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Review

N-Methyl D-Aspartic Acid Receptors: An Overview

Dilek Daşdelen[1], Aylin Kayaaltı[1], İlknur Altuntaş[1], Oytun Erbaş[1]

ABSTRACT

In the human brain, glutamate is the primary excitatory neurotransmitter and is widely distributed in the central nervous system. The vast majority of excitatory neurotransmission in the mammalian central nervous system is mediated by glutamate and its receptors, mainly ligand-gated ionotropic glutamate receptors (iGluRs). N-methyl D-aspartic acid receptors (NDMARs) differ from other iGluRs in that they exhibit voltage-dependent blocks by $Mg2^{+}$, provide high permeability for $Ca2^{+}$, and require simultaneous binding of glycine and glutamate for activation. They are widely distributed at all stages of development and are critically involved in normal brain function, including neuronal development and synaptic plasticity. Therefore, NMDAR dysfunction causes various neuropsychological disorders and diseases. In this review, the properties, working principles, and role of NDMARs in neurodegenerative disorders were explained.

Keywords: Glutamate, ionotropic glutamate receptors, NDMA receptors, neurotransmitters

N-methyl D-aspartic acid receptors (NDMARs) represent one of the ligand-gated non-selective ionotropic glutamate receptors (iGluRs), which prevent high density in the hippocampus and cerebral cortex and play very important physiological and pathophysiological roles in the central nervous system (CNS).[1] The primary stimulant neurotransmitter in the mammalian CNS is glutamate, also known as glutamic acid, which can attach to channel receptors (ionotropic) as well as intracellular signaling pathways (metabotropic).[2-4]

Metabotropic glutamate receptors (mGluRs) are G-protein-bound receptors that exert modulating effects on neuronal transmission. Ionotropic glutamate receptors, on the other hand, belong to ligand-gated ion channels, which play an important role in rapid neuronal signaling.[2] Based on the pharmacological properties of iGluR channels, it has been classified into three major receptor channel subtypes: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subtype, kainate subtype, and N-methyl D-aspartic acid (NMDA) subtype.[5] All iGluRs are ligand-gated ion channels permeable to cations.[6] Glutamate is sufficient for the activation of AMPA and kainate receptors. For activation, NMDA receptors exhibit voltage-dependent Mg^{2+} block, high Ca^{2+} permeability, and require simultaneous binding of co-agonists glycine (D-serine) and glutamate. These features distinguish NDMARs from AMPA/kainate receptors.[7] They are localized to the postsynaptic membrane but can also be expressed on presynaptic membranes.[8,9] Binding of glutamate and glycine to their sites on the NMDAR complex opens a cation-permeable pore responsible for postsynaptic depolarization. When NMDARs and other members of the ionotropic glutamate family (AMPA/kainate) are activated, they allow the passage of Na^{+} ions into the cell and K^{+} ions out of the cell, creating a short-lived depolarization called the excitatory postsynaptic potential (EPSP).[2] Unlike the other two subtypes of iGluRs, NMDAR ion channels can mediate significant Ca^{2+} influx during excitatory postsynaptic currents due to both high Ca^{2+} permeability and their long-lasting processes, affecting multiple intracellular signaling and processing systems.[2,7]

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey

Correspondence: Dilek Daşdelen. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: dilekdasdelen@gmail.com

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Short-term stable NMDAR-mediated Ca^{2+} influx leads to long-term potentiation of synaptic efficiency, while less pronounced Ca^{2+} influx for longer periods may cause long-term depression.[7] The NMDARs play a role in a variety of physiological functions, and their proper functioning is crucial for cellular homeostasis. Therefore, any deterioration in their functions may lead to the emergence of neuropsychiatric or neurological pathologies.[10,11] The function of NMDARs generally declines with age, possibly contributing to the decreased plasticity that leads to learning and memory loss.[3,10] For this reason, various different pathologies such as Alzheimer's disease (AD)[12], amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease (PD)[13], schizophrenia (SCZ), and major depressive disorder (MDD) are associated with NMDARs.[10]

