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Modulation of the glutamatergic system in neuropathic pain: The role of pregabalin

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Abstract

Neuropathic pain is a chronic pain condition caused by damage or disease of the somatosensory nervous system and is often resistant to conventional analgesic therapy. This condition involves complex pathophysiological mechanisms, including peripheral and central sensitization, neuroinflammation, and changes in synaptic plasticity. Dysfunction of the glutamatergic system, characterized by increased glutamate release and hyperactivation of glutamate receptors, plays a crucial role in maintaining neuronal excitability and persistent pain transmission. This review aims to examine the role of the glutamatergic system in the pathophysiology of neuropathic pain and to evaluate the effectiveness of pregabalin as an indirect modulator of the glutamatergic system in the management of neuropathic pain. This research is a narrative review based on a review of relevant scientific literature from international publications, including experimental studies, clinical trials, and review articles discussing neuropathic pain, modulation of the glutamatergic system, and the use of pregabalin. The review results indicate that glutamate accumulation and dysregulation of glutamate transporters lead to excessive activation of ionotropic and metabotropic glutamate receptors, which contributes to central sensitization. Pregabalin works by binding to the α2δ subunit of presynaptic calcium channels, thereby decreasing the release of glutamate and other excitatory neurotransmitters, as well as improving glutamate synaptic regulation, which impacts reducing pain intensity and improving patient quality of life. The glutamatergic system is an important therapeutic target in neuropathic pain. Pregabalin is effective as a first-line therapy through indirect modulation of the glutamatergic system, although its use still requires monitoring for side effects and individual patient response.

Keywords: Neuropathic pain, Glutamate, Glutamatergic system, Pregabalin, Central sensitization

Introduction

Neuropathic pain is a type of long-lasting pain caused by injury or illness of the somatosensory nervous system and is frequently associated with unusual sensory experiences like burning feelings, sharp pain, or allodynia. Unlike nociceptive pain, which is adaptive, neuropathic pain is maladaptive, persists long-term, significantly impacts patient quality of life, and is often difficult to manage with conventional analgesic therapy.[1,2] Complex alterations occur in both the central and peripheral nervous systems with this condition, including central sensitization and maladaptive neuroplasticity that persistently reinforce pain transmission.[3]

Dysfunction of the glutamatergic system plays a critical role in the development of neuropathic pain by disrupting the signaling of the main excitatory neurotransmitter, glutamate, in the central nervous system. This neurotransmitter is essential for transmitting pain signals and enhancing central sensitization. The build-up of glutamate in the back part of the spinal cord, combined with the stimulation of ionotropic and metabotropic receptors, heightens the responsiveness of neurons and enhances the sensation of pain. Furthermore, the activation of microglia and astrocytes worsens this condition through the release of proinflammatory mediators and dysregulation of glutamate uptake, thus creating a pathological cycle that maintains chronic pain.[3,4]

Neuropathic pain is modulated through intricate interactions between the nervous and immune systems. Proinflammatory cytokines, including interleukin-1β, tumor necrosis factor-α, and interleukin-6, contribute to increased nociceptor excitability and potentiation of excitatory neuronal activity by influencing ion channel function and glutamate-mediated signaling. This neuroinflammatory process not only reinforces pain at the peripheral level but also plays a crucial role in changes in synaptic plasticity in the central nervous system.[4]

Therapeutic modulation of the glutamatergic system plays a central role in the treatment of neuropathic pain. Pregabalin, a gabapentinoid compound, does

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not act via GABAergic receptors but instead targets the α2δ subunit of presynaptic calcium channels, resulting in decreased glutamate and other excitatory neurotransmitter release. Through this mechanism, pregabalin acts as an indirect modulator of the glutamatergic system capable of suppressing central sensitization and reducing neuropathic pain intensity.[2,3] Although widely used as first-line therapy, a deep understanding of pregabalin's role in modulating the glutamatergic system is still needed to optimize therapeutic strategies for neuropathic pain.

Pathophysiology of neuropathic pain

Neuropathic pain represents a chronic pain condition arising from injury or dysfunction within the peripheral and/or central nervous system. The underlying pathophysiological mechanisms encompass complex processes involving peripheral nerve structures, the spinal dorsal horn, and central nervous system pathways.

