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Review

Prospects and challenges in NMDAR signaling in spinal cord injury recovery and neural circuit remodeling

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ABSTRACT

N-methyl-D-aspartate receptors (NMDARs) are essential for excitatory synaptic transmission in the central nervous system, contributing to various physiological and pathological functions including learning, memory, neural development, synaptic transmission, and plasticity. NMDAR signaling plays a role in spinal cord injury outcomes, including restoring spinal circuits, modulating synaptic plasticity, reinstating synchronized functions, enhancing motor capabilities, and reducing neuropathic pain. Consequently, targeting NMDARs may serve as a promising approach to enhance axonal regeneration and reorganization of neural circuits following spinal injury.

Contents

Abbreviations: SCI, Spinal cord injury; NMDARs, N-methyl-D-aspartate receptors; GluRs, Glutamate receptors; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; KA receptors, kainate receptors; CTD, C-terminal domain; TMD, transmembrane domain; ATD, amino-terminal domain; LBD, ligand-binding domain; LTP, long-term potentiation; CaMII, calmodulin-dependent protein kinase II; CaM, calmodulin; LTD, long-term depression; PSD-95, postsynaptic density-95; nNOS, neuronal nitric oxide synthase; MAGUK, membrane-associated guanylate kinase; EAATs, excitatory amino acid transporters; EPSCs, excitatory postsynaptic potentials; CREB, cAMP response element-binding protein; TRPM2, transient receptor potential-2; NP, neuropathic pain; GABAR, γ-aminobutyric acid receptors; ROS, reactive oxygen species; KCC2, K^+-Cl^--co-transporter-2; MK-801, Dizocilpine; PCP, phencyclidine; Q-VD-OPh, ketamine and quinolyl-valyl-*O*-methylaspartyl-[2,6-difluorophenoxy]-methyl ketone; SOD, superoxide dismutase; MRZ2/579, Neramexane; DM, dextromethorphan; MF-CA3, mossy-fiber-CA3.

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1. Introduction

Spinal cord injury (SCI) is a common, refractory disease worldwide, often leading to impaired motor and sensory functions. Additionally, most patients experience neuropathic pain, spasticity, and autonomic dysreflexia. Glutamate receptors (GluRs), which transmit excitatory signals, influence the neurons in the brain, spinal cord, and peripheral nervous system. The complex and intricate structure of glutamate receptors and their functional regulation are key to enhancing synaptic plasticity [1]. Among these, N-methyl-D-aspartate receptors (NMDARs) subunits present in native cells exhibiting heterologous expression function as critical calcium ion channels in learning, memory, neural development, synaptic transmission, and plasticity. The inhibition of NMDA receptor activity has gained considerable attention as a novel therapeutic approach for SCI in recent years [2–6]. Advancements in understanding the regulators and functions of NMDA receptors at central synapses may provide new insights into the treatment of SCI and its complications. This article aims to provide an overview of the structural characteristics of NMDA receptors, explore current research advancements and the use of NMDA receptor antagonists for treating spinal injury-related complications. The primary objective was to investigate future research directions for targeting NMDA receptors as a potential therapeutic approach for SCI.

2. NMDA receptor structure and physiological characteristics

2.1. NMDA receptors: Structure and function

The ionotropic glutamate receptors (iGluRs) are categorized into four distinct types based on their pharmacological properties and structural similarities: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA receptors, GluA1-GluA4), kainate receptors (KA receptors, GluK1–GluK5), NMDA receptors (GluN1, GluN2A–GluN2D, GluN3A, and GluN3B), and δ receptors (GluD1 and GluD2). Among these, AMPA, NMDA, and KA receptors play crucial roles in the transmission of glutamate signals, neuronal excitation, and diverse physiological functions.

The NMDAR is a heterotetramer comprising two GluN1 and two GluN2 subunits, and the GluN2 subunit plays a crucial role in determining the functional properties of the receptor [7]. The subunit composition of the NMDA receptor typically includes a C-terminal domain (CTD), a transmembrane domain (TMD), and two extracellular domains: an amino-terminal domain (ATD) and a ligand-binding domain (LBD) [8]. The estimated NMDA receptor activation speed is approximately 10 ms, while the deactivation time depends on the specific GluN2 subunits present [9]. Phosphorylation of the GluN2A and GluN2B subunits is integral to the functionality of NMDA receptors. Compared with AMPA receptors, NMDA receptors exhibit slower activation kinetics and extended open durations.

