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Review Article

Exploring the role of NMDA receptor in memory

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Abstract

N-Methyl-D-aspartate (NMDA), a receptor belonging to the family of ionotropic glutamate receptors (iGluRs), plays various physiological and pathological roles in the central nervous system (CNS). Various other receptors located in the midbrain, such as NMDAR2B (NR2B), contribute to fear memory rather than spatial memory. Furthermore, NMDA-receptor channels produce calcium entry, essential for LTP induction; they also produce voltage-dependent excitatory postsynaptic potentials (EPSPs). Protein kinase C (PKC) activation is involved in the long-term physiological processes of LTP. This review aimed to determine the pharmacological properties of NMDA in front of native neurons.

Keywords: Receptor; ion channels; ligand; memory specific; neurons

Introduction

N-methyl-D-aspartate (NMDA) receptors, one of the most predominant ionotropic glutamate receptors (iGluRs), belong to the L Glutamate family, which regulates the majority of excitatory neuronal transmission in the brain [1]. NMDAR play an essential role in the physiological and pathological processes of the central nervous system (CNS) [2,3]. NMDARs are tetrameric ion channels and, together with different iGluRs, such as kainate and α-amino-3-hydroxy-5-methylisoxazole-4-isoxazole propionic acid (AMPA), are analytical in the quick modulation of synaptic plasticity with long-term depression (LTD) and long-term potentiation (LTP), which is essential for memory as well as learning function [4-7]. NMDA exhibits unique features that differentiate it from other ligand-gated iGluRs, such as increased permeability towards Ca^{2+} voltage-sensitive obstruction by extracellular Mg^{2+} and unusually delayed 'activation/deactivation' kinetics [7]. Furthermore, changes in endogenous physiological substances and redox states modulate NMDA receptors via protons [8]. NMDAR is most permeable to calcium, and through the outpouring of intracellular incidents that may trigger LTP and LTD of synaptic currents, the channel contributes to calcium influx [9,10]. Calcium influx via NMDAR is stimulated by the relief of Mg^{2+} and agonist binding, which ultimately modulates synaptic strength through a Ca^{2+} activated signaling cascade [11]. In ischemia at the time of stroke, intense NMDA receptor activation leads to cell death and increased Ca^{2+} entry [8].

Moreover, polyamines and extracellular Zn^{2+} act upon the receptor to adjust its behaviour. Over the past few years, various NMDA subunits have been discovered. The International Union of Pharmacology Committee has released new guidelines on receptor nomenclature and drug classification to normalize the classification and nomenclature of NMDAR [12]. NMDARs function as heteromeric assemblies comprising two subunits from seven homologous genes: GluN1, GluN2A-GluN2D, and GluN3A-GluN3B [13-16]. The role of different NMDA receptors is crucial for understanding normal transmission in the CNS [17]. NMDAR subunit expression differs with brain recognition and activity during the ontogenic period [18-24]. From a functional viewpoint, the various roles of individual NMDA subunits and NMDA receptor subtypes are a major challenge [25].

Function of NMDAR

NMDARs are glutamate-gated and possess high calcium permeability to mediate synaptic transmission and promote learning and memory. Excitatory neurotransmission is fundamental to the physiology of the CNS and is maintained by NMDARs [26]. NMDARs play a crucial role in the pathophysiology of different psychiatric and neurological disorders [27]. Functional NMDA receptors are formed by two GluN1 and two GluN2 arranged as a dimer of dimers that works at most of the synapses [28]. With the extensive diffusion of NMDARs in the CNS and from the embryonic stage to adulthood, GluN1 is pervasively expressed [29-31]. At most synapses, excitatory postsynaptic currents (EPSCs) are activated by the release of glutamate, which is described by two exponential elements analogous to the AMPA (an iGluR) [32] and NMDARs [33]. Stimulation of NMDARs mediates a slower component in parallel with the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, an iGluR) as well as kainate receptors [34-37].