Peripheral nerve damage is the initial mechanism that triggers neuropathic pain. Following nerve injury, Wallerian degeneration occurs, which is the destruction of the distal axon segment after injury. This process is often followed by abnormal nerve fiber regeneration, which triggers ectopic nerve activity and changes in neuronal excitability. This can lead to hyperalgesia and allodynia.[5,6]

Neurodegenerative processes involving segmental and distal demyelination cause loss of myelin integrity and damage to axon structure. The activation of microglia and astrocytes, along with the release of inflammatory cytokines and chemokines, leads to neuroinflammation that enhances neuronal excitability. Furthermore, these changes affect the function of NMDA and AMPA receptors, inducing changes in intracellular signaling pathways that increase neuronal excitability and chronic pain.[6,7]

Additionally, the immune system also plays a role in the pathophysiology of neuropathic pain. Macrophage activation triggers the release of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6.[7] This immune response results in glial cell activation, which induces neuroinflammation and increases neuronal excitability. Furthermore, changes in blood-brain barrier permeability can worsen chronic pain symptoms through interaction with inflammatory mediators.[6]

Peripheral sensitization occurs due to abnormal activity in damaged nerve fibers. This process involves the release of inflammatory mediators such as cytokines and chemokines, which activate pain receptors, including TRPV1 channels. Activation of TRPV1 at normal body temperature due to decreased excitability threshold causes a burning sensation that often worsens with heat stimuli but improves with cold stimuli.[5]

TRPV1 is located at peripheral nociceptor terminals and physiologically activates at noxious heat stimuli around 41ºC. When nerve damage occurs, TRPV1 decreases in number in the damaged nerve but increases in number in the C fibers of surrounding nerves. This condition causes the TRPV1 threshold to drop below 38ºC, leading to spontaneous nerve activation at normal body temperature. This sensation usually worsens with heat stimuli and improves with cold stimuli, without sensory deficit because the nerve fibers do not experience physical impairment.[5]

Central sensitization refers to a state of heightened neuronal excitability in the central nervous system induced by persistent input from damaged peripheral nerve fibers. This phenomenon is associated with neuroplastic changes in the spinal cord and brain, including cortical reorganization and modifications in neuronal excitability.[8] Central neuropathic pain typically results from lesions of the central nervous system, including stroke and spinal cord injury.[5]

In neuropathic pain, a modulation process occurs that affects the intensity of pain signals received by the brain. Pain processing occurs through the coordinated activity of ascending and descending pathways. Ascending pathways transmit pain signals from the periphery to higher brain centers via the spinothalamic tract, whereas descending pathways function to regulate and suppress nociceptive transmission. These descending systems involve the periaqueductal gray, rostral ventromedial medulla, and prefrontal cortex, with serotonin, norepinephrine, and endogenous opioids serving as key inhibitory mediators.9

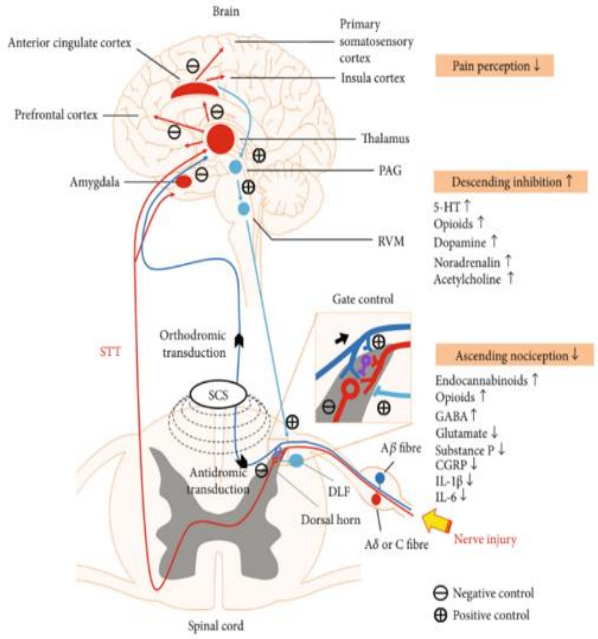

Fig 1. Mechanisms of nociceptive modulation in the spinal cord and brain. SCS: spinal cord stimulation; STT: spinothalamic tract; PAG: periaqueductal gray; RVM: ventrolateral medulla; DLF: dorsolateral funiculus.[9]