The activation of the calmodulin-dependent protein kinase II (CaMKII)/NMDAR complex is crucial for the induction of long-term potentiation (LTP). CaMKII, a synaptic protein dependent on Ca2+/calmodulin(Ca2+/CaM), can be activated through long-term depression (LTD) and by promoting the induction of LTP [10]; however, this process is complex. Initially, Ca2+ penetrates the cell via the NMDA receptors and binds with CaM to form the Ca2+/CaM complex, which activates CaMKII to induce Thr286 autophosphorylation, thereby exposing the GluN2B binding site. This facilitates the binding of CaMKII to the GluN2B subunit to form the CaMKII-GluN2B complex. The interaction between CaMKII and CTD of GluN2B triggers conformational changes in postsynaptic density-95 (PSD-95) scaffold proteins, affecting the stability of PSD-95. This alteration in PSD-95 stability influences its association with NMDA receptors, resulting in the formation of the NMDAR/PSD-95/neuronal nitric oxide synthase (nNOS) complex [11], which is crucial for maintaining synaptic plasticity. PSD-95, a member of the PSD scaffold protein family, belongs to the membrane-associated guanylate kinase (MAGUK), and nNOS is a constitutive nitric oxide synthase with PDZ domains. PSD-95 belongs to a class of PDZ domains that interact with nNOS via PDZ/PDZ interactions after binding [12]. Disruption of the nNOS-PSD-95 structure inhibits LTP, leading to excitotoxic neuronal responses [13]. This process requires glycine (Gly), which, in combination with glutamate, activates NMDARs [14]. The distribution patterns of NMDA receptor and PSD-95 are associated with the onset and progression of Alzheimer's disease, age-related memory decline, anxiety, depression, and chronic pain [15,16]. Furthermore, the absence of PSD-95 alters the inhibitory function of GABAergic neurons in the prefrontal cortex.

Typically, only a small fraction of glutamate reaches the postsynaptic membrane to bind with GluRs and exert physiological effects. Excitatory amino acid transporters (EAATs) can take up synaptic glutamate, which, after reuptake, is metabolized by glutamine synthetase into glutamine before entering the presynaptic neurons for recycling [17].

2.2. Ion characteristics of NMDARs

As ionotropic ligand-gated receptors, NMDARs allow Na^+ and Ca^{2+} to pass through the cell membrane, which is crucial for neuronal excitability, normal development, and functioning of the

central nervous system. In particular, high permeability to Ca^{2+} plays a substantial role in the pathological processes associated with many neurological disorders [18]. Ca^{2+} serves as a second messenger in signal transduction pathways and is essential for neuronal transmission and synaptic plasticity [19]. Moreover, high permeability of Ca^{2+} is a key driver of NMDAR-mediated excitotoxicity. Ca^{2+} influx plays a critical role in mediating excitatory postsynaptic potentials (EPSCs) via NMDARs. Increased intracellular Ca^{2+} levels activate downstream signaling pathways, including Ras-Raf, MAPK, and ERK1/2. Ca^{2+} serves as a crucial second messenger in signal transduction pathways essential for neuronal transmission and synaptic plasticity. Following the phosphorylation of ERK1/2, the cAMP response element-binding protein (CREB) undergoes phosphorylation at Ser133, triggering the transcription of genes encoding mRNAs such as brain-derived neurotrophic factor. This molecular cascade promotes neuronal survival, enhances dendritic arborization, and preserves synaptic integrity and function [20,21].

The entry of Ca^{2+} into cells via NMDA receptors is intricately linked to LTP. This theory is widely acknowledged because excessive glutamate stimulation results in calcium overload, which ultimately causes neuronal death and contributes to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, dementia, and stroke [22]. The excitatory impact of NMDARs can be diminished by inhibiting the cascade of reactions within the Ca^{2+} signaling pathway. Specifically, Burch et al. suggested that targeting transient receptor potential-2 (TRPM2) and CaMKII offers a potential strategy to suppress synaptic overexcitation following ischemia, ultimately leading to the restoration of compromised synaptic plasticity [23]. Intracellular Ca^{2+} concentration is not only influenced by NMDA receptor activation but also contributes to NMDA receptor-dependent excitotoxicity through its downstream signaling pathways. Therefore, quantifying the effect of Ca^{2+} is crucial for evaluating interventions targeting NMDA receptor function. Lacobucci et al. reported that single-channel patch clamp electrophysiology effectively quantifies the blocking effect of Ca^{2+} on NMDA receptors [24]. Additionally, Weacer et al. reported the application of whole-cell patch clamp electrophysiology to quantitatively measure Ca^{2+} permeability in NMDARs and found that estimating relative permeability through high monovalent ions aids in achieving measurement objectives [25].

