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REVIEW

The Functional and Molecular Properties, Physiological Functions, and Pathophysiological Roles of GluN2A in the Central Nervous System

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Abstract The NMDA receptor, which is heavily involved in several human brain diseases, is a heteromeric ligand-gated ion channel that interacts with multiple intracellular proteins through the C-termini of different subunits. GluN2A and GluN2B are the two primary types of GluN2 subunits in the forebrain. During the developmental period, there is a switch from GluN2B- to GluN2A-containing NMDA receptors in synapses. In the adult brain, GluN2A exists at synaptic sites more abundantly than GluN2B. GluN2A plays important roles not only in synaptic plasticity but also in mediating physiological functions, such as learning and memory. GluN2A has also been involved in many common human diseases, such as cerebral ischemia, seizure disorder, Alzheimer's disease, and systemic lupus erythematosus. The following review investigates the functional and molecular properties, physiological functions, and pathophysiological roles of the GluN2A subunit.

Keywords GluN2A · Properties · Physiological functions · Pathophysiological roles

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Introduction

The *N*-methyl-D-aspartate receptor (NMDAR) is a heteromeric protein containing two obligate GluN1 subunits and a variety of GluN2 and GluN3 subunits [1]. GluN2A is one of the primary types of GluN2 subunits in the forebrain. The predicted amino acid sequence for GluN2A exhibits a sequence of 1464 amino acids [2]. The 1464-aa predicted sequence encoded by human GluN2A cDNA exhibits a 95.2 % identity with those of its mouse and rat homologues. GluN2A contains four putative transmembrane domains (M1–M4) and a C-terminal extension of greater than 600 residues that provides additional target sites for cellular constituents [3]. The expression of the GluN2A gene is under developmental control. There is an increasing trend for GluN2A expression as development progresses. Synaptic activity and sensory experiences cause this developmental switch from GluN2B- to GluN2A-containing NMDARs [4]. Over the last decade, an increasing number of reports have demonstrated important roles for GluN2A in physiological and pathophysiological processes. The following review provides a summary of recent findings regarding the functional and molecular properties, physiological functions, and pathophysiological roles of GluN2A.

The Functional and Molecular Properties of GluN2A

Electrophysiological Properties

In neurons of the cerebral cortex and regardless of postnatal age, cells expressing GluN2A subunit messenger RNA (mRNA) have faster NMDAR excitatory postsynaptic currents than cells that do not express the GluN2A subunit [5]. Chen et al. reported that GluN1/GluN2A-mediated peak current densities are ~4 times larger than GluN1/GluN2B, and the peak channel open probability is significantly higher for GluN1/GluN2A than for GluN1/GluN2B [6]. The transition of NMDARs from the open to the closed state is also regulated by the GluN2 subunit. Based on calcium-dependent inactivation, GluN2A-containing NMDARs show a reversible inactivation that is highly similar to native NMDARs in cultured hippocampal neurons; however, those containing GluN2B exhibit no significant inactivation [7]. Moreover, recovery from desensitization was faster for GluN1/GluN2A- than for GluN1/GluN2B-containing channels [8]. The above results suggest that GluN2A-containing NMDARs desensitize more and take less time to recover than GluN2B-containing receptors [9]. These electrophysiological properties could enable GluN2A subunits to more flexibly regulate synapse activity.

Domains in the Extracellular Regions of GluN2A

From the N- to C-terminal, the GluN2A subunit contains an N-terminal domain containing a modulatory site that binds Zn^{2+} followed by an agonist-binding domain, a channel-forming domain comprised of four transmembrane segments (M1–M4) and an intracellular C-terminal domain [10]. The extracellular regions of GluN2A include an N-terminal region and an extracellular loop between M3 and M4 [11]. The agonist-binding domain and the extracellular loop form the glutamate-binding site. Although the subunit-specific gating of NMDARs is controlled by the region that is formed by the GluN2 N-terminal domain [12], the interface of the agonist-binding domain dimer between GluN1 and GluN2A could be a major structural determinant that controls the allosteric modulation of GluN2A [10]. Moreover, the N-terminal domains of both GluN1 and GluN2 subunits determine allosteric Zn^{2+} inhibition and the glycine affinity of NMDARs [13]. The extracellular N-terminal domain of GluN2A also contains an endoplasmic reticulum retention signal that can be specifically masked by the N-terminal domain of GluN1α [14].