Clinical manifestations of neuropathic pain

Manifestations of neuropathic pain often show sensory symptoms broader than the injury location. Neuropathic pain occurs due to damage or disease of the somatosensory system that triggers a series of pathophysiological processes, such as sensitization, disinhibition, and interaction between the immune and neuroendocrine systems. This process leads to increased neuronal excitability that manifests as two types of pain, namely spontaneous pain and evoked pain, which can appear in sensations such as burning, stabbing, or electric shock.[10,28]

This pain is also often accompanied by negative symptoms such as numbness, weakness, and loss of reflexes.[11,12] Pain sensations can persist after the stimulus is stopped (aftersensations) or occur in areas different from the injury location (referred pain). Hyperpathia, an abnormal pain reaction to repeated stimuli, is also often found in neuropathic pain patients.[8,13]

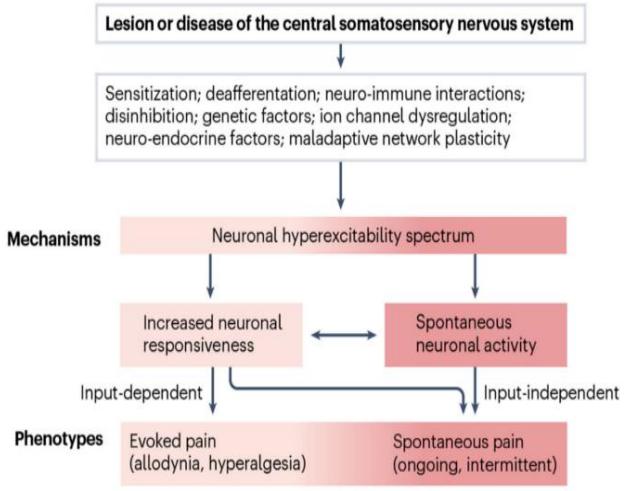

Fig 2 Mechanisms and clinical phenotypes of neuropathic pain[10]

Spontaneous pain

Spontaneous pain is one of the main symptoms in neuropathic pain that occurs without external stimulation. Patients often describe this pain as a burning, stabbing, or electric shock-like sensation, which can be continuous or appear intermittently. Additionally, patients may experience dysesthesia (painful abnormal sensation) or paresthesia (non-painful abnormal sensation).[8] According to Rosner (2023), patients often use metaphorical terms to describe their pain, such as "like having tinfoil under the skin," reflecting the paradoxical sensation of heat and cold felt simultaneously.[10]

Evoked pain

In addition to spontaneous symptoms, neuropathic pain can also be triggered by specific stimuli that normally do not cause pain in healthy individuals[8]. Evoked pain includes allodynia and hyperalgesia. Allodynia refers to the feeling of pain from insignificant stimuli that are usually not painful, like a light touch, whereas hyperalgesia is a heightened reaction to stimuli that typically only elicit minimal pain. Rosner (2023) adds that both types of pain often occur due to changes in central nervous system sensitivity and fall within the spectrum of somatosensory neuronal hyperactivity. This sensitivity occurs due to damage or disease of the nervous system, which disrupts normal ion channel function, genetic factors, and neuro-immune

interactions.[10,27]

Aftersensations

Aftersensations are pain sensations that persist after the stimulus is stopped. This occurs due to the process of central sensitization, which involves decreased inhibition and increased excitation in pain pathways in the brain and spinal cord.[8] Rosner (2023) highlights that this pain is often felt in body areas broader than the main pain area, due to abnormal dynamics of somatosensory neuronal responses.[10]

Hyperpathia

Hyperpathia is an intense, explosive pain reaction to stimuli above the pain threshold, especially repeated stimuli. This symptom involves complex mechanisms, including changes in neural tissue plasticity and deafferentation due to central nerve damage. According to Rosner (2023), this phenomenon reflects a combination of hypersensitivity in somatosensory neurons and ongoing maladaptation of tissue.[10]

Referred pain

The sensation of referred pain occurs when the body experiences discomfort in a region that is distinct from where the injury or source of pain is located. A classic example is pain felt in the lower limb area in patients with spinal cord injury, or bilateral facial pain in cases of neuralgia caused by brainstem lesions.[10]

Establishing the diagnosis of neuropathic pain

The diagnosis of neuropathic pain, both peripheral and central, is made based on three levels of confidence established hierarchically: possible, probable, and definite.[10]

It is said to be possible based on the patient's medical history showing a relevant lesion or disease in the central or peripheral nervous system, and pain that has an anatomical distribution corresponding to the suspected neuroanatomical lesion location. It is said to be probable if physical examination reveals somatosensory abnormalities, such as loss of sensation or hypersensitivity to mechanical or thermal stimuli.