Subunit composition diversity and expression

The functional diversity of NMDARs with unique properties was reported almost 30 years ago in a study of neuronal preparations [38,39]. This study demonstrated that natural NMDARs exist in a hetero-oligomeric configuration [40]. The two N1 subunits, two N2A/N2B subunits, one N2A subunit and one N2B subunit of the ionotropic glutamate receptor are responsible for the regulation of synaptic plasticity as well as memory function as shown in Figure 1 [41-43]. To date, seven different subunits have been identified: the GluN1 subunit, four different GluN2 subunits (GluN2A, GluN2B, GluN2C, GluN2D) encoded by four distinct genes, and a pair of GluN3 subunits (GluN3A and GluN3B).

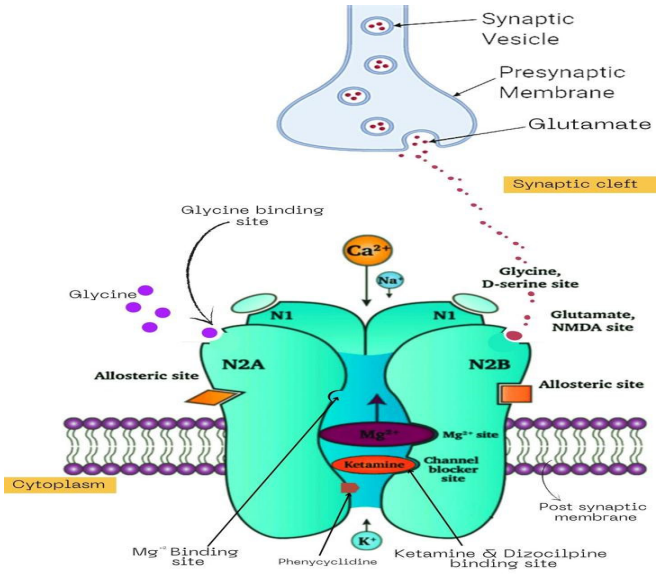

Figure 1. The N-methyl-D-aspartate receptor is an ionotropic glutamate receptor responsible for regulating synaptic plasticity as well as memory function. It consists of two N1 subunits, two N2A/N2B subunits, one N2A subunit, and one N2B subunit. Glutamate (and NMDA) binds to the NMDAR agonist site. Glycine and D-serine bind to the glycine d-serine site. The binding of glutamate and glycine results in the opening of the channel, which further results in the activation of NMDAR. This permits the influx of Na+ and small amounts of Ca2+ and the outflow of K+. Mg2+ blocks NMDAR, and ketamine acts as a non-competitive NMDA receptor antagonist. Inhibition of NMDAR by ketamine hinders the influx of Ca2+ and/ or Na+ ions, thereby preventing neuronal membrane depolarization. The following reduces the probability of a neuronal ring, preventing further propagation of the neuronal signal, neurotransmitter release, or downstream signalling mechanisms.

In the functioning of NMDARs as a hetero-tetrameric unit, GluN1 subunits are mainly associated with GluN2 subunits, or there is an amalgamation of GluN1 and GluN3 subunits [38,39,44]. Moreover, studies have shown that three cDNAs encode new glutamate receptor subunits: NMDAR2A (NR2A), NR2B, and NR2C [45]. NR1 is prominently expressed when compared with the other subunits, and the distribution of NR2A resembles that of NR1 [46]. NR2B is detected mainly in the forebrain, where learning and synaptic plasticity occur. The extracellular region of NMDAR subunits is arranged in a pair of domains that are distributed between functional and structural homologies with two bacterial periplasmic protein families. The N-terminal domain (NTD), along with other bacterial proteins such as isoleucine/leucine/valine-binding protein (LIVBP), displays the sequence affinity instead of The N-terminal domain (NTD), along with bacterial protein isoleucine/leucine/valine-binding protein (LIVBP), displays sequence affinity [47,48]. This domain is an essential component of subunit assembly [49]. The NTD includes specific binding sites for allosteric inhibitors such as ifenprodil and Zn^{2+} in NR2A and NR2B. Ifenprodil is an inhibitor of NMDA receptors, particularly the GluN1 and GluN2B subunits. The TM3-TM4 and pre-TM1 regions were included in the second domain. It manifests sequence affinity with

the glutamine-binding protein of bacteria, which holds the binding site of the agonist. Contemporaneous binding of the dual co-agonists, glycine (or D-serine) and glutamate, is required to stimulate NMDARs. NR1 and NR3 of the agonist binding domain (ABD) bind glycine, whereas glutamate is bound by NR2 ABDs [50,51].

