REVIEW

Derleme

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NMDA Reseptör ve Antagonistleri Nöropatik Ağrının Tedavisinde Neden Önemlidir?

ABSTRACT

Neuropathic pain (NP) is characterized by heightened sensitivity to stimuli, known as hyperalgesia, and nociceptive responses to normally non-harmful stimuli, referred to as allodynia. NP is reported to affect 5-10% of the world's human population and is often accompanied by conditions that negatively affect life, such as depression and sleep disorders. NP, which negatively affects quality of life, is tough to manage. Current treatments for NP are only moderately effective and have significant side effects, necessitating alternative therapeutic approaches for patients. Spinal glutamate N-methyl-D-aspartate receptor (NMDAR) hyperactivity is an important mechanism of chronic NP. NMDARs in primary afferent terminals may contribute to hyperalgesia by increasing neurotransmitter release. Therefore, antagonizing these receptors is of interest in the treatment of NP. Following nerve injury, increased activation of NMDARs in the spinal cord and brain results in increased calcium ion influx. This also enhances pain signals. Increased NMDAR activity also plays a role in the initiation and maintenance of chronic pain states. Therefore, modulating NMDAR activity is one of the cornerstones of pharmacological therapy in the management of neuropathic pain.Several drugs with (variable) antagonistic activity at NMDAR are available in clinical practice. These include xenon, nitrous oxide, magnesium, methadone, amantadine, riluzole, memantine, phenytoin, carbamazepine, valproic acid, and ketamine. Among these, antagonists that do not have motor side effects such as sedation and motor impairment, which are frequently associated with NMDAR antagonism, are attracting attention as targets for the treatment of NP.Pharmacological approaches emerging from phase III clinical trials and preclinical studies hold promise for effective treatment.

KeyWords

Amantadine, Hyperalgesia, Ketamine, Neuropathic pain, NMDAR

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ÖZ

Nöropatik ağrı, hiperaljezi olarak bilinen uyaranlara karşı artan hassasiyet ve allodini olarak adlandırılan, normalde zararlı olmayan uyaranlara karşı nosiseptif tepkiler ile karakterize edilir.Nöropatik ağrının, dünyadaki insan nüfusunun %5-10'unu etkilediği ve sıklıkla depresyon, uyku bozuklukları gibi yaşamı olumsuz etkileyen durumlarla birlikte görüldüğü bildirilmektedir. Yaşam kalitesini olumsuz etkileyen nöropatik ağrının yönetimi oldukça güçtür. Nöropatik ağrı için mevcut tedavilerin çoğunun orta düzeyde etkililiğe sahip olması ve kullanımlarını sınırlayan ciddi yan etkilere sahip olması nedeniyle hastalar için başka terapötik yaklaşımlara ihtiyaç vardır. Spinal glutamat N-metil-D-aspartat reseptör (NMDAR) hiperaktivitesi kronik nöropatik ağrının önemli bir mekanizmasıdır. Primer afferent terminallerdeki NMDAR'leri nörotransmitter salınımını artırarak hiperaljeziye katkıda bulunabilmektedir. Dolayısıyla nöropatik ağrı tedavisinde bu reseptörlerin antagonize edilmesi durumu göze çarpmaktadır. Sinir yaralanmasının ardından, omurilik ve beyindeki NMDAR'lerinin artan aktivasyonu, artan kalsiyum iyon akışıyla sonuçlanır. Ayrıca bu durum, ağrı sinyallerini de güçlendirmektedir. Artan NMDA reseptör aktivitesi, kronik ağrı durumlarının başlatılmasında ve sürdürülmesinde de rol oynamaktadır. Bu nedenle, NMDAR aktivitesini modüle etmek, nöropatik ağrının yönetiminde farmakolojik tedavinin temel taşlarından biridir. Klinik uygulamada NMDAR'de (değişken) antagonistik aktiviteye sahip birkaç ilaç mevcuttur. Bunlar arasında ksenon, nitröz oksit, magnezyum, metadon, amantadin, riluzol, memantin, fenitoin, karbamazepin, valproik asit ve ketamin bulunur. Bunlardan özellikle NMDAR antagonizmasıyla sıklıkla ilişkilendirilen sedasyon ve motor bozukluğu gibi motor yan etkilere sahip olmayan antagonistler nöropatik ağrı tedavisinde hedef olabilmesi açısından dikkat çekmektedir. Faz III klinik çalışmalar ve klinik öncesi çalışmalardan ortaya çıkan farmakolojik yaklaşımlar etkili tedavi için ümit vaat etmektedir.