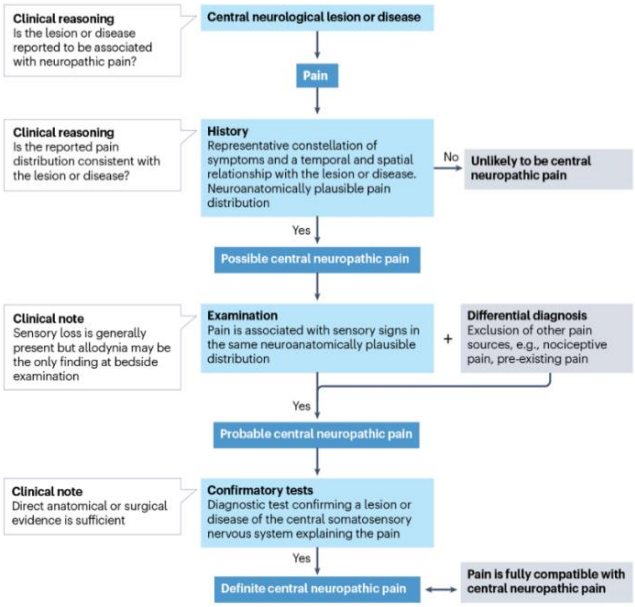

Fig 3. Diagnosis of neuropathic pain.[10]

This examination aims to confirm the relationship between the lesion location and the pain distribution. Meanwhile, a definite diagnosis is achieved with confirmation through additional tests, such as neuroanatomical imaging (MRI, CT scan) or neurophysiological evaluation, which show the presence of a lesion or disease that can explain the pain distribution.[10]

In addition to the clinical approach, diagnostic tools such as neurological imaging and neurophysiological studies are important in establishing the diagnosis of neuropathic pain.

Neurological Imaging: MRI and CT scan are primary tools for detecting structural lesions in the central nervous system, such as stroke, Spinal Cord Injury (SCI), or demyelinating lesions. These imaging studies are useful for determining the lesion location and estimating its pathological mechanism.[10]

Neurophysiology: Electrophysiological studies, such as measuring evoked pain-related potential responses and cortical electrical stimulation, are used to evaluate the function of the nociceptive sensory system and support clinical diagnosis.[10]

Management of neuropathic pain

The management approach for neuropathic pain involves an integrated multidisciplinary approach, covering pharmacological, non-pharmacological, and surgical intervention modalities.[14]

Pharmacological therapy

In the pharmacological context, first-line therapy includes the use of antidepressants and anticonvulsants.

Antidepressants: Tricyclic antidepressants, including amitriptyline, and SNRIs such as duloxetine and venlafaxine modulate neuropathic pain primarily by enhancing the activity of descending inhibitory pain pathways within the central nervous system.[15]

Anticonvulsants: Gabapentin and pregabalin are effective in alleviating neuropathic pain through their interaction with the α2δ subunit of voltage-gated calcium channels in the dorsal root ganglion, leading to reduced excitatory neurotransmitter release and suppression of nociceptive signaling.[15]

Table 1. First-line pharmacological therapy for neuropathic pain[14]

	Drug	Dosage	Side Effects
First-line therapy			
Gabapentinoids	Gabapentin	150-600 mg/day	Fatigue, dizziness, peripheral edema, blurred vision
	Pregabalin	300-3600 mg/day	Fatigue, dizziness, peripheral edema, weight gain
Tricyclic antidepressants (TCAs)	Amitriptyline	10-150 mg/day	Anticholinergic effects, QT prolongation (arrhythmia), suicide risk, urinary retention
Serotonin-norepinephrine reuptake inhibitors (SNRI)	Duloxetine	20-120 mg/day	Nausea, fatigue, constipation, ataxia, dry mouth
	Venlafaxine	150-225 mg/day	Nausea, dizziness, fatigue, hyperhidrosis, hypertension