NMDA in the storage of working memory

To store working memory, a memory-specific subset of neurons must be lifted within the prefrontal cortex network [52]. The lifting is sustained by a pulsating process [53], in which active neurons selectively excite each other with the help of recurrent connections. Recurrent excitatory synapses with similar synaptic strength are constantly linked to pyramidal cells. Whenever there is a need to store a memory item, cell subsets are excited with an abrupt informational input corresponding to the external network. This memory item is maintained in the working memory when the active cells are continuously fired after external input cases [54]. The transmission becomes conditional due to voltage dependency on NMDA-receptor channels; glutamate binding is required for transmission, and substantial postsynaptic depolarization is required. Therefore, once an active cell liberates glutamate from another active cell, the NMDA receptor opens from pre-existing postsynaptic depolarization. The emerging inward current inhibits the regular repolarisation process and therefore complements the lifting of these cells. Whenever an active cell liberates glutamate upon an inactive cell, the postsynaptic voltage is almost near the resting potential as a voltage range in which NMDA-receptor channels are not open absolutely and are almost entirely blocked. Global GABAergic feedback inhibition prevents small NMDA-receptor currents in these cells; dormant cells remain inactive [55].

Plasticity of NMDA receptor NR2B subunit in memory

Glutamatergic synapses play a condemning role in brain functions and disease. NMDA and AMPA are crucial for learning-related plasticity and synaptic changes. In the CNS, the action of NMDAR is mainly an activity-dependent coincidence detector. Central synapses are widely known to bear high plasticity, and long-term modifications can provide variable brain functions. To date, two important forms of plasticity have been identified, long-term potentiation (LTP) and long-term depression (LTD). LTP is majorly involved in enhancing synaptic functions in the central areas of the brain, while LTD decreases the potency of synaptic transmission. The mechanism of central LTP differs depending on the induction protocols, input fibers, regions of the CNS, and postsynaptic neurons recorded [56-60].

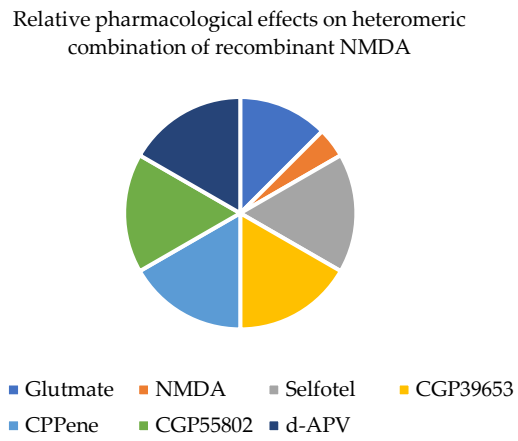

Figure 2. Various actions on the heteromeric combination of rNMDA (recombinant N-methyl D-aspartate receptor. Selfotel- competitive NMDAR antagonist, directly competing with glutamate for binding to the receptor, CGP39653- employed as radioligand to auto radiographically label the NMDA receptor in rat and human brain.

LTP includes many potential functions that play a potent role in brain function in addition to learning and memory [61-64]. NR2B-NMDA is required for synaptic potentiation in several CNS areas. NMDA receptor-mediated currents are performed mainly by NR2A-containing NMDA receptors. Different signaling pathways are recruited for different LTP-inducing protocols. For instance, tetanus stimulation-evoked LTP in the amygdala involves NMDA receptors, whereas the pairing protocol LTP involves L-VGCCs but not NMDARs [65]. Hippocampal LTP involves NR2B-NMDA receptors, which rely on induction protocols [61]. Moreover, NR2B-NMDA receptors have different significance under two protocols: one is fast calcium transients, better than the second protocol, which is slow calcium transients [61]. The heteromeric recombinant NMDA includes various pharmacological effects, and the relative value action with glutamate

antagonists (containing glutamate, NMDA, CGP39653, CPPene, CGP55802, d-APV) under study [66-69] is depicted in Figure 2.