Signaling Proteins Associated to the Intracellular C-Terminal of GluN2A

The C-terminal of GluN2A provides additional target sites for downstream signaling molecules (Fig. 1). The 1349–1464 amino acid sequence in the C-terminal of GluN2A is responsible for the binding of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [15]. The last three amino acid sequences in the C-terminal of GluN2A binds directly to several neuronal scaffolding proteins, including postsynaptic density protein-95 (PSD-95), postsynaptic density protein-93 (PSD-93), synapse-associated protein 102 (SAP102), and synapse-associated protein 97 (SAP97). Based on these scaffolding proteins, GluN2A could transduce many signal types to its downstream proteins.

Among the scaffolding proteins mentioned above, PSD-95 is the most widely studied. PSD-95, p35, and cyclin dependent kinase-5 (cdk5) can form a complex in synaptosomes [16]. Phosphatase and tensin homolog located on chromosome 10 (PTEN) contains a PDZ-binding motif at its C-terminus, and NMDAR activation triggers a PDZ-dependent association between PTEN and PSD-95 [17]. PSD-95, GluN2A, and PTEN interact with each other at the synapse [18]. The PDZ3 domain of PSD-95 and the SH2 domain of Fyn are responsible for the association between the two proteins [19]. The 43–57 amino acid sequence in the N-terminal region of PSD-95 is essential for the interaction between PSD-95 and Src [20]. Proline-rich tyrosine kinase 2 (Pyk2) can bind to the SH3 domain of PSD-95, and this binding is facilitated by the Src-induced phosphorylation of PSD-95Y523 [21]. PKCα has a classic T/SXV motif (QSAV) and can interact with all three PDZ domains of PSD-95 and SAP102 [22, 23].

Additional scaffolding proteins can also couple the signaling of several proteins. PSD-93 also interacts with GluN2A and with Fyn in the mouse cerebral cortex [24]. A ternary complex assembled by PSD-93 with GluN2A and nNOS also exists in cultured cortical neurons [25]. SAP97 directly associates with GluN2A through its PDZ1 domain, and the CaMKII-dependent phosphorylation of SAP97-Ser-232 disrupts its interaction with GluN2A [26].

Physiological Functions

Synaptic Plasticity

Many studies have indicated that GluN2A is a critical factor that determines the polarity of synaptic plasticity. However, the exact role of GluN2A in long-term potentiation (LTP) and long-term depression (LTD) is still a matter of controversy (Table 1).

With regard to the role for GluN2A in LTP, several research groups have observed opposing results. Following the targeted disruption of the mouse NR2A gene, the LTPs induced by high-frequency stimulation in the hippocampal CA1 and juvenile superior colliculus were significantly reduced [27] and blocked [28], respectively. Furthermore, there was a considerable reduction in LTP in CA1 slices from 3-month-old GluN2A C-terminal-truncated mice, and this

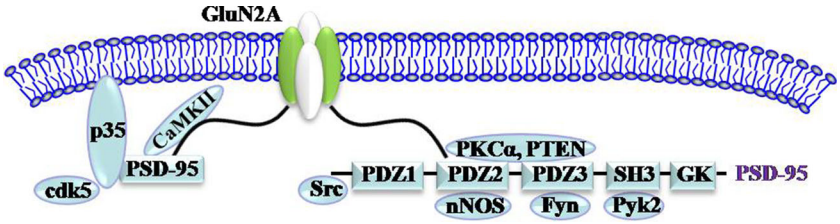

Fig. 1 Signaling molecules associated to the C-terminal of GluN2A. The amino acid sequence in the C-terminal of GluN2A is responsible for the binding of CaMKII and PSD-95. Based on the scaffolding protein PSD-95, GluN2A could transduce many signal types to its downstream proteins. PSD-95, p35, and cdk5 can form a complex in synaptosomes. The N-terminal region of PSD-95 is essential for the interaction between PSD-95 and Src. PKCα, PTEN, nNOS, and Fyn are the PDZ ligands of PSD-95. Pyk2 can bind to the SH3 domain of PSD-95

reduction could be due to impairments in cellular signal transduction events involved in LTP induction [29]. However, using RNA interference (RNAi) and overexpression, Foster et al. found that GluN2A is not essential for LTP that is induced by pairing postsynaptic depolarization to 0 mV with presynaptic stimulation consisting of 200 pulses at 2 Hz [30]. In addition, these researchers determined that the cytoplasmic tail of GluN2A appears to carry inhibitory factors for LTP. However, in these genetic experiments, indirect effects on synaptic plasticity resulting from compensatory mechanisms were difficult to describe. In addition, the stimulations used were also different from other experiments.