Topical Anesthetics: Lidocaine patches are used for local neuropathic pain such as postherpetic neuralgia. Capsaicin patches are also an option for chronic peripheral pain cases.[2] If first-line therapy is ineffective, the next step includes low-dose opioids such as tramadol and tapentadol. However, their use is limited due to the risk of tolerance and dependence.[2]

Table 2. Advanced pharmacological therapy for neuropathic pain[14]

	Drug	Dosage	Side Effects
Second-line therapy			
Opioids	Tramadol	25-400 mg/day	Nausea/vomiting, constipation, fatigue, seizures, ataxia
	Tapentadol	50-600 mg/day	Nausea/vomiting, constipation, fatigue, seizures, ataxia
Topical treatments	Lidocaine	Patch or gel 5%	Local erythema, itching and rash
	Capsaicin	Patch 8%	Pain, erythema, itching; rare cases of high blood pressure
Thire-line therapy			
Potent opioids	Morphine	10-120 mg/day	Nausea, vomiting, constipation, dizziness and fatigue
	Oxycodone	10-120 mg/day	Nausea/vomiting, constipation, fatigue, respiratory control
Neurotoxins	Botulinum toxin	25-300 U BTX-A 0.9% saline	Pain at injection site

Non-Pharmacological therapy

Non-pharmacological modalities are often combined with pharmacological therapy to improve treatment outcomes. Non-pharmacological modalities involve Cognitive Behavioral Therapy (CBT) and other psychological approaches to improve long-term patient function and quality of life.[2,15]

Physical therapy: Directed physical activities such as aerobic exercise and stretching can help improve physical condition and reduce pain. Exercise can also reduce inflammation and increase natural endorphin production.[2]

Psychological therapy: Cognitive Behavioral Therapy (CBT) is an effective approach in helping patients cope with pain through changing thought and behavior patterns. This approach can reduce anxiety and depression that often accompany neuropathic pain.[15]

Integrative approaches: Meditation, yoga, acupuncture, and music therapy have shown benefits in reducing pain intensity in some patients.[2]

Glutamate

Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system, involved in various biological functions such as pain signal transmission, synaptic plasticity, and neuronal development. However, increased extracellular glutamate levels can cause excitotoxic damage to neurons and glial cells, closely related to various pathological conditions, including neuropathic pain.[16–18]

There are two main groups of glutamate receptors involved in pain modulation: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs).[16,17] Ionotropic receptors such as NMDA (N-methyl-D-aspartate) play an important role in pain transmission by increasing synaptic activity. Additionally, metabotropic glutamate receptors (mGluRs) are involved in the regulation of slower and more complex pain responses through signal modulation mechanisms.[19] Glutamate and gamma-aminobutyric acid (GABA) are considered primary determinants in pain regulation through central mechanisms.[20]

Ionotropic Glutamate Receptors (iGluRs)

Ionotropic glutamate receptors, such as N-Methyl-D-Aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate are commonly found at synapses. These receptors are Fast-Acting receptors for inducing excitatory potentiation in target neurons. Activation of these receptors increases the flow of Na^+ and Ca^{2+} ions.[21]

Activation of NMDA receptors involves high Ca^{2+} ion flow. This increased Ca^{2+} influx is involved in synaptic plasticity associated with chronic pain or neuropathic pain. These receptors also play a central role in the development of central hyperalgesia. Unlike NMDA receptor activation, AMPA receptor activation is faster and involved in acute pain transmission. AMPA receptors are responsible for the initial excitatory response that transmits pain signals to the brain through sensory neurons.[21]

Metabotropic Glutamate Receptors (mGluRs)

Unlike iGluRs, metabotropic glutamate receptors (mGluRs) work more slowly through second messengers such as cyclic AMP and protein kinase C. Metabotropic glutamate receptors (mGluRs) belong to class C G-protein-coupled receptors (GPCRs), consisting of eight different subtypes (mGluR1-8). Based on their structure and function, these receptors are divided into three main groups.