The NR2B-NMDA receptor contributes to fear memory rather than to spatial memory. Recent studies have reported that similar administration of NMDA receptors attenuates fear destruction but not re-destruction recall [70]. Based on various studies of NR2B-NMDA receptors in behavioural learning and memory, several proposals have been made to develop NR2B-NMDA receptor function to enhance memory in low-IQ adults to free patients from memory loss. We are starting to understand how the central synapse undergoes plastic changes during learning [71].

Working of NMDA receptor

LTP induction by amino acids

The NMDAR channel complex plays a fundamental role in several properties, such as the voltage-dependent blocking of its channel by Mg^{2+} [72]. Because of this, NMDA functions as a molecular coincidence detector. The two incidents must occur concurrently to trigger the induction of LTP and the opening of the NMDA channel. There should be enough membrane depolarization to remove Mg^{2+} from NMDA channels at the same time that L-glutamate has, and by binding to NMDA receptors, which leads to the opening of channels [73].

Channel activation depends on neurotransmitter release from the presynaptic membrane and depolarization of the postsynaptic membrane [74]. Following the depolarization of the postsynaptic membrane, Mg^{2+} and the channel are separated, whereas the receptor and transmitter are binding open channels. There is an inward movement of Ca^{2+} into the intercellular spaces [75], thereby assisting as a second messenger for activating the sequence of biochemical reactions, ensuring the demonstration of LTP. The involvement of non-NMDA glutamate receptors demands the stimulation of NMDA receptors, which include AMPA and KA receptors. In the resting state, low-frequency synaptic transmission is regulated by non-NMDA glutamate receptors, which also act as major receptors of sodium ion (Na+) and potassium ion (K+) permeability [76]. The fast component, excitatory postsynaptic potential (EPSP), and the slow EPSP component constituted in NMDA come under the non-NMDA glutamate receptors, which synchronize in the formation of LTP. Due to synaptic transmission, glutamate release from the presynaptic membrane functions concurrently on the NMDAR, AMPA receptor, and KA receptors. Owing to Mg^{2+}, NMDA receptors are usually in a non-active state. With the help of the AMPA receptor channel, the stimulus reaches a certain intensity, which increases Na + and K + and permits adjacent NMDA receptors that are confined in the postsynaptic membrane to depolarize, which ultimately causes the mobilization of Mg^{2+} and therefore assists in the activation of NMDA receptors [76]. Cooperativity, connectivity, and input-particularity are some of the properties of LTP that can be explained easily. For reducing the level of the Mg^{2+} block of the NMDA channel, there is a need for depolarization in the cooperating threshold. Only a few fibers are activated by the 'weak stimuli', which fails to evoke LTP because the invalid input provides a depolarization to the level that could not sufficiently reduce the Mg^{2+} block. When a 'strong' stimulus simultaneously stimulates many fibers, the unblocking of NMDA channel depolarization spreads between neighbouring synapses [74].

The induction of LTP through tetanic activation is hindered by various NMDA antagonists, including antagonists such as MK-801 [77], which play a major role in the channel and at the allosteric glycine site, and mainly at the receptor, such as 2-amino-5-phosphonopentanoate (AP5) [78]. It is very evident that the stimulation of these receptors triggers the process.

The metabotropic glutamate receptor (mGluR) antagonists 2-amino-4-phosphonic butanoate (AP4) and 2-amino-3-phosphonopropionic (AP3) reduce the period of LTP [79,80]. The participation of 2-amino-4-phosphonic butyrate (APB) recognition sites in maintaining LTP was examined in rat hippocampal slices. The activity of APB's D (-)- and L (+)- isomers were tested on orthodromic EPSP, and spike responses were documented extracellularly from CA1 pyramidal cells.