Others studies have used pharmacological approaches to study the direct effect of GluN2A on LTP. Several have indicated that the inhibition of GluN2A by NVP-AAM077

Table 1 The role of GluN2A in LTP and LTD

Methods for regulating GluN2A	Animals	Cerebral regions	LTP		LTD		References
			Stimulations	Effect	Stimulations	Effect	
GluN2A knockout	Mice	Hippocampal CA1	2 HFS (100 Hz) or LFS (1 Hz)-HFS (100 Hz)	Reduced	NR	NR	[27]
GluN2A knockout	Mice	Superior colliculus	HFS (20 Hz)	Blocked	LFS (1 Hz)	Unaltered	[28]
GluN2A C-terminal knockout	Mice	Hippocampal CA1	HFS (100 Hz)	Reduced	NR	NR	[29]
GluN2A RNAi	Rats	Hippocampal CA1	PPD-LFS (2 Hz)	Enhanced	NR	NR	[30]
Overexpression of GluN2A+GluN2B RNAi	Rats	Hippocampal CA1	PPD-LFS (2 Hz)	Blocked	NR	NR	[30]
Overexpression of GluN2A	Rats	Hippocampal CA1	PPD-LFS (2 Hz)	Blocked	NR	NR	[30]
GluN2B-RNAi+GluN2B*-2A tail	Rats	Hippocampal CA1	PPD-LFS (2 Hz)	Blocked	NR	NR	[30]
GluN2B-RNAi+GluN2A*-2B tail	Rats	Hippocampal CA1	PPD-LFS (2 Hz)	Restored	NR	NR	[30]
GluN2B-RNAi+GluN2BΔC	Rats	Hippocampal CA1	PPD-LFS (2 Hz)	Blocked	NR	NR	[30]
GluN2B-RNAi+GluN2AΔC	Rats	Hippocampal CA1	PPD-LFS (2 Hz)	Enhanced	NR	NR	[30]
NVP-AAM077	Rats	Hippocampal CA1	HFS (100 Hz) or 3 HFS (100 Hz)	Blocked	LFS (1 Hz) or 3 LFS (3 Hz)	Unaltered	[31]
NVP-AAM077	Rats	Hippocampal CA1	HFS (100 Hz)	Blocked	LFS (1 Hz)	Blocked	[32]
NVP-AAM077	Mice	Lateral amygdala	2 HFS (100 Hz), IN, or EC	Reduced	LFS (1 Hz) or PP-LFS	Blocked	[34]
NVP-AAM077	Rats	Hippocampal CA1	NR	NR	LFS (2 Hz)	Reduced	[36]
NVP-AAM077	Rats	Hippocampal CA1	NR	NR	Chem-LTD	Blocked	[36]
NVP-AAM077	Mice	Nucleus accumbens	NR	NR	3 HFS (100 Hz)	Blocked	[37]
NVP-AAM077	Normal mice	Hippocampal DG	4 HFS (100 Hz)	Blocked	LFS (1 Hz)	Enhanced	[33]
NVP-AAM077	Runner mice	Hippocampal DG	4 HFS (100 Hz)	Blocked	LFS (1 Hz)	Blocked	[33]
NVP-AAM077	P12-P18 mice	Visual Cortical	NR	NR	LFS (1 Hz)	Unaltered	[35]
NVP-AAM077	P21-P28 mice	Visual Cortical	3 HFS (100 Hz)	Reduced	LFS (1 Hz)	Reduced	[35]
NVP-AAM077	P45-90 mice	Visual Cortical	3 HFS (100 Hz)	Blocked	NR	NR	[35]

RNAi RNA interference, *HFS* high-frequency stimulation, *LFS* low-frequency stimulation, *NR* not reported, *PPD-LFS* pairing postsynaptic depolarization to 0 mV with presynaptic stimulation consisting of 200 pulses at 2 Hz, *PP-LFS* 1 Hz for 15 min, 2 trains, 40-ms interval paired-pulse-LFS, *Chem-LTD* 20 μM NMDA for 5 min

blocked or reduced LTP in the hippocampal CA1 [31, 32], dentate gyrus [33], lateral amygdala [34], and visual Cortical [35]. Although these results are highly consistent, there are two issues worth addressing. One is that the selectivity of NVP-AAM077 drops to tenfold for rodent GluN2A over GluN2B; at the concentrations used, NVP-AAM077 also partially blocks GluN2B. The second is how to interpret the effects of NVP-AAM077 on GluN1/GluN2A/GluN2B NMDARs.