STRUCTURE AND FUNCTION OF NMDA RECEPTORS

The majority of NDMARs are heteromeric complexes found not only on the postsynaptic membrane but also on the presynaptic side of glutamatergic synapses in the CNS.[14] While receptors located at presynaptic locations contribute to neuroplasticity and synaptic transmission, receptors located at postsynaptic locations also contribute to the regulation of plasticity.[15] The genes GRIN1, GRIN2, and GRIN3 code for NMDA receptors and their subunits. Various NDMA receptor subtypes affect the biophysical, pharmacological, and signaling properties of the NMDA receptor.[6] Mutations in GRIN1 (encoding GluN1 subunit), GluN2B, and GluN2D expressed during embryonic development exhibit more severe clinical phenotypes, including severe intellectual disability and developmental delay, compared to GluN2A mutations.[9] The NMDA receptors consist of two GluN1 obligate subunits encoded by a gene, eight variants originating from alternative splicing, and two regulatory subunits including the glutamate binding site.[14] These regulatory subunits are encoded by different genes. There are four GluN2 subunits (GluN2A, GluN2B, GluN2C, and GluN2D) encoded by four different genes, and two GluN3 subunits (GluN3A and GluN3B) encoded by two other genes.[6,14] The NMDA receptors require two different types of ligand molecules, glutamate, and glycine, for activation. Binding sites for glycine and glutamate are on two separate NMDAR subunits, GluN1 and GluN2, respectively.[16] Functional NMDARs are heterotetramers containing two GluN2 or GluN3 subunits together with two obligate GluN1 subunits, and mutations in GRIN1 have a significant effect on neuronal activity.[9,17]

Expression of functional recombinant NMDARs in mammalian cells is associated with at least one GluN1 subunit. and requires co-expression of a GluN2 subtype.[18] GluN3 subunits (GluN3A and GluN3B) can form functional receptors by combining with GluN1 subunits without including GluN2 subunits.[1] There are significant differences in both developmental and regional expression levels of glutamate-binding GluN2 subunits (GluN2A-D).[7] Receptors containing GluN2A have a much faster deactivation time than other GluN2 subtypes and are also less sensitive to glycine and glutamate than other subtypes.[19] GluN2A and GluN2B are major regulatory subunits in CNS regions related to cognitive functions such as the hippocampus and prefrontal cortex. During prenatal life, NMDA receptors containing the GluN2B subunit predominate, and GluN2B is the main regulatory subunit expressed throughout embryonic development in studied mammals. Early in postnatal life, there is an increase in GluN2A expression in both transcription and translation, while GluN2B expression remains low and stable. As a result, the GluN2A/GluN2B ratio increases during this period known as the NMDAR developmental transition.[14] GluN2A and GluN2B subunits are highly expressed in the cortex and hippocampus, while GluN2C is predominantly limited to the cerebellum, and GluN2D is limited to regions in the midbrain.[20] However, the physiological roles of the glycine-binding GluN3 subunits have been clarified recently. It is thought that NMDA receptors containing GluN3 are responsible for specific permeability properties and magnesium sensitivity.[2]

All subunits have a significant level of homology and are highly related in structure to a protected area organization. An extracellular amino-terminal domain (ATD) is bound to an extracellular ligand-binding domain (LBD) that binds to a transmembrane domain (TMD) forming the ion channel. The transmembrane helices in turn communicate with an intracellular cytoplasmic C terminal domain (CTD).[17] The C terminal domain regulates receptor trafficking and intracellular signaling through protein-protein interactions. In addition, the CTD is the only one unaffected by allosteric modulators.[21] S1 is the peptide sequence between the ATD and the first membrane-associated domain (M1) and S2 is the segment between the third and fourth membrane-associated domains (M3 and M4). The ligand binding domain forms a similar bilobed structure (referred to as D1 and D2 according

to their constituent regions) where two extracellular segments (S1 and S2) form the two halves of the capped structure.[25] The S1 region is a highly conserved domain involved in significant interaction with the carboxylate of the ligand via an arginine residue. Conversely, the S2 region is less conserved across different subtypes; this allows the production of particularly subtype selective ligands.[2] The energy provided by closing the LBD triggers the receptor to undergo a series of conformational changes that ultimately open the ion channel pore.[26] Combined closure of GluN1 and GluN2 LBDs allosterically transmits a TMD change corresponding to a higher probability of open channels.[25]