LTP induction by the effect of Calcium ion

Ca^{2+} ions are permeable to NMDA channels [72,81,82]. It is assumed that the dendritic spines are the usual location of the NMDA receptors, and it is considered that to localize the Ca^{2+} signals, spines may take action. Furthermore, Spines limit Ca^{2+} dispersal [83]. Using Ca^{2+} imaging techniques have shown that tetanic stimulation promotes Ca^{2+} inside dendrites and spines [84,85].

Ca^{2+} imaging experiments indicated that the Ca^{2+} ion that pervades NMDA channels increases by releasing Ca^{2+} ions from intracellular stones. The synaptic stimulation of NMDARs in connection with the Ca^{2+} transient is considerably lowered in the presence of thapsigargin or ryanodine [86], drugs that preferably deplete the intracellular Ca^{2+} stored and inhibit Ca^{2+} -induced Ca^{2+} release. To stimulate mGluRs, inositol 1,4,5- triphosphate. (InsP3) is generated along with Ca^{2+} pervading through NMDA channels and is involved in releasing Ca^{2+} from intracellular stores. This suggests that the NMDAR-induced calcium ion (Ca^{2+}) signal can be replaced by releasing Ca^{2+} from intracellular stores [73]. The inward flow of Ca^{2+} into the postsynaptic membrane activates LTP, increasing the concentration of free Ca^{2+} ions in the postsynaptic membrane, which is a required condition for the emergence of LTP [87]. Various calcium-dependent enzymes are activated due to the enhancement in the concentration of free calcium ions (Ca^{2+}) in the postsynaptic membrane. These Ca^{2+} dependent enzymes may lead to further emancipation of intracellular calcium because the concentration of cytoplasm is increased with Ca^{2+}, which activates protein kinases to induce LTP [76].

Protein kinase C (PKC)

PKC is a member of a family of multi-subtype proteins. PKC isozymes are PKC I, PKC II, and PKC III and are calcium (Ca^{2+})-dependent; thus, group A of the PKC gene encodes them [76]. PKC II is mostly distributed in the presynaptic area, whereas PKC III is widely distributed in the postsynaptic area. The liberation of calcium-dependent glutamate is increased by the impulse of PKC, which elevates the inflow of Ca^{2+} ions via voltage-gated channels and the sensitivity of the postsynaptic membrane to neurotransmitters [88]. Due to an increase in the levels of Ca^{2+} ions, the phosphorylation of substrate proteins is activated by PKC, which is most intricate in the long-term physiological method of LTP.

Calmodulin/Calcium (Ca2+)-dependent protein kinase II

Calmodulin/calcium (Ca^{2+}) -dependent protein kinase II (CaMKII) consists of no less than five subunits, where the important allocation (alpha and beta subunits) is situated in the brain, which is an important characteristic of postsynaptic densities [89]. Ca^{2+} activated CaMKII plays a vital role in postsynaptic mechanisms. Following the activation of CaM K II, the subtypes of the AMPA receptor of GluR1 are phosphorylated, and the AMPA receptors are re-organized to synaptic sites from non-synaptic sites. Resting synapses become functional synapses when functional AMPA receptors are activated. Simultaneously, the rise in single-channel α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor synaptic transmission, as well as the evolution of a phosphorylation site, leads to a significant increase in AMPA function [90]. CaM K II phosphorylates AMPA receptors, due to which the changes develop mostly in the postsynaptic area, so therefore, the activity of CaM K II is chiefly by the phosphorylation of pre-and postsynaptic target proteins, and therefore there is the participation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors in induction and maintenance of LTP [76].

Ethanol inhibition of NMDA receptor

NMDA receptor expression increases when treated with chronic alcohol, whereas the excitatory activity of glutamate at the NMDAR is inhibited by acute alcohol [91,92]. Studies have demonstrated that treatment with acute alcohol results in phosphorylation of NMDA receptor subunits [92-94]. Much research in laboratories has reported that NMDA receptor functioning is inhibited by acute alcohol treatment [75]. It is presumed that the harmful outcomes of ethanol, such as developing tolerance to alcohol dependence and alcohol withdrawal syndrome" instead of such as developing tolerance to alcohol, alcohol dependence, and alcohol withdrawal syndrome, are controlled by NMDA receptors. Behavioural effects, such as sedation, cognitive impairment, and anxiolysis, on the intake of acute

ethanol, have been reported due to several changes in the CNS. When ethanol is applied in vivo, NMDA induces neuronal activity that is potentially inhibited in the inferior colliculus and hippocampus [95].