Most studies concluded that GluN2A plays a critical role in LTD. NVP-AAM077 can prevent LTD in hippocampus [32, 36], lateral amygdala [34], and nucleus accumbens [37]. However, several conflicting results have been reported. Liu et al. showed that the preferential inhibition of GluN2A did not affect the appearance of LTD [31]. Vasuta et al. found that exercise can significantly alter the contribution of GluN2A to LTD and that NVP-AAM077 prevented LTD in running but not control animals [33]. It was also observed that LTD can be reduced by NVP-AAM007 in P21-P28 mice but not in P12-P18 or P45-90 mice [35].

In view of the switch of GluN2B to GluN2A during development and the dominant expression of GluN2A in synapses, GluN2A could play an important role in the production of both LTP and LTD.

Learn and Memory

Behavioral assays have demonstrated an important role for the GluN2A subunit in mediating physiological functions, such as learning and memory.

Studies have shown that GluN2A is involved in the learning process, and spatial or discrimination learning impairments have been observed in mice lacking the GluN2A subunit [27, 38]. GluN2A is also required for vestibular-cerebellar motor learning through potentiation at the mossy fiber to granule cell synapse [39]. The blockade of GluN2A in the dorsal striatum impairs the learning of complex motor skills [40].

There is increasing evidence to indicate that GluN2A is closely related to hippocampal-dependent spatial memory. Mice lacking GluN2A exhibit impairments in rapidly acquired spatial working memory [41] and also perform poorly in spatial pattern separation tasks [42]. The suppressed expression of GluN2A by peroxisome proliferator-activated receptor α (PPARα) knockdown rendered animals markedly impaired in their consolidation of spatial memory, whereas the introduction of PPARα to the hippocampus of PPARα-null mice increased hippocampal GluN2A and improved spatial learning and memory [43]. Mice treated with dexamethasone for 21 consecutive days showed significantly impaired spatial memory during the Morris water maze task, which could be due to the reduction in the expression of GluN2A/B [44].

GluN2A also plays an important role in fear memory. Contextual fear conditioning is impaired in GluN2A C-terminal-truncated mice [29]. The expression of GluN2A in the amygdala [45], hippocampus [46], retrosplenial cortex [47], or prelimbic medial prefrontal cortex [48] contributes to contextual or trace fear memories. The coactivation of GluN2A and GluN2B induces resistance to fear extinction, and patients with posttraumatic stress disorder could benefit from the antagonism of specific GluN2 subunits [49].

Several results have indicated an important role for GluN2A in auditory activity. Sensory and neuronal injury affects the expression level of GluN2A protein in rats [50]. GluN2A transcripts increase significantly in both the IMAN and Area X of zebra finches, and this increase is critical for vocal learning during the song-learning period between posthatching day 20 and 40 [51].

Pathophysiological Roles

NR2A has been implicated in many common human diseases, such as cerebral ischemia, seizure disorder, Alzheimer's disease, systemic lupus erythematosus, depression, schizophrenia, Parkinson's disease, Huntington's disease, anxiety, and bipolar disorder.

Cerebral Ischemia

Excitotoxicity induced by the overactivation of NMDAR is a critical mechanism that contributes to neuronal damage during cerebral ischemia. It is generally accepted that GluN2B has neurotoxic effects; however, the contribution of GluN2A to excitotoxicity remains controversial.

The regular pattern of GluN2A expression following cerebral ischemia changes could be increase–decrease–increase over time. At early time points, such as 0.5 h for bilateral common carotid artery occlusion in gerbils [52, 53] and 3 h for middle cerebral artery occlusion in rats [54], the expression of GluN2A was increased. From 6 to 24 h after challenge, especially in the rat four-vessel occlusion model, the level of GluN2A was decreased [55–57]. After 48 h, there was a reversal in GluN2A expression [57, 58], and at the 1-week time point, the expression of GluN2A decreased again [57]. The age of rats also influences the expression of GluN2A [59]. In addition, the expression of GluN2A in the penumbra was significantly increased 3 h after focal cerebral ischemia and was then reversed after 24 h [60].