Anahtar Kelimeler

Amantadin, Hiperaljezi, Ketamine, Neuropathic pain, NMDAR

INTRODUCTION

Neuropathic pain and its causes

Neuropathic pain (NP) is characterized by heightened sensitivity to stimuli, known as hyperalgesia, and nociceptive responses to normally non-harmful stimuli, referred to as allodynia (1, 2). Neuropathic pain is reported to affect 5-10% of the world's human population and is often accompanied by conditions that negatively affect life, such as anxiety, depression, irritability and sleep disorders (3). Today, effective treatment of NP, which negatively affects the quality of life, continues to be an important medical need (4). It is stated that only 30-60% of NP patients, which are difficult to manage, have a limited treatment effect (5). It is known that NP can be caused by various cases such as nevre compression, channelopathies, metobolic disorders, viral infections-induced neuropathy, autoimmune disorders, injuries affecting the central nervous system (1, 6). Diagnostic accuracy can be optimized by determining the neurobiological changes underlying the pain condition. As a result, it is stated that it will be clinically possible to benefit from mechanism-based therapeutics for maximum analgesic effect (6). Current NP treatments have moderate efficacy and significant side effects, highlighting the need for alternative therapies (1).

High intensity prolonged pain stimuli are known to trigger a cascade of events that activate the N-methyl-D-aspartate receptor (NMDAR). Activation of the NMDAR has been associated with abnormalities in the sensory (peripheral and central) system, resulting in neuronal excitation and abnormal pain symptoms (spontaneous pain, allodynia, hyperalgesia). The mechanism of the neurodegenerative process caused by the activation of NMDA receptors, which play a role in neuropathic pain, is shown in Figure 1. Blockade of these NMDARs by antagonists can prevent or reverse pain pathology, resulting in pain relief (7). This review briefly mentions studies on NMDARs as well as pharmacological agents that antagonize them and why they are important in treating neuropathic pain.

NMDARs in neuropathic pain

NMDARs are present in both postsynaptic and presynaptic locations, particularly in the central terminals of primary neurons within the spinal dorsal horn (2, 8). The location of NMDARs, which play an active role in NP, is also of great importance. The majority of neurons in spinal lamina II are glutamatergic excitatory interneurons involved in nociceptive transmission (2). Continuous stimulation of pain-related receptors leads to activation and positive regulation of synaptic NMDARs in the dorsal horn of the spinal cord, which has been reported to result in increased pain signal transmission to the brain (central sensitization) (9, 10). Glutamate NMDAR antagonists have been used to treat NP (2, 8, 10). It has been hypothesized that intrathecally administered NMDAR antagonists target postsynaptic NMDARs in the spinal cord (2).