Ethanol sensitivity corresponds very well with ifenprodil, a non-competitive antagonist that preferentially stops the receptor comprising the NR2B subunit [96]. Moreover, ethanol consumption impairs memory at the concentrations associated with mild intoxication" instead of Moreover, ethanol consumption impaired memory at concentrations associated with mild intoxication. Studies suggest that not only the NMDA receptor mediates the effects of ethanol in the brain; against NMDA receptors, there is an anticonvulsant outcome of ethanol [74]. Both NMDARs and GABA are complex in the anticonvulsant activity of ethanol in vivo [97]. Systemic administration of an appropriate pharmacological dose of ethanol (1.5 g/kg body weight) in rats has been shown to suppress NMDA-induced electrophysiological action in the median septum region of the brain [98]. The electrophysiological activity was evoked by NMDA inhibition and examined only in the neuronal segments. An alcoholic dose of ethanol administration (2.5 g/kg body weight) administered via the systemic route suppressed NMDA-induced neuronal activity by only 60 % but completely suppressed the behavioural activity of rats.

In contrast, a dosage of NMDA antagonist MK-801 (0.6 mg/kg body weight) inhibited NMDA-induced neuronal activity but completely increased behavioural activity. These results show that all the behavioural effects of ethanol cannot be caused by the suppression of NMDA-induced activity alone, the suppression of NMDA-mediated synaptic action produces the activity of ethanol on the CNS, and ethanol directly affects NMDAR function [96]. Therefore, ethanol's suppression of NMDA-induced neuronal activity affects various parts of the brain [99,100]. Instead of being expressed as a global effect in the CNS, the response to acute ethanol exposure only is constricted to specific receptors. The sensitivity to NMDA receptor-restricted ifenprodil explains why ethanol antagonizes the NMDA response containing the NR2B subunit only in some neurons [101,102].

Upgradation of intracellular calcium levels was demonstrated in oocytes and HEK293 cells in the ethanol sensitivity of NR1/NR2A receptors [103]. Polyamines and glycine on NMDARs undergo ethanol intervention. NMDAR antagonism at the PCP binding site moderates ethanol-induced effects [104]. The development and intensity of ethanol withdrawal seizures decrease with the administration of the NMDAR antagonist MK-801 without causing drowsiness [105,106]. Continuous exposure to ethanol produces neuropathological substitutions in the brain [92,107]. The inhibition of NMDA receptors through ethanol mainly emphasizes ethanol toxicity.

Effect of hormone and neurotransmitters on NMDA receptor

The functions of the brain and plasticity in cerebral areas are influenced by estrogen throughout life. The action of estrogens in brain areas is implicated mainly in memory, affective states, emotions, and motor coordination [108].

The glutamate system is recognized as the most essential excitatory neurotransmitter in the hippocampal region. The stimulation of glutamate receptor intermediate processes is mainly related to learning and memory, synaptic plasticity [109,110], and epileptogenesis [111-113]. Neuron sensitivity to NMDARs and glutamate is altered by estradiol therapy [114-116] which corresponds to alterations in sensorimotor actions in the cerebellum [117]. Activation of glutamate involves a minimum of three different categories of receptors: the metabotropic glutamate receptor, AMPA/non-NMDA kainate, and NMDA ionotropic receptors [118]. The function of the channel can be regulated by estradiol through the specific binding domains of the ion channel complex/NMDA receptor. These positions mainly consist of 1) the competitive antagonists' site that binds 3-((+)-2-carboxy piperidine-4-yl)-propyl-1-phosphonate (CPP) and (2) the transmitter recognition site that binds agonists such as glutamate and NMDA [119] and CGP 39653 [120]. CPP is a ligand used previously to characterize the binding activity and selectivity of NMDA receptors in rat brain membranes (3H).