The function of NMDARs is also regulated by Mg^{2+}, which exhibits high permeability to Mg^{2+} and voltage dependency on Mg^{2+} [26]. As ion channels, NMDARs can be inhibited by extracellular Mg^{2+} levels in their resting state [27]. The removal of Mg^{2+} triggers Ca^{2+} influx, leading to the activation of PSD-95 and signaling kinases that mediate synaptic plasticity. Additionally, Zn^{2+} binds to the ATD of GluN2A in a proton-dependent manner, maintaining the stability of the LBD structure and keeping the receptor in a "non-active" state [28,29]. (Fig. 1).

3. NMDARs and neural plasticity

Research on NMDARs has primarily focused on their role in treating brain, memory, and cognition disorders. The activation of NMDARs is crucial for LTD and LTP [30]. These receptors are recognized as Hebbian coincidence detectors and play pivotal roles in neuronal function and disease mechanisms. By regulating LTP and LTD, NMDARs substantially influence synaptic plasticity, which is essential for learning, memory formation, and overall cognitive function [7]. In the hippocampal CA3-CA1 region,LTD, LTP play decisive roles in synaptic plasticity. Applying multi-site Hebbian plasticity in the corticospinal system can increase motor neuron synapses and restore limb motor function in patients with spinal cord injuries [31].

LTP and LTD play key roles in the remodeling of neural circuits and synapses following SCI. Therefore, we emphasized the influence of NMDARs on LTP and LTD, indicating that targeting NMDARs is a promising approach for treating spinal cord injuries and their related complications.

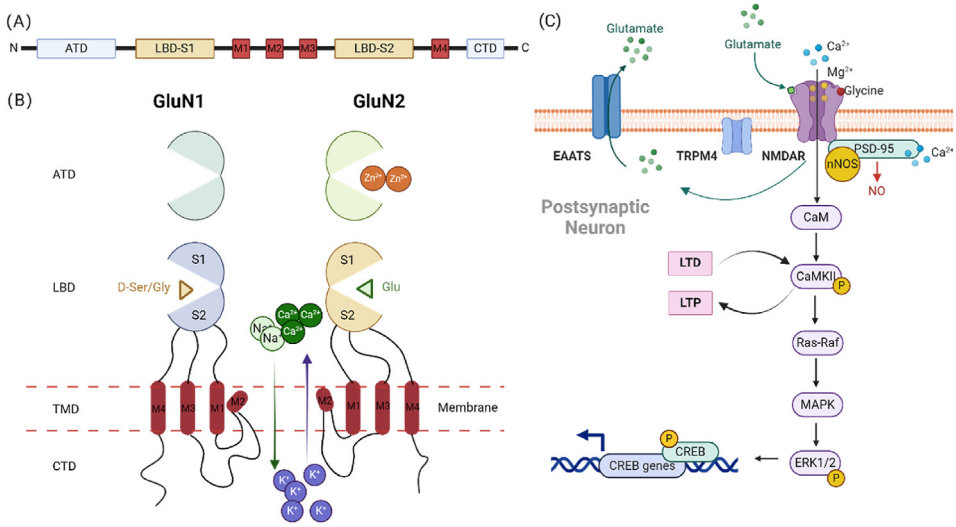

Fig. 1. Structure and mechanisms of NDMAR. (A) Linear representation of the ATD, LBD, TMD, and CTD within a polypeptide chain containing an NMDAR subunit. The LBD is composed of two polypeptides (S1 and S2) that fold into clamshell-like structures. The TMD comprises three transmembrane helices (M1, M3, and M4) and a membrane-reentrant loop (M2). (B) NMDARs are heteromeric proteins composed of two identical or distinct subunits, GluN1 and GluN2. This diagram illustrates the structure of GluN1/GluN2 NMDARs. The combination of GluN1 and GluN2 subunits is essential for the formation of an effective non-selective cation channel that allows for Ca2+ and Na + influx and K+ efflux. NMDARs play key roles in diverse physiological and pathological processes because of their high calcium permeability. Each component of NMDAR includes a sizable extracellular ATD, an agonist-binding area (ABD), a transmembrane section (TMD), and a CTD. The transmembrane domain consists of M1, M3, M4 and M2. (C) Role of NMDAR and its molecular axes involved in synaptic plasticity under physiological conditions. Activation of NMDARs facilitate Ca^{2+} influx, leading to the activation of nNOS via a calcium-dependent pathway involving calmodulin. Upon binding to Ca^{2+}, CaM activates CaMKII, leading to activation of Ras-Raf, MAPK, and ERK pathways, which subsequently induce the transcription of CREB. (Figure created with BioRender.com.)