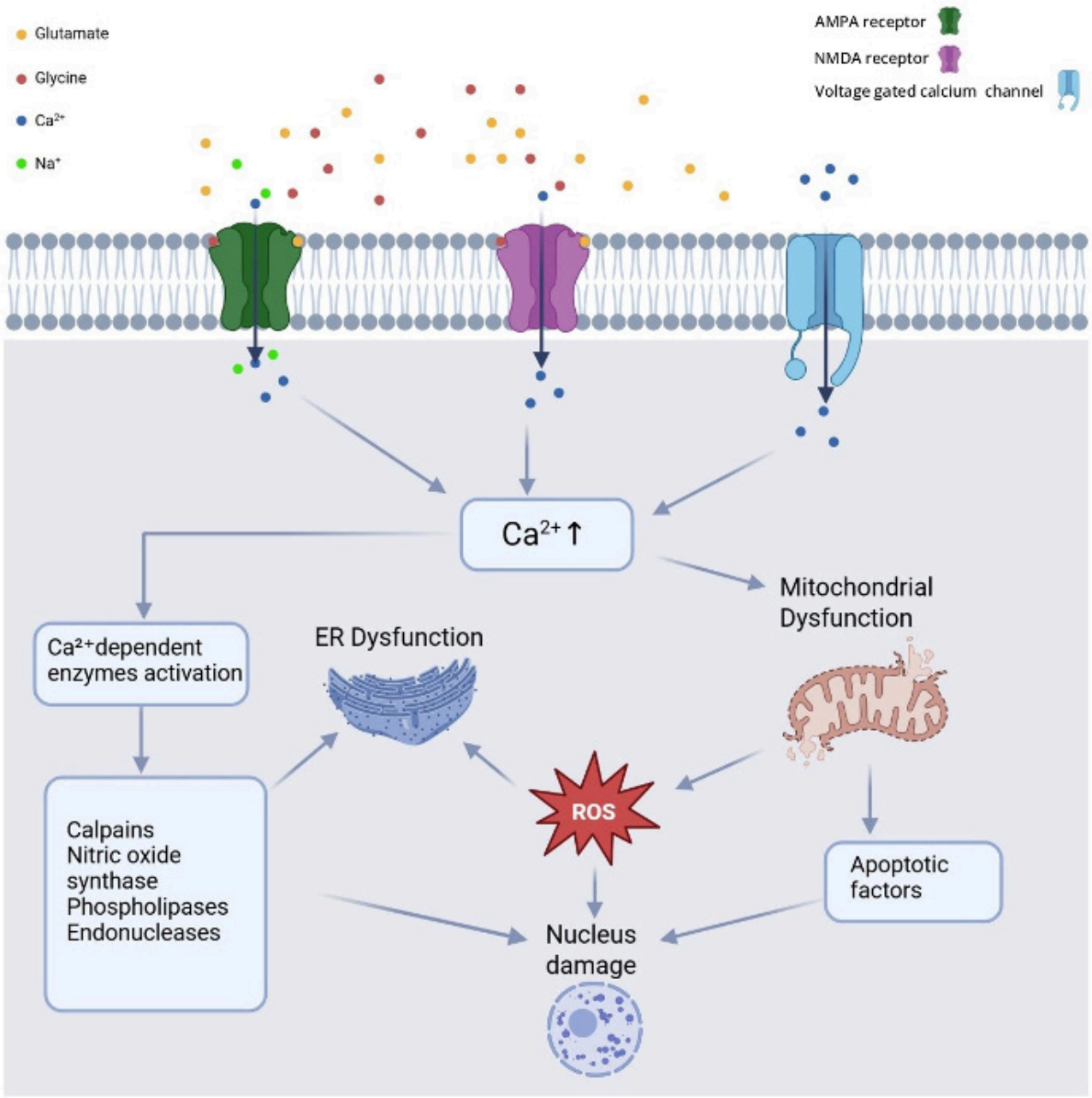

Figure 1. The mechanism of neurodegenerative process caused by the activation of NMDA receptors.

The primary source of central sensitization is known to be activation of the NMDAR for glutamate. Central sensitization has been reported to be a state of increased spinal excitability due to repetitive painful input. In neuropathic conditions, hyperexcitable spinal neurons exhibit increased responsiveness to multiple sensory modalities and expand their receptive fields. This is the most plausible explanation for dynamic, static, and cold allodynias and is reflected in increased thalamic neuronal coding (6).

Current treatment of neuropathic pain

Current treatment of neuropathic pain includes tricyclic antidepressants (TCAs), gabapentinoids (gabapentin, pregabalin), and serotonin norepinephrine reuptake inhibitors (duloxetine and venlafaxine) as first-line medications. Drugs with weak recommendations include capsaicin 8% patches, lidocaine patches, and subcutaneous injections of botulinum toxin type A for peripheral neuropathic pain only (11, 12). Tricyclic antidepressants should be used with caution because of possible side effects (anticholinergic effects, cardiac side effects, urinary retention, xerostomia and constipation) (13). There is also some evidence for the efficacy of tramadol and opioids. These drugs are generally recommended for chronic cancer pain because of toxicity profile when there is no other option (11, 14, 15). Sodium channel blockers such as carbamazepine, lacosamide and lamotrigine have been suggested to be effective in subgroups of patients with neuropathic pain and carbamazepine and oxcarbazepine are known to be recommended first-line treatments for trigeminal neuralgia

Table I. The pharmacological properties and side effect profiles of developed NMDA receptor antagonists