In adult female rats, experimental manipulation of estradiol helped researchers in demonstrating "oestradiol-induced changes in the density of postsynaptic sites of excitatory input in the hippocampus, dendritic spines, require activation of NMDA receptors" and discovery of the modifications in

hippocampal dendritic spines [121,122], as levels of estradiol and progesterone frequently oscillate throughout the five-day estrous cycle [122,123]. In CA1 pyramidal cells, the density of dendritic spines was reduced as the circulating ovarian steroids were removed by ovariectomy; this reduction could be avoided or inverted by therapy with estradiol. Oscillations within dendritic spines throughout the estrous cycle matched well with hormone levels; that is, during proestrus, while ovarian steroid levels increased, spine density was highest, and 24 h later, steroid levels decreased to their minimum values throughout estrus. Spine density also decreased to its lowest value. Estradiol persuaded modifications in the density of hippocampal dendritic spines muse alteration in neuronal connectivity by showing that in CA1 pyramidal cells, the density of axospinous synapse dendrites oscillates together with dendritic spine density, both in the case of estradiol manipulation and throughout the estrous cycle [124].

The probability that stimulation of particular neurotransmitter systems plays a role in the reaction of estradiol on hippocampal dendritic spine density was initially noted by the fact that, despite CA1 pyramidal cells, spine density is sensitive to estradiol, in situ hybridization, immunocytochemistry, and in vivo autoradiography that estradiol receptors may be absent in these neurons. The absence of estradiol receptors in CA1 pyramidal cells demonstrated that the action of this hormone on spine density could be mediated obliquely. The inspection that dendritic spines are structurally dependent on their afferents [125,126] proposes that an afferent population may control spine density, the activity of which is sensitive to estradiol.

Action of estradiol on temporal memory requires hippocampal ca1 NMDARs

In slices and cultured neurons of the hippocampus, NMDAR is active at the membrane surface, investigating extrasynaptic and synaptic compartments [127-129]. With the unique qualities of the "irreversible" open-channel blocker (+)-MK-801, a unique method was developed to check whether NMDARs are secured at the growing hippocampal synapses [130]. MK-801 is a strong-affinity label to tag synaptic NMDA receptors because it is a use-dependent antagonist that opens in response to synaptically released glutamate. MK-801 functions as a tag. Therefore, NMDA receptor-mediated synaptic activity is increasingly and irreversibly blocked by replicated synaptic activation in the presence of MK-801 [131].

The sex hormone 17β- oestradiol (E2) is the most powerful physiological regulator of NMDA receptor-dependent memory and hippocampal plasticity. E2 is produced in the hippocampus in both men and women. Sensitivity to NMDAR-mediated synaptic inputs, NMDA receptor agonist binding, and GluN2B-NMDA excitatory post-synaptic current binding is increased by E2 at the molecular level [132-134]. Antibodies directed against extracellular epitopes of NMDAR were used in the hippocampal preparations. This issue has been addressed using single-nanoparticle tracking combined with electrophysiology in hippocampal neurons. Inside the plasma membrane, the NMDA receptor explores wide areas throughout synapses and spreads in a GluN2 subunit-dependent manner [135]. The synaptic distribution of surface GluN2B-NMDA receptors changes quickly through an increase in the surface distribution. The NMDAR surface distribution is acutely blocked and prevents long-term potentiation at hippocampal synapses through anti-GluN1/2 B subunit antibodies generated from immunized animals or encephalitis patients with neuropsychiatric symptoms and memory deficits. As calcium-calmodulin-activated kinases, CaMKII and casein kinase II (CKII) regulate activity-dependent upregulation of GluN2B-NMDAR surface diffusion, which indicates that it demands the direct binding of CaMKII to GluN2B.