3.1. NMDARs and LTP

LTP is an enduring increase in synaptic strength following short-repeated synaptic stimulation. This phenomenon is characterized by pathway specificity and cooperativity, indicating that LTP can only be induced when the received stimuli are sufficient to activate the axon [32,33]. Owing to the limited capacity for regeneration and plasticity in the spinal cord, preventing or reversing inflammation and neural damage at the injury site following a SCI is extremely challenging. The neural or synaptic plasticity that occurs after such injuries often varies and includes collateral sprouting, structural synaptic remodeling, long-distance axonal regeneration, and motor cortex plasticity [34,35]. Spinal LTP may contribute to changes, such as inflammation and hypersensitive pain responses, following SCI, which depend on the activation of NMDARs [14,36]. LTP induces an increase in PSD and dendritic spine growth.

The accumulation of Ca^{2+} within the cell via NMDARs is the initial step in the induction of LTP. Subsequently, the CaMKII-NMDA receptor complex drives and sustains LTP. LTP activation requires a substantial influx of Ca^{2+} into the postsynaptic terminals following NMDA receptor stimulation.

3.2. NMDARs and LTD

LTD occurs predominantly at excitatory glutamatergic synapses. However, NMDARs play a unique and indispensable role that cannot be substituted by other types of GluRs [37]. Some theories suggest that NMDARs, rather than Ca^{2+} influx, play a crucial role in LTD. The onset of LTD primarily relies on NMDA receptor activation [38].

A moderate increase in intracellular Ca^{2+} concentration is optimal for inducing LTD, in contrast to the conditions required for LTP [39]. Theoretically, high-frequency stimulation induces LTP. However, inhibition of Ca^{2+} influx through NMDARs leads to the induction of LTD [40]. LTD triggered by NMDA receptor activation results in the contraction or even disappearance of dendritic spines, which are crucial for synaptic plasticity. This process contributed to atrophy of dendritic spines in mice. Additionally, blocking NMDARs inhibited LTD in adult rats [41–43].

Another theory posits that decreased intracellular Ca^{2+} concentration is responsible for LTD inhibition. The introduction of a Ca^{2+} chelator can prevent LTD in postsynaptic neurons [44,45]. When NMDA receptor antagonists are used to block the ion channel function of NMDAR, the metabolic activity of NMDAR suppresses active synapses without increasing postsynaptic calcium levels, thereby refining and broadening the mechanisms that regulate synaptic plasticity. Furthermore, the downregulation of PSD-95 contributes to NMDA receptor-induced LTD [46], which could be attributed to the CaMKII-mediated phosphorylation of PSD-95 at Ser73. However, modulating the protein levels of PSD-95 may not influence LTD.

4. Pathological and physiological roles of NMDARs in SCI and its complications

The research and application of NMDARs in brain disorders are extensive, with therapeutic strategies for various central nervous system diseases achievable through the modulation of NMDA receptor function and expression. Currently, several drugs are used for clinical management; however, the clinical application of NMDARs in SCI and its complications remains limited. Nevertheless, NMDARs have recently garnered attention as a therapeutic target for spinal injuries. NMDARs play pivotal roles in the recovery of motor function following injury, alleviation of neuropathic pain, and improvement in muscle spasms. The impact of NMDARs is primarily attributed to their excitotoxic effects and their role in synaptic plasticity regulation, which are key factors in spinal injuries and related complications.

4.1. Pathological changes of NMDARs after SCI

Under normal physiological conditions, glutamate is maintained at low concentrations within the synaptic cleft and the extracellular space [47]. However, following SCI, mGluRs and NMDARs are overactivated and overexpressed, whereas glutamate transporters are downregulated, resulting in glutamate accumulation and excitotoxicity. This imbalance induces a cascade of reactions that cause inflammation in the spinal cord and chronic neuropathic pain (NP) [48–53].

Excitotoxic neuronal damage occurs because of abnormal metabolism and increased glutamate levels in neuronal cells during the acute and subacute phases of SCI [54]. This persistent excitotoxicity, inflammatory responses, and oxidative stress lead to early spinal cord tissue damage and the subsequent onset of NP [53,55]. Lee et al. discovered that after SCI, glutamate and its receptors influence neuronal activity by regulating neuronal ion channels. Specifically, NMDARs downregulate K^+-Cl^--co-transporter-2 (KCC2) function through Ser940 dephosphorylation, resulting in depolarization mediated by γ-aminobutyric $acid_A$ receptors ($GABA_AR$) [56]. Furthermore, NMDARs influence neuronal excitability by regulating intracellular calcium ion concentrations, thereby altering the transport and diffusion capabilities of GABARs. While moderate activation of NMDARs can enhance receptor stability at synapses, excessive activation may result in synaptic dispersion [57]. Following SCI, excessive activation of GluRs increases sustained inward Ca^{2+} currents, resulting in mitochondrial dysfunction, accumulation of reactive oxygen species (ROS), and other detrimental effects that ultimately lead to neuronal loss [58]. These alterations collectively contribute to excitotoxicity, and the magnitude and duration of NMDAR activation influence the severity of excitotoxicity. Conversely, AMPAR receptors are involved in calcium ion permeability. SCI induces mitochondrial damage, endoplasmic reticulum stress, cell apoptosis, and death in spinal cord neurons, resulting in excitotoxicity and excessive calcium influx after injury [59]. Additionally, NMDARs influence the plasticity of spinal circuits following SCI.