Channel activation of the NMDARs requires simultaneous binding to glutamate and glycine binding sites, including glutamate binding sites formed by GluN2 subunits and glycine binding sites provided by GluN1 and GluN3 subunits.[23]

The NMDA receptors composed of GluN1/GluN3 require only glycine for activation. Some other co-agonist molecules can activate NMDA receptors such as L-serine, D-alanine, and L-alanine.[20] The NMDA receptors channel is blocked by Mg^{2+} at the neuronal resting membrane potential, resulting in decreased permeability to Ca^{2+} and inhibition of NMDA receptor-mediated currents.[10,23] Postsynaptic depolarization induced by the activation of AMPA receptors reverses Mg^{2+} blockage and provides Ca^{2+} flow.[23] Since the NMDA receptor is a non-selective cation channel, its activation and opening result in a simultaneous influx of Na^{+} and Ca^{2+} ions and an influx of K^{+} ions, and a significant amount of Ca^{2+} enters neurons.[1,20] Numerous intracellular signaling and processing systems are affected by the intracellular passage of Ca^{2+} ions. Ca^{2+} influx through NMDA receptors can induce long-term potentiation (LTP), a long-term improvement in signal transduction thought to play a critical role in regulating synaptic plasticity, a cellular mechanism underlying learning and memory. However, excessive Ca^{2+} intake may cause neuronal cell death by activating various Ca^{2+}-dependent proteolytic enzymes such as calpains and endonucleases.[2]

EFFECTS OF NMDA RECEPTORS

The N-methyl-D-aspartic acid receptors play a critical role in synaptic plasticity and transmission, and overstimulation of glutamate receptors, especially NMDA type, may cause excitotoxic effects on neurons.[18] The presence of NMDARs in both extrasynaptic and presynaptic locations plays a role in neuronal survival and activation of protective genes. These receptors also play an important role in synaptic plasticity, the molecular mechanism underlying learning, and memory.[27,28] Due to their important role in excitatory neurotransmission, disruption of normal signaling via iGluRs plays a direct and indirect role in a wide variety of neuropathological disorders and diseases such as MDD, SCZ, PD, AD, HD, multiple sclerosis, epilepsy, and brain injury.

ALZHEIMER'S DISEASE

Alzheimer's disease is a type of dementia in the aging population and is also the most common form of dementia.[14,18,29] Dementia is a general term used to indicate the loss of memory and other cognitive abilities that is severe enough to interfere with people's daily activities.[18] Alzheimer disease progression has been associated with gradual damage to function and structure in the hippocampus and neocortex, which are vulnerable brain areas related to memory and cognition.[14,29] Excessive NMDAR activity causes excitotoxicity and supports cell death, which underlies a potential neurodegeneration mechanism that occurs in AD. [27] Neuropathology of AD is characterized by the accumulation of insoluble amyloid protein resulting from amyloidogenic processing of a much larger metalloprotein - amyloid precursor protein (APP), which routinely leads to the formation of extracellular neuritic amyloid plaques containing the amyloid beta (Aβ) peptide. Other important pathological features include misfolded, abnormally phosphorylated microtubule-associated unit (tau) protein, astrocytosis and microgliosis, inflammatory changes, oxidative stress, and neurofibrillary tangles (NFTs) composed of neuropil threads with them.[30,31] In aging, the intracellular redox state mediates a shift in Ca^{2+} regulation, including NMDAR hypofunction to alter synaptic plasticity and increased Ca^{2+} release from intracellular stores. NMDA receptors are one of the most highly regulated receptors in the nervous system, such that a number of mechanisms may act alone or in combination, underlying the decrease in NMDA receptor-mediated synaptic responses during aging.[32]

Cognitive impairment of AD is closely related to synaptic plasticity, in which NMDARs play a critical role.[29] Extra-synaptic NMDARs have been found to play a role in AD neuropathology and regulation of Aβ production. Overstimulation of NMDA receptors via glutamate excitotoxicity is thought to be largely responsible for Aβ-mediated death in AD and other diseases associated with progressive neuronal loss.