Group I (mGluR1, mGluR5) plays a role in increasing intracellular calcium through the phospholipase C pathway. This group generally increases neuronal excitability and contributes to chronic pain by increasing pain sensitivity through strengthening synapses in dorsal horn neurons.[21,22]

Unlike Group I, Group II (mGluR2, mGluR3) and Group III (mGluR4, mGluR6, mGluR7, mGluR8) are more associated with reducing cyclic adenosine monophosphate (cAMP) and decreasing calcium channel activity. Both groups play an inhibitory modulation role, decreasing excessive excitation in neurons and glutamate release, thus potentially becoming therapeutic targets for inflammatory and neuropathic pain.[21,22]

The role of glutamate in neuropathic pain

Neuropathic pain is a chronic disorder caused by dysfunction or injury to the somatosensory system, in which glutamate serves as a key mediator of synaptic hyperactivity in the spinal cord and brain. Physiologically, extracellular glutamate levels are controlled through reuptake by glial cells via glutamate transporters such as EAAT2, thereby maintaining synaptic balance. Dysfunction of this mechanism can lead to glutamate accumulation, triggering hyperactivation of glutamate receptors, and affecting neuropathic pain pathways.[18]

Increased glutamate release and decreased reuptake capacity by glutamate transporters cause glutamate accumulation at the synapse, which strengthens pain sensitivity.[19] Glutamate receptors, particularly NMDA and metabotropic glutamate receptors, contribute to central sensitization by increasing the responsiveness of spinal cord neurons to nociceptive input. Sustained activation of these receptors triggers the release of other pain mediators, such as substance P and calcitonin gene-related peptide, leading to the amplification of neuropathic pain.[18]

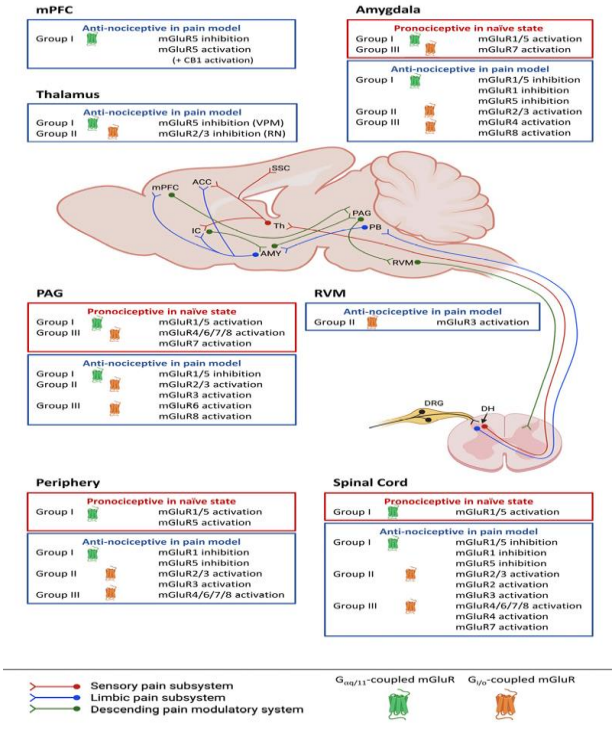

Fig 4. Role of metabotropic receptors in pain signaling processes.[19]

In the spinal cord, activation of mGluR1 and mGluR5 receptors (Group I) increases pain sensitivity. This occurs under normal conditions where these receptors mediate excitation of neurons involved in pain signal transmission. Conversely, activation of mGluR2, mGluR3, mGluR4, mGluR6, mGluR7, and mGluR8 (Groups II and III) has anti-nociceptive effects in pain models. These receptors work by decreasing glutamate release and inhibiting pain transmission to the next neuron.[19]

In the thalamus, activation of mGluR1 and mGluR5 receptors increases pain perception, while inhibition of these receptors has anti-nociceptive effects in pain models. Activation of mGluR2, mGluR3 and mGluR4 in this region also suppresses pain transmission. Pathways connected to the medial prefrontal cortex (mPFC) and amygdala contribute to the modulation of emotional and cognitive aspects of neuropathic pain.[19]

In the amygdala, activation of mGluR5 strengthens emotional pain responses (pronociceptive), while its inhibition can reduce pain intensity. In the PAG (Periaqueductal Gray), Group I mGluRs play a role in reinforcing pain, while Group II (mGluR2,3) and Group III (mGluR4,7,8) help suppress pain transmission through modulation of descending pain inhibitory pathways.[19]

In the RVM (Rostral Ventromedial Medulla), activation of mGluR2,3 receptors in the RVM reduces pain transmission through inhibition of excitatory neurotransmitter release such as glutamate, supporting anti-nociceptive effects in neuropathic pain.[19]