Glutamate as a target in schizophrenia

Since NMDA maintains excitatory neurotransmission in the central nervous system, its hypofunction in GABAergic neurons and mutations in its subunits result in neurodevelopmental diseases such as schizophrenia [136,137]. Of all the subunits, NR2 signaling is altered in this disease, and the underlying mechanism is NMDAR hypofunction and anti-NMDAR Ab involvement [138,139]. The first clue for NMDAR hypofunction in schizophrenia arises from the observation that the non-

competitive subclass of NMDA blockers, Ketamine, and phencyclidine (PCP), induce negative, cognitive, and psychotic symptoms in patients with schizophrenia [140-142]. However, a compound of the same class of non-competitive antagonists, which also acts as an open channel blocker, MK-801, induces greater specificity and affinity than PCP and Ketamine [142,143]. However, all open channel blockers do not produce PCP-like behavioural effects, as memantine inhibits NMDA, but it does not induce psychotomimetic symptoms and is well tolerated [144]. Systemic administration of Ketamine, PCP, and MK-801 induces a higher dopamine release, whereas chronic PCP treatment inhibits prefrontal dopamine release [145,146]. These abnormalities in dopamine release are pathological in schizophrenia [147,148]. In addition, the competitive NMDAR antagonists CGS 19755 and CPP induce psychotic symptoms similar to schizophrenia [141]. Therefore, disruption of normal synaptic transmission could lead to the psychotomimetic effect of NMDAR antagonists [141]. NMDAR antagonists mostly affect specific neurons present in cortical and hippocampal sites. The primary target of MK-801 is GABAergic neurons, as systemic injection of the same in mPFC awake rats reduces the firing of GABAergic interneurons. At the same time, disinhibition raises the firing rates in pyramidal neurons [149].

Moreover, Ketamine has a negligible effect on inhibitory postsynaptic currents (IPSC) in pyramidal neurons and significantly suppresses excitatory postsynaptic currents (EPSC) in GABAergic neurons. Ketamine exerts its disinhibitory action by blocking synaptic NMDARs. Thus, NMDARs are more specific to the EPSPs than the pyramidal neuronal cells.

According to recent investigations, metabotropic glutamate receptors (mGluRs) can be used for symptomatic relief in patients with schizophrenia [150]. In animal models, positive allosteric modulators (PAMs) of mGlu5 receptors in preclinical studies have proven effective for all symptom domains. Attractively, the PAMs of biased pure mGlu5 receptors, which cannot amplify the coupling of the following receptors to NMDAR, do not possess neurotoxic effects related to the PAMs of mGlu5. Therefore, this provides a better therapeutic approach to treating the symptoms of schizophrenia. Furthermore, PAMs of mGlu5 receptors regulate the release of dopamine within the stratum, which may play an antipsychotic role. Along with mGlu1 and mGlu5 receptors, mGlu2/3 receptor agonists induce precognitive and antipsychotic effects in rodents and can therefore be used as an effective therapy for schizophrenia in a handful of patients. Interestingly, in rodents, stimulation of mGlu3 receptors enhances cognition, which suggests that an agonist of the mGlu3 receptor/PAM may be useful in treating schizophrenia [151,152].

Conclusion and future perspectives

NMDARs are glutamate-gated ion channels that conciliate most neuronal transmissions in the brain. Obtaining hippocampus-dependent memory, especially for 'episodic-like' hippocampal NMDARs, is essential.

NR2B-NMDA plays an important role in fear memory and is required for synaptic potentiation in various areas of the CNS. The NMDAR channel and Mg^{2+}, Ca^{2+}, and non-NMDA glutamate receptors (AMPA and KA) play a vital role in forming LTP. The action of NMDAR antagonists correlates well with the consolidation and acquisition of spatial memory of CA1 place cells upon long-term stability. One of the major challenges for further studies on NMDA in working memory is to produce a unique paradigm in which place cell activity and memory can be evaluated.

With the help of multidisciplinary studies, which consist of conditional transgenic technology, intelligent behavioural paradigms, and in vivo multi-unit recording, our supreme goal should be to comprehend the neuronal, molecular, and cellular ensemble action mechanisms for learning and memory a step closer, which ultimately turns out to be hippocampus-dependent.

Authors contribution

All the authors have contributed equally.

Declaration of interest

The authors declare no conflict of interest.

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