This section comprehensively analyzes research on NMDARs in SCI and their complications, highlighting that these receptors can serve as crucial targets for treating spinal cord injuries. Adverse outcomes can be mitigated by modulating the abnormal expression of NMDARs after injury.

4.2. Impact of NMDARs on motor function following SCI

Following SCI, the disruption of ascending and descending fibers impairs motor function. However, long-distance axons possess regenerative capabilities, and spinal neuroplasticity facilitates neuronal reorganization and the reshaping of motor circuits. Central pattern generators are spinal circuits that produce stereotypical movement patterns. Despite the interrupted connections above the injury site, spinal circuits can still utilize sensory information to generate motor functions. Therefore, neuronal and axonal regeneration are crucial for treating SCI. Sprouting of neurons in the corticospinal and reticulospinal tracts plays a crucial role in the recovery of motor function [60]. The plasticity of the spinal cord allows motor cortex signals to be reprojected onto spinal cord circuits.

Bertuzzia et al. reported that spinal motor neurons responsible for axial movements in adult zebrafish stimulated the expression and release of glutamate at neuromuscular junctions, thereby

enhancing neuronal motor output [61]. Byrnes et al. demonstrated that mGluR5 agonists enhanced white matter preservation, mitigated inflammatory responses, reduced neurotoxicity, and improved motor function in a rat model of SCI [62]. Suzuki et al. reported that CPTX application induced AMPAR redistribution and NMDAR clustering, which increased the frequency of EPSCs at neuronal synapses. GluR modulation improved motor function in mice with SCI [63]. Additionally, following cervical SCI, NMDAR upregulation contributes to spontaneous neural plasticity. Enhancing NMDAR expression in phrenic motor neurons aids in the recovery of ipsilateral diaphragmatic activity [64,65]. Bradley et al. found that NMDA receptor signaling and CREB-mediated transcription facilitated the generation of new corticospinal tract relay neurons, inhibiting the activity-dependent formation of corticospinal circuits, thereby limiting the recovery of motor function following SCI [66].

In summary, NMDARs play a crucial role in the remodeling of disrupted motor circuits following SCI. Therefore, modulating glutamate receptor signaling is a promising therapeutic strategy for enhancing motor function recovery after SCI.

4.3. Involvement of NMDARs in the pathological pain after SCI

Most patients with SCI experience NP that substantially affects their quality of life. Conventional treatments are often ineffective and can lead to negative side effects such as drug resistance and increased pain thresholds. GluRs in the spinal cord transmit signals that counteract the development of central sensitization and play a crucial role in pain regulation [67]. Excessive NMDA receptor activation is a key factor in NP, particularly those in the spinal dorsal horn contribute to the development of pain hypersensitivity [68].

Yoon et al. reported that the intrathecal injection of the NMDA receptor antagonist MK-801 alleviated acute pain and hypersensitivity to pain caused by injury [69]. Yu et al. confirmed this theory and found that NMDA receptor agonist D-serine increased the severity of SP after SCI in rats [70], highlighting that NMDA expression plays a crucial role in the development of SP after SCI. A study by South indicated that NMDAR1 in the adult spinal dorsal horn is essential for central sensitization. The conditional deletion of this receptor reduced NMDA currents and injury, thereby alleviating the pain response [71]. NMDAR pathology induces hyperexcitability in spinal dorsal horn neurons following SCI, contributing to NP [72]. Calcium ion influx also plays a crucial role in this process [73]. Activation of NMDA-2B receptors is the primary mechanism through which NMDARs contribute to central sensitization and NP following SCI, thereby inducing synaptic transmission and LTP [74]. Kim et al. reported similar findings without focusing on motor SCI. Using an NMDAR2B blocker, they observed an increase in mechanical nociceptive thresholds after SCI, suggesting that NR2B may be a selective target for regulating SCI [75]. NMDAR is associated with downstream signaling pathways involving PSD-95 and nNOS. Li et al. found that targeting both nNOS-PSD-95 and GABAAR could reduce tolerance to therapeutic drugs for NP [76]. Furthermore, Bhagwani et al. have suggested that sustained glutamate-mediated neuronal hyperexcitability leads to inadequate GABAergic inhibition in the spinal dorsal horn, resulting in NP [49]. Xie et al. found that preNMDARs in spinal nociceptors play a critical role in pain sensitization [77]. Huang et al. indicated that, following SCI, KCC2 modulates the specific excitability of dorsal horn neurons by regulating NMDA receptor activity. This modulation enhances nociceptive transmission in the spinal excitatory interneurons, resulting in pain hypersensitivity [78]. By increasing NMDA receptor numbers, EPSP and intracellular Ca^{2+} are released, resulting in neuronal excitotoxicity, central sensitization, and pain.