The potential of glutamate as a therapeutic target

Currently, modulation of the glutamatergic system has been researched and considered to have potential for neuropathic pain therapy. Several mechanisms considered potential are through targeting NMDA receptor antagonists, modulation of mGluR receptors, and improvement of glutamate transporter function.[18]

NMDA receptor antagonists

NMDA receptors are an important target in neuropathic pain treatment due to their role in

reinforcing pain signals through central sensitization mechanisms. Drugs such as ketamine show analgesic effects by inhibiting NMDA receptors, although their use is limited due to side effects such as hallucinations and perceptual disturbances.[18]

Modulation of MGLUR receptors

- **Mglur5 antagonists:** Antagonists of these receptors, such as fenobam, have shown analgesic effects in animal neuropathic pain models. This effect occurs through inhibition of excessive neuronal excitation.[18]
- **MGluR2/3 agonists:** Activation of these receptors helps suppress glutamate release at synapses and reduces neuronal hyperactivity, supporting anti-nociceptive effects in neuropathic pain.[18]
- **MGluR4/7/8 agonists:** These Group III receptors have similar effects in reducing glutamate release and suppressing pain transmission, especially at the spinal and thalamic levels.[18]

Glutamate transporters

Improving the function of glutamate transporters such as EAAT2 is considered another strategy to lower extracellular glutamate levels and reduce excitotoxicity. Pharmacological efforts to increase EAAT2 expression are being developed as potential therapy.[18]

Pregabalin

Pregabalin, a member of the gabapentinoid class, acts by binding to the α2δ subunit of voltage-gated calcium channels within the central nervous system. This binding attenuates the release of excitatory neurotransmitters such as glutamate, noradrenaline, and substance P, contributing to the reduction of neuropathic pain and abnormal neuronal excitability. This effect contributes to pregabalin's analgesic properties, as well as helping to improve the sleep quality of patients with neuropathic disorders.[23,24]

Although its structure resembles gamma-aminobutyric acid (GABA), pregabalin does not interact directly with GABA receptors, but works through modulation of calcium channels to produce analgesic and anxiolytic effects. This mechanism makes pregabalin effective for reducing pain without significant depressive effects on the central nervous system.[23]

Furthermore, pregabalin affects glutamate transporters by increasing EAAT3 expression on the plasma membrane of neurons and glial cells, which functions to lower glutamate concentration in the synaptic cleft. This reduces NMDA receptor activity and neuronal excitability.[25] This effect not only provides analgesic benefits but also anticonvulsant and anxiolytic effects, although it does not directly affect GABA receptors. This anxiolytic effect helps reduce anxiety that often occurs in patients with chronic pain.

Pregabalin has rapid absorption ability, with peak plasma concentration reached about one hour after consumption on an empty stomach. Another advantage is that pregabalin does not bind to plasma proteins, allowing for broad and even distribution throughout the body.[24]

Effectiveness of pregabalin in the treatment of neuropathic pain

Pregabalin has shown evidence of being successful in decreasing nerve pain, including in cases of diabetic peripheral neuropathy and postherpetic neuralgia. In various clinical trials, pregabalin doses of 300-600 mg per day provided a significant reduction in pain levels felt by patients compared to placebo.[24,26] However, the effectiveness of pregabalin against some other types of pain, such as radicular pain, still requires further research. In several trials, pregabalin was reported to have higher side effects compared to the benefits obtained by patients.

On the other hand, pregabalin also improves patient sleep quality, which is often disturbed due to neuropathic pain.[26] Significant pain reduction with pregabalin also positively impacts related symptoms such as fatigue and depression.[26]

Dosage of pregabalin in the treatment of pain and various diseases

The effective dose of pregabalin for neuropathic pain ranges from 150-600 mg per day, given in two or

three divided doses. In clinical studies, higher doses provided greater benefits, but also increased the risk of side effects such as dizziness and sedation. Therefore, dose increases are done gradually to minimize these side effects.[23,26]

In patients with impaired kidney function, the dose must be adjusted according to the severity of kidney function decline to avoid drug accumulation that can cause toxicity.[23] The recommended pregabalin treatment doses for pain management in more detail are as follows:

Neuropathic pain

Pregabalin is typically prescribed in two to three divided doses per day, ranging from 150 to 600 mg, for managing neuropathic pain like diabetic neuropathy and postherpetic neuralgia. Studies show that this dose significantly reduces pain levels compared to placebo. Nevertheless, the effectiveness of pregabalin against conditions such as radicular pain still requires further research because the reported benefits are often limited.[23]