Following cerebral ischemia, there exists a persistent phosphorylation of GluN2A in the hippocampus [61]. The tyrosine phosphorylation of GluN2A occurs as early as 15 min after reperfusion and is sustained for at least 24 h [62–64]. Tyrosine kinases, such as Fyn, Src [65], protein kinase C [66], and Pyk2 [67], are involved in the tyrosine phosphorylation of GluN2A.

This phosphorylation of GluN2A could induce the redistribution of NMDA receptors between synaptic lipid rafts and postsynaptic densities [68] and leads to rapid clustering from extrasynaptic to synaptic membrane fractions [69].

Although it is generally agreed that GluN2A plays an important role in ischemic damage, it is still a matter of controversy whether GluN2A mediates prosurvival signals (Table 2). Zhou et al. reported that NMDA-mediated toxicity is caused by the activation of GluN2B- but not GluN2A-containing NMDARs and that the switch from GluN2B to GluN2A in adult rats led to the invulnerability of adult hippocampal slices to NMDA treatment [70]. Subsequently, Liu et al. found that the activation of GluN2B results in excitotoxicity, while the activation of GluN2A promotes neuronal survival both in mature cortical cultures and in an in vivo rat model of focal ischemic stroke [71]. Similarly, Chen et al. found that the GluN2A subtype-specific antagonist NVP-AAM077 enhanced neuronal death following transient global ischemia and abolished the induction of ischemic tolerance; GluN2B was found to have an opposite role [72]. However, other groups have disputed these findings. Morikawa et al. found that, after a 2-h middle cerebral artery occlusion, brain injury volumes revealed a significantly smaller injury size in GluN2A subunit knockout mice [73]. Wang et al. observed that endogenous cdk5 activated by forebrain ischemia can phosphorylate GluN2A at Ser1232 and induce CA1 pyramidal neurons damage [74]. Choo et al. found that activation of NR2A-containing NMDARs was associated with JNK phosphorylation that was neuroprotective in neuronal cultures subjected to excitotoxicity [75]. Zhou et al. reported that overexpression and molecular knockdown of GluN2A exacerbate and attenuate NMDAR-mediated neuronal death, respectively [76]. They proposed that the magnitude and duration of GluN2A activation could be a key factor which determines neuronal fate [77]. It was also found that the downregulation of GluN2A by a GluN2A antisense construct [78], Co 101244 and Zn^{2+} [79], conantokin G [80], PSD-95 antisense construct [81], or PP2 [82], a potent inhibitor of Src family kinases, significantly reduced excitotoxic cell death. Moreover, enhanced glutamate excitotoxic vulnerability with age is associated with a substantial increase in GluN2A in vitro [83, 84]. Interestingly, von Engelhardt et al. found that 50 nM NVP-AAM077 increased the toxicity induced by submaximal 5 μM NMDA in DIV21 cortical cultures [83].

In a word, GluN2A might mediate both prosurvival and prodeath signalings. The GluN2A-PTEN-TDP-43 (TAR DNA-binding protein-43) [85] and GluN2A-CaMKIV-TORC1 (transducers of regulated CREB activity 1) [86]

Table 2 The role of GluN2A in cerebral ischemia

Models	Regulation of GluN2A	Methods	Animals	Cerebral regions	Effect on damage	References
NMDA exposure	Downregulation	NVPAAM-077	Rats	Hippocampal slices	Unaltered	[70]
NMDA exposure	Downregulation	NVPAAM-077	Rats	Cortical cultures	Enhanced	[71]
NMDA exposure	Downregulation	GluN2A knockout	Mice	Cortical cultures	Unaltered	[71]
OGD	Downregulation	NVPAAM-077	Rats	Cortical cultures	Enhanced	[71]
MCAO	Downregulation	NVPAAM-077	Rats		Enhanced	[71]
Four-vessel occlusion	Downregulation	NVPAAM-077	Rats	Hippocampal CA1	Enhanced	[72]
NMDA exposure	Downregulation	NVPAAM-077	Rats	Cortical cultures	Unaltered	[75]
MCAO	Downregulation	GLUN2A knockout	Mice		Reduced	[73]
BCCAO	Downregulation	S1232A-GluN2A Overexpression	Rats	Hippocampal CA1	Reduced	[74]
GluN2A-EYFP transfection	Downregulation	GluN2A antisense construct		NR1-C02′-EYFP cells	Reduced	[78]
NMDA exposure	Downregulation	NVPAAM-077	Mice	Cortical cultures (DIV 21)	Enhanced	[83]
NMDA exposure	Downregulation	NVPAAM-077	Mice	Cortical cultures (DIV 21)	Unaltered	[83]
Glu exposure	Upregulation	Naturally over time	Rats	Hippocampal cultures (DIV 7–23)	Enhanced	[84]
NMDA exposure	Downregulation	Co 101244 and Zn^{2+}	Rats	Hippocampal cultures	Reduced	[79]
NMDA exposure	Downregulation	CGX-1007	Rats	Hippocampal slices	Reduced	[80]
Four-vessel occlusion	Downregulation	PSD-95 antisense construct	Rats	Hippocampus	Reduced	[81]
Four-vessel occlusion	Downregulation	PP2	Rats	Hippocampus	Reduced	[82]
NMDA exposure	Upregulation	GluN2A Overexpression	Rats	Cortical cultures	Enhanced	[76]
NMDA exposure	Downregulation	GluN2A knockdown	Rats	Cortical cultures	Reduced	[76]