Antagonist type	Drug	Receptor	Developmental phases	Pharmacological effect	Side-effects	Ref
Competitive antagonist	D-AP5 D-AP7	Non-selective	Preclinical studies	Block fear acquisition Block/interfere with psychostimulants	Hallucinations Depression Confusion Ataxia	24,30,31
	DCKA	GluN1	Preclinical studies	Neuroprotective and anxiolytic effect	Motor impairments Hallucinations Cognitive disturbances	30,31
	CPP	GluN2A	Terminated at phase II	Neuroproctive and antiepileptic effect	Gait ataxia Sedation Confusion Disorientation	30, 31
	SDZ-220-040	GluN2B	Preclinical studies	Attenuate neuropathic pain Anticonvulsant effect Protection against focal ischemia	Confusion Sedation Disorientation Ataxia	30, 31
	L689-560	GluN1	Preclinical studies	Anticonvulsant effect Anxiolytic effect	Confusion Disorientation Gait ataxia Sedation Motor impairments Hallucinations	30, 31
	ST3	GluN2A GluN2B	Preclinical studies	Neuroprotective effect	Hallucinations Confusion Memory deficits Ataxia	30, 31
	PPDA	GluN2A GluN2D	Preclinical studies	Neuroprotective effect	Motor dysfunction	30, 31
	NVP-AAM077	GluN2C GluN2B	Preclinical studies	Antidepressant	Motor dysfunction	30, 31
Non-competitive antagonist	Memantin	Open-Channel blocker	Phase IV	Neuroprotective effect Anti-convulsant effect Anti-dyskinesia	Confusion Headaches Constipation Dizziness Nausea	1,17,28
	MK-801	Open-Channel blocker	Preclinical studies	Neuroprotective effect Anti-convulsant effect	Psychotic symptoms Death	24,31
	Agmatine	Non-selective	Phase II	Alleviating symptoms in several types of neuropathy	Psychotic symptoms	25,32
	Ketamine	Open-Channel blocker	Phase IV	Anticonvulsant Antidepressant Anaesthetic effect	Psychotic symptoms Cognitive deficits	2,5,27
	Amantadine	Open-Channel blocker	Phase IV	Anti-dyskinesia Neuroprotective agent	Dry mouth Visual hallucination Blurred vision Delirium Urinary retention	33,34

(13, 16). In refractory cases, spinal drug administration or neuromodulation may be considered (11). The tolerability and side effects of these medications for treating neuropathic pain are of greater concern (17). Many patients unfortunately do not achieve adequate pain relief at tolerated doses. When single drug therapy is partially but insufficiently effective, combination therapy is usually used.

Following nerve injury, increased activation of NMDARs in the spinal cord and brain results in increased calcium ion influx. Pain signals also amplify. The increase in NMDAR activity has also been implicated in the initiation and maintenance of chronic pain states. Therefore, modulating NMDAR activity is a target for pharmacological treatment in the management of neuropathic pain (10). It has been stated that when there is nerve damage, α2δ1 proteins bind to glutamate NMDARs and cause neuropathic pain. The sigma 1 receptor promotes the formation of α2δ1-NMDAR complexes and therefore it has been emphasized that the emergence of mechanical allodynia depends on the interaction between these proteins (18). In animals with intact spinal cord and descending tracts, intraplantar injections of formalin or sciatic nerve injury have been reported to induce long-term potentiation (LTP) due to NMDAR activation in the dorsal horn (19). A study has shown that activation of pannexin 1 channels is required to initiate and maintain nociceptive signaling of NMDARs in the spinal cord in neuropathic rats (20).

Spinal glutamate NMDAR hyperactivity is an important mechanism of chronic NP. Presynaptic NMDARs primarily amplify the primary afferent input to spinal excitatory neurons in NP. While presynaptic NMDARs are essential for chemotherapy-induced pain hypersensitivity, postsynaptic NMDARs in spinal excitatory neurons have been reported to play a predominant role in chronic pain caused by traumatic nerve injury (21). Spinal administration of Ro 25-6981, an NMDA-2B receptor antagonist, has been shown to have a significant antinociceptive effect at the spinal level (22). NMDARs at the spinal cord level have been reported to play an important role in central sensitization and neuropathic pain following nerve injury (2). One study showed that paclitaxel treatment or sparing nerve injury increased the frequency of NMDAR-mediated miniature excitatory postsynaptic currents (mEPSCs) and dorsal root-evoked EPSCs in vesicular glutamate transporter-2 dorsal horn neurons in male and female mice (21). Additionally, brain-derived neurotrophic factor, which is released during NP and plays an important role in the etiology and maintenance of NP, has been shown to strengthen NMDARs in primary afferent terminals (8, 23).