In summary, excessive NMDAR excitation contributes to the plasticity of nociceptive information and synaptic inhibition following SCI, playing a crucial role in NP.

4.4. Influence of NMDARs in muscle Spasticity after SCI

Most patients with SCI experience muscle spasticity characterized by involuntary excessive muscle activity leading to muscle stiffness, which considerably affects their quality of life. Given that current clinical management strategies are often ineffective and cause undesirable side effects, developing novel strategies for treating spasticity is imperative.

Muscle spasticity following SCI is directly associated with hyperexcitability of motor neurons after injury. Treatment typically aims to regulate spinal cord excitability, restore normal spinal cord circuitry, and inhibit abnormal synaptic plasticity induced by injury [79]. The primary objective is to reduce excessive muscle tension. Petrosyan et al. discovered that low levels and reduced activity of NMDARs in neuronal networks facilitate spinal cord electrical stimulation to enhance signal transmission, restore functional neuromuscular circuits, and improve motor outcomes in animals with SCI [80]. However, studies on the use of NMDARs for treating muscle spasticity post-SCI are limited.

We believe that inhibiting NMDA receptor neurotoxicity is a safe and effective strategy for treating neuroexcitation. This approach may suppress inflammatory responses, improve synaptic plasticity, and maintain normal neuronal discharge, potentially alleviating muscle spasticity after SCI (Fig. 2).

5. NMDA receptor regulation and the use of related drugs in SCI and its complications

NMDAR modulators can be roughly divided into four categories: competitive antagonists, negative allosteric modulators, positive allosteric modulators, and channel blockers. Among them, channel blockers including memantine, ketamine, Riluzole and MK-801 are common NMDA receptor antagonists used in clinical practice and research.

5.1. Dizocilpine (MK-801)

Dizocilpine (MK-801) is a classic NMDA receptor blocker, commonly used in research to inhibit NMDA receptor function. MK-801 effectively blocks neuronal LTD [40] and inhibits LTP. MK-801 functions as a neuroprotective agent for cells following SCI and prevents hypersensitivity caused by spinal cord ischemia [81,82]. MK-801 inhibits ischemia-induced increase in glutamic acid at the site of SCI through NR2B expression [83]. MK-801 counteracts peripheral nerve injury-induced neuronal loss and promotes neuronal regeneration [84]. Additionally, MK-801 reduces spinal cord neuron apoptosis in hemisected rats, creating a conducive environment for cell survival in rats undergoing cell transplantation therapy [85]. In addition, the intrathecal injection of MK-801 can block thermal hyperalgesia behavior [86].

In summary, MK-801 ameliorated the damage caused by spinal cord ischemia-reperfusion injury, mitigated loss of spinal cord neurons post-injury, and inhibited glutamate-induced excitotoxicity, highlighting its therapeutic potential for SCI.

5.2. Memantine and ketamine

Ketamine and memantine are NMDA receptor antagonists commonly used to treat central nervous system disorders. Although they accelerate proliferation and differentiation of