OGD oxygen-glucose deprivation, *MCAO* middle cerebral artery occlusion, *BCCAO* bilateral common carotid arteries occlusion

signaling pathways could mediate the prosurvival effect of GluN2A. In contrast, cdk5 could be a downstream prodeath molecule for GluN2A [74].

Seizure Disorder

There may be a connection between increased glutamatergic neurotransmission and seizure activity. The selective increase in the coexpression of GluN2A/2B and GluN1 in dysplastic neurons of human epileptic cortex could contribute to focal seizure onset [87, 88]. In seizures induced by pentylenetetrazole in rats, GluN2A was markedly increased in the cortex during the early seizure development process [89]. In the subiculum of seizure-sensitive gerbils, GluN2A/B immunoreactivity increased significantly at 12 h postictal [90]. It has also been found that GluN2A knockout mice were more resistant to audiogenic-like seizures induced by stimulating the inferior colliculus [91]. Moreover, tyrosine phosphorylation of GluN2A in the rat hippocampus was enhanced following KA-induced status epilepticus [92] or Li/pilocarpine-induced status epilepticus [93].

Seizure activity can also influence the expression of GluN2A and contribute to cognitive changes in seizure patients. In the hippocampus of flurothyl- or kainite-treated neonatal rats, the expression of GluN2A protein was decreased significantly [94, 95]. Recurrent seizures in animal models of early-onset epilepsy resulted in a decrease in the expression of the GluN2A subunit, which could be delayed by at least 5 days but persists for at least 3 to 4 weeks [96]. Alterations in the gene encoding the GluN2A subunit are a major genetic risk factor for idiopathic focal epilepsy [97]. However, other studies have shown opposing results. Except for those with hippocampal sclerosis, all temporal lobe epilepsy patients showed increased GluN2A and GluN2B hybridization densities in dentate granule cells [98]. Following multiple perinatal seizures induced by kainic acid, rat pups showed a robust increase in GluN2A/2B labeling specific to cortical layer V throughout the retrosplenial, parietal, and temporal cortices [99]. Prolonged febrile seizures induce an increase in the hippocampal levels of GluN2A [100]. No differences were found in the expression of GluN2A and GluN2B in the amygdalas of patients with mesial temporal lobe epilepsy [101].

GluN2A might also be involved in the pathological processes of seizures. Ganor et al. found that subpopulations of epilepsy patients show significantly elevated levels of autoantibodies to a peptide of the GluN2A subunit [102]. This type of GluN2A autoantibodies could damage the brain [103].

It is found minocycline could exert an anticonvulsant effect by preventing the increase in GluN2A [104]. Neuropeptide Y could inhibit seizures via the downregulation of the functional expression of GluN2A and GluN2B [105]. Therefore, a pharmacological strategy directed to the GluN2 subunit might help to limit the onset or diffusion of seizures [106].

Alzheimer's Disease

Many have observed NMDARs dysfunction in Alzheimer's disease (AD) patients, which is responsible for the cognitive deficits of AD. Sultana et al. observed a significantly decreased level of GluN2A in the hippocampus of subjects with amnestic mild cognitive impairment, a prodromal stage of Alzheimer's disease [107]. Sze et al. reported that nonphosphorylated and phosphorylated GluN2A were selectively reduced in the entorhinal cortex of AD patients [108]. These researchers also found reductions in GluN2A mRNA levels in the hippocampus [109]. Hynd et al. reported that the transcript and protein expression of both GluN2A and GluN2B was markedly attenuated in susceptible regions in subjects with AD pathology, such as the cingulate gyrus, hippocampus, and superior temporal cortex [110]. However, Mishizen-Eberz et al. found that the expression of GluN2A subunit mRNA and protein were unchanged during AD progression and that neuronal mRNA expression revealed a significant increase in the GluN2A subunit in subjects with moderate neurofibrillary tangle neuropathology [111]. Marcello et al. found that SAP97, which is responsible for the trafficking of GluN1 and GluN2A and is connected to GluN2A and GluN2A localization in hippocampus, is not altered in AD patients [112]. These contradictory results could be due to a small sample size.

