病變、脊髓損傷、癌症、中風與退化性神經病變等。近期研究指出周邊神經受損後，特別的細胞與分生變化會影響細胞膜的興奮性，並且誘導一連串的基因調控，而增加對刺激的反應。此外，神經瘤的異位性脈衝、鈉離子和鈣離子通道的變化、交感神經的激發、與中樞神經抑制路徑的缺乏皆會參與病態性神經疼痛的機轉。

目前病態性神經疼痛的治療仍深具挑戰，三環抗憂鬱劑與抗癲癇藥物仍是治療病態性神經疼痛的基礎，然而，治療的滿意度依舊令人失望。既然周邊神經的刺激會形成中樞神經系統的敏感性，治療病態性神經疼痛除了是針對周邊神經的損傷，還需顧及中樞神經的變化。爲了能夠對病變性神經疼痛有更好的控制，必須針對致病機轉選擇適當的治療，未來期望藉新的藥物治療、臨床試驗與對致病機轉的進一步了解，能夠對於病變性神經疼痛有更佳的預防及治療。(長庚醫誌 2005;28:597-605)

關鍵字：疼痛，病態性神經疼痛，中樞神經系統可塑性。

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