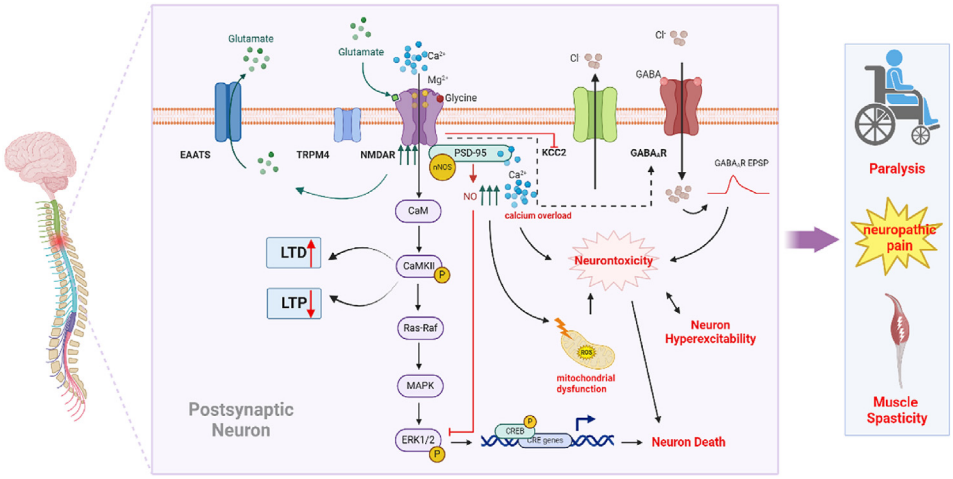

Fig. 2. Pathological changes in NMDARs after SCI. Following SCI, excessive activation of postsynaptic NMDARs leads to a substantial influx of Ca^{2+} into the cells, which inhibits KCC2 expression and induces excitatory postsynaptic potentials (EPSPs) via GABAARs, resulting in excitotoxicity. The overactivation of the PSD-95/nNOS complex produces excessive nitric oxide (NO), triggering oxidative stress and mitochondrial dysfunction. Calcium overload, along with NO-mediated impairment of ERK activation and reduced CREB transcription, contributes to neuronal excitotoxicity. These pathological mechanisms result in neuronal overexcitation or neuronal death, leading to paralysis, neuropathic pain, and muscle spasticity after SCI (Figure created with BioRender.com).

progenitor cells in the dentate gyrus, their application in SCI and related complications is less common.

Ketamine is an NMDA receptor antagonist that primarily provides neuroprotection by inhibiting the extrasynaptic NMDARs [87]. Euler et al. suggested that ketamine has neuroprotective effects on cerebral ischemia in rats but does not have similar effects on ischemic SCI. Therefore, ketamine should not be used for neuroprotection or for similar treatments after SCI [88]. However, Ehrlich et al. found that ketamine significantly mitigates nerve damage caused by ischemia-reperfusion after SCI [89]. Aydoseli et al. Demonstrated that the co-administration of ketamine and quinolyl-valyl-*O*-methylaspartyl-[2,6-difluorophenoxy]-methyl ketone (Q-VD-OPh) effectively prevented necrosis and apoptosis, thereby preventing secondary damage after SCI [90]. Ozkürkçügil et al. found that ketamine can treat overactive detrusors after SCI by modulating the micturition reflex pathway [91]. Chen et al. discovered that memantine mitigates pain by inhibiting the Kir2.1 channel and suppressing the activation of microglia in the mouse spinal dorsal horn [92]. Panthee et al. found that serum ketamine concentrations exceeding 4.5 ng/mL exert spinal protective effects [93]. Ketamine, derived from phencyclidine (PCP), is widely used as an anesthetic. Clinically, it is frequently used as an analgesic, anesthetic, and antidepressant [94,95]. Ketamine functions primarily through the inhibition of the GluN2B subunit. However, their use in patients with SCI has not received sufficient attention. Tai et al. administered ketamine to rats with spinal cord hemisection injuries for 10 days, starting 1-week post-injury. The rats exhibited reduced pain-like behaviors and improved motor function, which could be attributed to its ability to reduce signal transmission via the MAPK pathway, NF-κB, and IL-1β following the injury, thereby restoring the levels of excitatory amino acid transporter 2 [96]. Yu et al. demonstrated that ketamine can effectively protect against and alleviate spinal cord ischemia/reperfusion injury by inhibiting superoxide dismutase (SOD)activity, thereby reducing oxidative stress and related damages after injury [97]. Moreover, Kose et al. reported that S-ketamine effectively reduced the levels of acute-phase lipid peroxidation in rats with SCI, more effectively than methylprednisolone in preventing SCI [98]. Rabi et al. indicated that the local application of 10 % ketamine effectively alleviated neuropathic pain associated with SCI, with high satisfaction reported by most participants [99]. However, the sample size was relatively small, which limits the generalizability of these findings.

5.3. Riluzole

Riluzole is a clinical drug approved by the US Food and Drug Administration for the treatment of amyotrophic lateral sclerosis. It demonstrates high permeability across the blood - spinal cord barrier. When administered in the acute phase after injury, it can effectively inhibit damage propagation and enhances SCI prognosis [100]. It can inhibit post - injury excitotoxicity, modulate KCC2 expression in spinal neurons, and eliminate the rise of intracellular Ca^{2+} [101]. Meanwhile, riluzole can stimulate the M2-like polarization of microglia/macrophages, inhibit inflammatory responses, and improve motor function after SCI [102]. Riluzole exerts neuroprotective effects on SCI by dual modulation of glutamate dynamics, which includes inhibition of presynaptic glutamate release and enhancement of astrocytic glutamate reuptake. This dual action attenuates glutamate-induced excitotoxic neuronal death following SCI. Riluzole has been studied in preclinical SCI research for years and is deemed safe in acute SCI treatment [103,104]. Current research shows that riluzole benefits SCI patients by blocking acute-phase neuronal pathological changes, but there's insufficient clinical evidence for its chronic phase application. Additionally, application of riluzole in neuropathic pain is now widely researched [105]. However, there is no conclusive evidence demonstrating its efficacy for SCI - related neuropathic pain. The multicenter randomized controlled RILUSCI trial, conducted by Cotinat et al., provided the first clinical evidence supporting efficacy of riluzole in alleviating muscle spasticity in patients with chronic SCI [106].