Refractory focal epilepsy

For refractory focal epilepsy, pregabalin is used as add-on therapy with a dose of 150-600 mg per day in two divided doses. In clinical trials, pregabalin was able to reduce seizure frequency by up to 50% compared to placebo. However, its use is limited to add-on therapy and is not recommended as monotherapy.[23]

Restless legs syndrome

Pregabalin is effective in managing restless legs syndrome, with doses ranging from 150-450 mg per day. Its effect in reducing symptoms can last up to one year of routine use.[23]

Chronic pruritus

Pregabalin is used to relieve chronic pruritus due to conditions such as uremic pruritus, especially in patients with chronic kidney disease. In this population, the recommended starting dose is 25 mg at night, which can be increased as needed. In patients undergoing dialysis, pregabalin is given three times a week after dialysis sessions to provide optimal effects.

Because its elimination is through the kidneys, pregabalin dose must be adjusted based on the patient's level of kidney function. In patients with creatinine clearance (eGFR) 30-60 mL/min, the recommended starting dose is 75 mg per day with a maximum of 300 mg per day, while for eGFR below 30 mL/min, the starting dose is 25-50 mg per day with a maximum of 150 mg per day. In hemodialysis patients, pregabalin is usually given after dialysis sessions at 25–50 mg per session.[23]

Fibromyalgia

Pregabalin is also used for fibromyalgia pain in some countries, although not approved in Australia. The common dose is 300-450 mg per day, which has been shown to reduce pain and improve the quality of life of certain patients. However, side effects such as dizziness and fatigue often limit its use.[23]

Other uses

In addition to the above, pregabalin is often used off-label for acute postoperative pain, although its analgesic effect is considered small and the risk of side effects such as dizziness, visual disturbances, and sedation increases at high doses.[23]

Adjusting pregabalin dosage is important to minimize the risk of side effects such as sedation, dizziness, or dependence. This is especially important in elderly patients or those with impaired kidney function, where drug accumulation can cause toxicity. Close monitoring is necessary to ensure the effectiveness and safety of using this drug.[23]

Weaknesses and side effects of pregabalin

The most common side effects of pregabalin are dizziness, sedation, visual disturbances, and gastrointestinal disturbances such as nausea and diarrhea. These side effects are usually mild to moderate and dose-dependent. At high doses, the risk of side effects increases significantly.[23,26] These side effects tend to increase in intensity with increasing drug dose. At the highest prescribed dose (600 mg/day), the incidence of dizziness can reach 70%, blurred vision 63%, and headache 31%.[25]

Central nervous system side effects can be related to pregabalin's main mechanism of action which inhibits various types of calcium channels in the brain, such as type P, Q, and N channels, resulting in decreased depolarization-dependent neurotransmitter release. The predominant expression of these channels in the cerebellum and hippocampus suggests that their dysfunction or reduced activity may influence vestibulocerebellar structures and brainstem function, thereby contributing to dizziness, blurred vision, ataxia, and cognitive impairment.[25]

The use of pregabalin is also associated with the risk of dependence and abuse. Pregabalin is often abused because of its sedative and euphoric effects. This risk is higher in individuals with a history of substance abuse.[23] Furthermore, gabapentinoids, including pregabalin, can increase the risk of toxicity if used together with other sedative drugs, such as opioids or benzodiazepines.

Conclusion

Neuropathic pain is a complex chronic pain condition with multifactorial pathophysiology, in which dysfunction of the glutamatergic system plays a central role in the occurrence of peripheral and central sensitization. Increased glutamate release, hyperactivation of glutamate receptors, and impaired glutamate transporter function contribute to increased neuronal excitability and pain persistence. Pregabalin has been proven effective as first-line therapy for neuropathic pain with the main mechanism of action being the reduction of excitatory neurotransmitter release, including glutamate, through modulation of the α2δ subunit of presynaptic calcium channels, as well as improvement of synaptic glutamate regulation. Nevertheless, pregabalin's therapeutic response varies and its use is still limited by side effects and the risk of abuse with long-term use. Therefore, therapeutic approaches for neuropathic pain need to be individualized and multidisciplinary, and supported by a deeper understanding of the modulation of the glutamatergic system as a basis for developing safer and more effective non-opioid therapies in the future.

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