Current understanding indicates that apoptosis mainly damages acetylcholine-containing neurons and glutamate-containing neurons and is the main cause of brain cell death in AD. Currently, there is no definitive cure for AD, but treatments are available for the symptoms. Existing drugs such as galantamine, rivastigmine, donepezil, and memantine can delay the worsening of dementia symptoms and improve the quality of life of patients.[18] Memantine, a drug that blocks NMDARs, is widely used in the treatment of AD patients, although its mechanism is still controversial. Memantine is a low-efficacy NMDA receptor antagonist approved by the Food and Drug Administration (FDA) for the treatment of AD patients.[29] Memantine's mechanism of action includes noncompetitive inhibition of the NMDA receptor. The drug specifically binds to cation channels controlled by the NMDA receptor. Neurodegeneration is triggered by a persistently high amount of glutamate in the brain of dementia patients, which overturns the blockade of voltage-dependent NMDA receptors via Mg^{2+} ions. This can successfully stop the continuous flow of Ca^{2+} ions into cells via NMDA.[18] In clinical studies, memantine has shown significant benefits for AD patients in aspects of cognition such as language, memory, praxis, functional communication, and activities of daily living.[29,33]

PARKINSON'S DISEASE

Parkinson's disease is a chronic neurodegenerative disorder characterized by motor and non-motor symptoms. Typical clinical findings of PD are motor control disorders such as tremors, muscle stiffness, and bradykinesia.[34,35] The pathological feature of PD is the loss of dopaminergic neurons and the emergence of Lewy bodies in the nigrostriatal system.[30,36] Other areas affected in PD are the hypothalamus, entorhinal cortex, locus coeruleus, hippocampus, and amygdala.[37]

Abnormal glutamate signaling and alterations in glutamatergic transmission play a role in the pathophysiology of PD. Activation of NMDA receptors requires co-agonist binding of glycine/D-serine and glutamate; therefore, antagonists that disrupt co-agonist binding effectively block NMDA activity. Hyperphosphorylation and consequent overactivation of NMDA receptors have been identified in PD and cause worsening of PD.[34] Subtypes of NMDA receptors contribute to the pathogenic process in PD by playing a role in excitotoxic processes.[38] Thus, NMDA receptors are a class of excitatory amino acid receptors that have several important functions in the motor circuits of the basal ganglia and are seen as important targets for the development of new drugs to prevent or treat PD. The most effective symptomatic treatments are those that replace dopaminergic stimulation using dopamine L-3,4-dihydroxyphenylalanine (L-DOPA or levodopa) biosynthetic precursor or direct agonists of dopamine receptors such as pramipexole or ropinirole.[39,40]

MAJOR DEPRESSIVE DISORDER

Major depressive disorder, major depression, or clinical depression is an important public health problem and is one of the most common forms of psychopathology.[41] There is evidence that glutamatergic neurotransmission dysfunction is involved in the pathophysiology of MDD, particularly through NMDARs. The majority of neurons and synapses in brain regions and circuits that mediate complex cognitive-emotional behaviors use glutamate as a neurotransmitter, and long-term changes in these areas and circuits represent the biological basis of mood disorders.[23] Depression is associated with neuronal atrophy and decreased synaptic connections in the prefrontal cortex, limbic brain regions, and hippocampus.[42]