A majority of studies show that amyloid-β (Aβ) can alter NMDARs activity, contributing to its neurotoxicity. Aβ25-35 treatment resulted in elevated tyrosine phosphorylation of GluN2A in the CA1 subfield of the rat hippocampus and facilitated the interactions of GluN2A and Src kinases [113]. Aβ oligomers directly activate NMDARs, particularly those with the GluN2A subunit [114]. Amyloid precursor protein mutations associated with familial Alzheimer's disease enhanced the trafficking of GluN2A to the cell surface [115]. Aβ induces dendritic spine loss via a pathway involving GluN2A-containing NMDARs [116]. However, Liu et al. found that Aβ leads to a loss of synaptic proteins via the suppression of GluN2A function and the activation of GluN2B function [117]. The combined oligomer Aβ(1–40) and stress treatment decreased GluN2A/2B expression in the hippocampus [118].

There is also a relationship between GluN2A and Tau. The blockade of GluN2A induces Tau phosphorylation in rat hippocampal slices [119]. This effect could be related to the GluN2A-PKC-glycogen synthase kinase-3β (GSK3β) signaling pathway [120].

Systemic Lupus Erythematosus

The anti-NMDAR autoantibodies in patients with systemic lupus erythematosus (SLE) is a typical example that suggests that antibodies can alter emotion. DeGiorgio et al. found that lupus antibodies cross-react with GluN2A and GluN2B, gain access to cerebrospinal fluid, and might mediate abnormalities of the central nervous system [121]. Subsequently, autoantibodies directed against GluN2A were found in the sera of patients with SLE [122]. Omdal et al. considered that neuropsychiatric disturbances in SLE are associated with antibodies against GluN2A and GluN2B [123]. A breach in the integrity of the blood–brain barrier could expose neurons to these potentially pathogenic antibodies [124]. Indeed, the levels of anti-NR2 antibodies in the cerebrospinal fluid were significantly elevated in patients with diffuse psychiatric/neuropsychological syndromes, whereas there were no significant differences in serum anti-NR2 levels [125]. The administration of the nonnaturally occurring D form of the DWEYS pentapeptide, a sequence present in the GluN2A and GluN2B subunits, prevents these antibodies from depositing in glomeruli and from mediating neuronal excitotoxicity [126]. An anti-GluN2A antibody could be a predictor for neuropsychiatric systemic lupus erythematosus [127]. However, Harrison et al. reported that no significant association was found between the anti-GluN2A antibody and cognitive dysfunction, depressive symptoms, or anxiety in SLE patients [128].

Anti-GluN2A autoantibodies might induce the apoptosis of GluN2A-expressing neurons [129]. The underlying mechanism could be the promotion of NMDAR-mediated excitotoxicity [130] and enhancement of Ca^{2+} influx through the inhibition of the binding capacity of zinc [131].

Depression

Growing evidence implicates a role for GluN2A signaling in depression. GluN2A knockout mice [132] or mice expressing mutant GluN2A with a Tyr-1325-Phe mutation, which prevents the phosphorylation of this site [133], showed antidepressant-like profiles in the forced swim test and tail suspension test. GluN2A and its downstream molecules might contribute to chronic mild stress susceptibility [134].

Depression also has an effect on GluN2A. The decreased expression of GluN2A in the perirhinal [135] and prefrontal [136] cortex in major depression patients has been observed. The levels of GluN2A were reduced in different brain regions in prenatally stressed juvenile offspring showing depression-like behavior [137], while the levels of GluN2A in the lateral amygdala were elevated in depressed patients [138]. GRIN2A, which encodes GluN2A, was also found to be hypermethylated in both the prefrontal cortex and hippocampus of recurrent depression patients [139].