As a highly promising drug with a favorable safety profile, Riluzole has already been recognized for its neuroprotective effect in the acute phase of SCI. Further exploration of its clinical application value during the chronic phase could be a highly meaningful research direction.

5.4. Others

Neramexane (MRZ2/579) and dextromethorphan (DM), newly developed NMDA receptor antagonists, exhibit some adverse

effects in clinical trials related to neuroscience [107]. D-AP5 inhibits the excitatory effects of NMDARs by blocking GluN2A, thereby preventing LTP [108]. Felbamate is a non-competitive GluN2B antagonist that inhibits Ca^{2+} influx and NMDA receptor activity and has been approved by the US Food and Drug Administration for treating epilepsy [109]. Neto1 is a TMD that forms a part of the NMDA trafficking complex. Neto1 contains a CUB domain and interacts with the extracellular structure of GluN2 and the synaptic protein PSD95, which binds to receptors on the cell membrane [110]. Ng et al. found that the loss of Neto1 reduces GluN2A expression, leading to negative effects on hippocampal LTP, complex learning, and memory [111]. In addition, Neto1 protein regulates the expression of KA receptors in nociceptive neurons of the dorsal root ganglia, which can modulate the presynaptic release of glutamate in spinal synapses. Wyeth et al. found that deletion of Neto1 alters the composition of NMDA receptor subunits by modulating mossy-fiber-CA3 (MF-CA3) synaptic currents, affecting the recruitment of NMDARs [112].

The endogenous co-agonist of NMDARs, glutamate, can synaptically modulate D-serine, which improves the integrity of brain circuit development, increases synaptic density, and enables rats to possess more compact visual receptive fields [113]. However, D-serine increases NP after traumatic SCI by upregulating the expression of NMDARs. Decreasing D-serine levels can inhibit central sensitization, suppress NMDA receptor-induced pain sensitization, degrade D-amino acid oxidase, and trigger nociceptive responses, leading to hyperalgesia [114]. PCP can be considered an Mg^{2+} blocker. Through non-competitive antagonism, PCP blocks Ca^{2+} influx through NMDARs, thereby preventing neuronal depolarization and inhibiting the activation of downstream signaling cascades [115].

6. Conclusion

The regulation of synaptic plasticity by NMDARs following SCI is critically important and offers promising potential as a therapeutic target for SCI and associated complications. By inhibiting excitotoxicity resulting from excessive NMDA receptor activity post-injury, we can potentially reduce secondary damage at the injury site and prevent maladaptive plasticity. NMDARs play key roles in modulating synaptic transmission and plasticity.

This paper provides a comprehensive overview of research on NMDARs in neurological diseases and SCIs. This highlights that the current application of NMDARs as regulatory targets in SCI research is relatively limited, with researchers typically focusing on their roles in NP following SCI. Addressing abnormal changes in NMDARs following SCI could positively impact various complications and offer effective management strategies. This underscores the therapeutic potential of NMDA receptor regulation in treating patients with SCIs and associated complications.

Overall, NMDA receptor inhibitors, inverse agonists, and related drugs can improve the prognosis and enhance the quality of life of patients with SCI. Future research should focus on developing efficient treatment strategies with minimal side effects that can be widely applied clinically. This not only promises better treatment options for SCI patients but also brings new breakthroughs to this field of research. Through continued in-depth studies, we hope to offer safer and more effective treatment choices for SCI patients in the near future.

Author contributions

Han Gong: Writing– review & editing. **Zuliyaer Talifu:** Literature search. **Xin Xu:** Literature search. **Chun-Jia Zhang:** Literature search. **Yu-Zhe Sun:** Literature search. **Zhao-Ming Yue:** Literature search. **Jia-Sheng Rao:** supervision. **Liang-Jie Du:** for its technical support and Elsevier's WebShop for assisting with the proofreading of this manuscript.

Declaration of competing interest

I would like to declare that the work described was original review that has not been published previously and is not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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