Glutamate is an important excitatory neurotransmitter in the CNS as well as a key player in many brain functions. Abnormalities in glutamatergic neurotransmission play a role in the development of psychiatric disorders such as schizophrenia, bipolar disorder or depression, and MDD has reported abnormal glutamate levels in studies.[40-43] Therefore, the glutamatergic system plays an important role in the neurobiology and treatment of depression.[42] Ketamine, an NMDA receptor antagonist, is used as an antidepressant in the treatment of this disease. This non-selective NMDA antagonist exhibits a rapid and robust single fraction and has high therapeutic efficacy, especially in treatment-resistant majors.[44] Ketamine induced glutamate burst in synaptogenesis and increases the release of brain-derived neurotrophic factors, thus causing the synthesis of synaptic proteins required for the formation of new spine synapses.[42]

The most important positive effects of ketamine in the treatment of depression are its rapid, robust, and continuous antidepressant effect in treatment-resistant depression (TRD) and bipolar depression.[43] Recently, rapastinel (GLYX-13), another treatment targeting the glutamatergic system, has been investigated as a fast-acting antidepressant for TRD, with an effective profile that increases cognitive

function and does not produce psychotomimetic side effects.[45]

SCHIZOPHRENIA

Schizophrenia is a chronic mental disorder that affects 0.5-1% of the population worldwide and generally occurs in late adolescence and early adulthood.[24] Different perspectives emphasize that genetic, developmental, and environmental factors are involved in the etiology and pathophysiology of SCZ.[46] The symptoms and manifestations of SCZ are complex and varied and are generally divided into three titles.[47] It is characterized by positive symptoms (hallucinations, delusional behaviors, and thought disorder), negative symptoms (anhedonia, social withdrawal, speech impoverishment, and apathy), and cognitive dysfunction (capacity reduction).[48] In addition to memory and attention deficits, SCZ patients also have impairments in various cognitive functions such as lack of insight, reasoning, and executive functions.[47]

Abnormalities in glutamatergic neurotransmission mediated by NMDA play a role in the pathophysiology of SCZ, although the exact mechanisms are unknown.[49] Phencyclidine and ketamine, a subclass of noncompetitive NMDAR antagonists hypothesized to be mediated by the NMDAR in SCZ, have been observed to induce behaviors reminiscent of the three symptoms of SCZ such as positive, negative, and cognitive in human subjects.[50]

Genetic mutations encoding the protein structure of any of the NMDA receptor subunits, which are a key element in guiding glutamate neural pathways, may allow NMDA hypofunction and the resulting symptoms of SCZ.[51] Post-mortem tissue studies were also conducted to examine the effect of NMDA receptors in SCZ, and depending on the brain region examined and the methodology used, decreased cortical expression of NMDA receptor subunits was observed in patients with SCZ.[11] A possible association between SCZ and polymorphisms of the NMDA receptor subunit GRIN2B gene has also been described. The GluN2C NMDARs are involved in fear conditioning and memory consolidation, and the expression of this subunit was found to be significantly lower in patients with SCZ.[48] In addition, rare mutations were detected in 25 of the patients in an exon sequencing of six GRIN subunits (excluding GRIN2B) performed in 370 Japanese SCZ patients, indicating that extremely rare variants in GRIN genes contribute to the genetic risk of SCZ.[50]

Currently available antipsychotics treat positive symptoms but are largely ineffective at treating negative symptoms and cognitive dysfunction. D-cycloserine (DCS), a GluN1 glycine region partial agonist, has been subjected to extensive preclinical and clinical studies for various neuropsychiatric disorders.[48] There is hope for further development of DCS as a treatment for SCZ based on clinical findings.

In conclusion, experimental and bioinformatic studies have provided us with more detailed information about the organization of NMDA receptors, helping us to better understand its role in the CNS. As research on the roles of NMDA receptors in neuronal development, cognition, behavior, and nervous system pathology deepens, the search for treatments for many neurological diseases involving NMDA receptors will accelerate. In addition, more specific studies should be conducted on the subunits of the mechanism of action of more agonist and antagonist compounds in order to develop treatments against the diseases caused by NMDA receptors.

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