Schizophrenia

There is growing evidence in support of the hypothesis that hypofunction of NMDARs is involved in the pathophysiology of schizophrenia. Mice lacking the GluN2A exhibit several behavioral abnormalities related to schizophrenia, including hyperlocomotion and cognitive impairments [140]. A microsatellite repeat in the promoter of the GluN2A subunit gene suppresses transcriptional activity and is correlated with chronic outcome in schizophrenia [141]. Reduced GluN2A expression is correlated with negative symptoms in the postmortem cerebellum during chronic schizophrenia [142]. GluN2A is also decreased in the prefrontal cortex during schizophrenia [143, 144]. Dysbindin, a schizophrenia-susceptibility gene that is widely expressed in the forebrain, prevents the expression of GluN2A in the hippocampus [145]. However, several studies did not report changes in GluN2A expression in the dorsolateral prefrontal and anterior cingulate cortex [146], the medial temporal lobe [135], the thalamus [147], and cerebellum [148] of schizophrenia patients.

Parkinson's Disease

GluN2A might be linked with impaired LTP in patients with Parkinson's disease and dyskinesia induced by long-term L-DOPA therapy. Hippocampal LTP is altered in both neurotoxic and transgenic models of Parkinson's disease and these alterations are associated with impaired dopaminergic transmission and a decrease in the GluN2A/GluN2B subunit ratio in synaptic NMDARs [149]. The modulation of the composition of synaptic NMDAR using TAT2A, a cell-permeable peptide targeting GluN2A, during the development of dyskinesias led to a reduction in the percentage of Parkinsonian rats that developed dyskinetic movements [150].

Huntington's Disease

There is growing evidence indicating the involvement of GluN2A in Huntington's disease. Variation in the GluN2A receptor gene can affect the age of onset for Huntington disease [151]. The GluN2A expression in the hippocampus of R6/2 transgenic Huntington's disease mice was found to be decreased [152]. A significant decrease in the percentage of cells expressing GluN2A at all ages is observed in the R6/2 mouse model of Huntington's disease [153]. However, Jarabek et al. observed no change in GluN2A in the striata of N171-82Q mice, a new transgenic model of Huntington's disease [154].

Anxiety

A number of different classes of NMDAR antagonists have been shown to exhibit anxiolytic effects in different laboratory

tests of anxiety [155]. The underlying mechanism of these antagonists could act through their blocking effect on GluN2A [156]. GluN2A knockout mice exhibit decreased anxiety-like behavior relative to wild-type littermates across multiple tests [132]. Prenatal stress reduced GluN2A expression in the hippocampus, the prefrontal cortex, and striatum in the offspring, and the altered expression of GluN1 and GluN2A could have a potential impact on anxiety-like behavior [157].

Bipolar Disorder

Disturbances in glutamate-mediated synaptic transmission could be involved in the pathophysiology of bipolar disorder (BD). There is a decrease in the expression of GluN2A in the anterior cingulate cortex [158], the perirhinal cortex [135], and hippocampus during bipolar disorder [159].

Perspectives

The absence of a highly selective rodent GluN2A antagonist might be the largest obstacle for studying the pathophysiological role of GluN2A. The selectivity of NVP-AAM077, the most widely used selective GluN2A antagonist, against rodent GluN2A is still a matter of controversy. In contrast, TCN-201 and TCN-213 displayed submicromolar and micromolar potency at GluN1/GluN2A receptor, respectively, although they did not show activity at GluN2B-containing receptor up to 50 μM concentration [160]. These novel antagonists might be useful in deeply understanding the physiological and pathophysiological roles of GluN2A in brain functions.

PDZ-containing proteins are typical scaffolding proteins associated with GluN2A. The human genome contains hundreds of different PDZ ligand-containing proteins, and all of these proteins are likely to be downstream molecules of GluN2A. Therefore, the signaling of GluN2A is likely to be highly complicated. The spatial distribution, cooperation, and relative importance of these signaling proteins remain unclear.

The tyrosine phosphorylation of GluN2A can be regulated by Src, Fyn, or cdk5; however, the phosphatases related to the dephosphorylation of GluN2A have not been reported.

GluN2A, a primary type of NMDAR subunit in the brain, is involved in the pathogenesis of many types of brain diseases. However, the causality between GluN2A and these brain diseases has not been determined. Moreover, only a small number of reports have suggested treatment strategies based on GluN2A or its signaling pathways. In view of the controversy on whether GluN2A mediates prodeath signaling or not, the specific prodeath signaling pathways of GluN2A should be determined in the future. Blocking the actions of the downstream prodeath molecules of GluN2A could be an effective strategy to treat brain diseases.

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