NMDAR antagonists, their advantages and disadvantages in NP treatment

Several drugs with (variable) antagonistic activity at NMDAR are available in clinical practice, including xenon, nitrous oxide, magnesium, methadone, amantadine, riluzole, memantine, phenytoin, carbamazepine, valproic acid and ketamine (5) (Table I). Ketamine has been used for many years to treat NP. Furthermore, intrathecal administration of NMDAR antagonists, such as MK801 and AP5, has been reported to effectively reduce NP behaviors in animals exposed to peripheral nerve injury (2, 24). Evidence from randomized controlled clinical trials is lacking that ketamine has sustained, large effects in the treatment of NP, but it is important to consider the potential selective efficacy of ketamine in patients experiencing central sensitization, opioid-induced hyperalgesia, or opioid tolerance (5). There is some small clinical experience in which intranasal esketamine combined with intranasal midazolam for the treatment of postoperative pain is similar in terms of efficacy, satisfaction and safety compared with standard intravenous hydromorphone with morphine. However, a higher frequency of nystagmus was reported in the esketamine group and dry mouth in the morphine group (9).

NMDAR including NR2B has been reported to be required for spinal LTP induction and are promising targets for the treatment of neuropathic pain (19). Agmatine primarily antagonizes NMDARs containing Glun2B subunits in the spinal cord. Agmatine, a decarboxylated form of L-arginine, does not have the motor side effects such as sedation and motor impairment that are commonly associated with non-subunit selective NMDAR antagonism. In one study, agmatine was reported to reduce the development of SNI-induced tactile hypersensitivity in controls with ifenprodil (a GluN2B subunit selective antagonist), but had no effect in subjects with low levels of GluN2B subunits. In GluN2B deficient mice, MK-801 reduced NMDA-induced nociceptive behaviors, but the effect of agmatine was reduced and ifenprodil had no effect (25). In a study, gabapentin and NMDAR antagonists (dekstrometorfan and MK-801) were shown to have a synergistic effect and alleviate allodynia in rats with neuropathic pain (26).

It is now well known that nonanesthetic doses of ketamine produce a strong analgesic effect by inhibiting NMDARs and enhancing descending inhibitory pathways. When the analgesic effect of ketamine is considered as a short-term analgesic effect, an associated reduction in postoperative chronic pain and opioid consumption is well documented perioperatively. On the other hand, the number of clinical studies on its long-term benefits is still limited (27). It has been stated that the failure of NMDA antagonists such as ketamine and dextromethorphan is due to clinical intolerance and complete NMDA blockade. For example, the significant side effects of ketamine use, such as sedation, hallucinations and mood changes, have limited the clinical applicability of this drug in the management of neuropathic pain (17).

The adamantane derivative, memantine, is a noncompetitive NMDAR antagonist (1). Memantine binds to the NMDA receptor with medium to low affinity. As a result, it causes fewer side effects than other NMDA blockers.

For this reason, it can be said that memantine surpasses other NMDA antagonists (17). Trial NCT01536314 investigated the effects of Memantine in postmastectomy NP; patients treated with Memantine (started 2 weeks before surgery and administered for 4 weeks) reported significantly less pain 3 months after mastectomy (1). Additionally, in a clinical study examining the effect of memantine on diabetic neuropathy, significant improvement was shown in the use of gabapentin + memantine compared to those using gabapentin alone. Memantine has been indicated to be a useful agent in the treatment of diabetic neuropathy and significantly improves the quality of life of diabetic patients (17). In a clinical study where different doses of memantine were tested in patients with diabetic neuropathy, it was reported that 40 mg/day memantine was effective and well tolerated. In another study, adverse effects were found to be mild in patients treated with memantine and dizziness and nausea were more common compared to placebo (28).

CONCLUSION

Perspectives in the treatment of NP include the development of new compounds and a more personalized therapeutic approach made possible by recent advances in the evaluation and understanding of NP (29). Studies have shown that NMDAR antagonists are effective in NP, providing significant reductions in some of its symptoms, such as allodynia and hyperalgesia. On the other hand, studies are needed to evaluate the effectiveness of NMDAR antagonist agents and the severity of their possible side effects. It would be good to focus more on developing selective NR2B antagonists or nonselective NMDAR antagonists with a milder side effect profile for the treatment of neuropathic pain and testing them in preclinical and clinical studies.

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