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Abstract.

The N-methyl D-aspartate receptor is one of the key receptors in the human brain. As a result of radioligand analysis, it was found that the highest density of this receptor is located in the hippocampus, striatum, cortex, and amygdala. Associative memory, learning, and synaptic density are all directly related to the effective functioning of the NMDA receptor. Recent studies have shown that the number of NMDA receptors and their morphological structure decreases with age, in particular, some subunits change their shape, as well as the use of antidepressants, such as selective serotonin reuptake inhibitors, cause a delayed side effect, which manifests itself in the form of a quantitative decrease in NMDA in the brain. The antagonist of this receptor – memantine, inhibiting it can reduce the clinical picture of Alzheimer's disease, reducing tremor and papillary reflex. Another NMDA antagonist, ketamine, was used for anesthesia, but due to strong hallucinations during the period of recovery from anesthesia, it became less and less used. These substances also contribute to the work of the NMDA receptor in the future, and also affect synaptic density. Therefore, it is important to know the composition of the receptor, its downstream signaling pathways, and age-related changes in order to effectively prevent neurodegenerative diseases of the brain.

Key words. Alzheimer's disease, NMDA, CREB, glutamate, MgMg2+, GluN2, ion channels, neurodegeneration, excitotoxicity, synaptic density.

Introduction.

Currently, age-related changes in cognitive processes occurring at the molecular level are poorly understood. Studies in rodents show that with age, there is a decrease in the number of N-methyl-D-aspartate receptors (NMDARs) in synapses, which consist of GluN2B subunits. There is a correlation between a decrease in these subunits and a deterioration in cognitive function.

Excitatory glutamatergic neurotransmission via the N-methyl-D-aspartate receptor (NMDAR) is crucial for synaptic plasticity and neuronal survival. However, excessive NMDAR activity causes excitotoxicity and promotes cell death, which is at the heart of a potential mechanism of neurodegeneration that occurs in Alzheimer's disease (AD). Studies show that different outcomes of NMDAR-mediated reactions are induced by regionalized receptor activity followed by different downstream signaling pathways. Activation of synaptic NMDARs initiates plasticity and stimulates cell survival. In contrast, activation of extrasynaptic NMDARs promotes cell death and thus contributes to the etiology of AD, which can be blocked by the drug AD-memantine, an NMDAR antagonist that selectively blocks the function of extrasynaptic NMDARs. In this regard, it is possible to use new methods for the prevention of senile brain diseases. In particular, increasing the stimulation of NMDARs, as well as preventing neurodegenerative diseases from a young age, to preserve NMDARs receptors and prevent their loss with age.

The aim of the study was to study the NMDA receptor and its effect on both the pathogenesis of Alzheimer's Disease and its physiological features. The aim of the study was to study the effects of synaptic density and various secondary messengers on the biochemical cascade after activation of this type of receptor.

Materials and methods.

Foreign articles devoted to the study of various NMDA stimulation were analyzed NMDA. The analysis included the results of preclinical studies conducted for the period from 2015 to 2020.

Alzheimer's disease.

There is increasing evidence that a decrease in the number of synapses and a deterioration in their receptor composition correlates with a decrease in cognitive function, as well as with age in rodents and primates [1,2]. AD progression was associated with gradual damage to the function and structure of the hippocampus and neocortex, vulnerable brain regions used for memory and cognition. Synapse loss can be caused by the inability of living neurons to maintain functional axons and dendrites, or by neuronal death. Synaptic dysfunction may be caused by excessive synapticCa2+uptake in response to excessive activation of glutamate receptors, namely NMDARs. Glutamate is the main excitatory neurotransmitter in the brain, acting on ionotropic and metabotropic glutamate receptors. Ionotropic glutamate receptors (iGluRs), responsible for rapid neuronal communication at excitatory synapses, consist of three subfamilies: a-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA), kainate receptors, and NMDAR. However, over-stimulation of glutamatergic signaling leads to excitotoxicity [3].

NMDAR activity has recently been linked to the theory of AD as a synaptic dysfunction. AbnormalCa2+signaling leads to a gradual loss of synaptic function and eventual death of neuronal cells, which is clinically correlated with a progressive decline in cognitive functions and memory and the development of pathological foci in the brain. This, in turn, confirms the reasonableness of clinical trials of Memantine, an NMDAR antagonist, as a symptomatic and neuroprotective treatment for AD. Memantine, an competitive NMDA receptor antagonist, is approved for use in moderate to severe AD. It has been widely prescribed to relieve symptoms and improve quality of life in AD, even if it did not improve over-arousal and hippocampal or general brain atrophy.

It is also important to take into account the fact that the areas affected by AD are mainly composed of NMDARs receptors NMDARs consisting of GluN2A and GluN2B subunits [3].

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According to the World Health Organization, Alzheimer's disease is the leading cause of dementia, accounting for 60-70% of cases. The symptom of this chronic neurodegenerative disease worsens over time from early forgetfulness to gradual deterioration of speech, orientation, and behavior, and late severe loss of memory and some body functions until final death.

The etiology of AD is complex and multifactorial. The early onset of familial asthma is caused by a genetic mutation(s) in the genes of presenilins (PS1, PSE1, PS2) and amyloid-like precursor protein (APP), which affect a single pathogenetic mechanism in APP synthesis and proteolysis and cause excessive production of amyloid β (Aβ) [4]. However, the reason for the late occurrence of sporadic AD remains poorly understood. It is believed that the main risk factor is genetics involving multiple genes. Other risk factors include aging, apolipoprotein (Apo) E4 genotype, head injury, and vascular disease. The main deterministic and risky AD genes are listed in Table 1.

**NMDAR for BA**

The defining features of AD are marked changes in both brain histology and human behavior. AD of the brain is characterized microscopically by extracellular amyloid plaques and intraneuronal NFTs. Accumulated data have shown that the soluble forms of Aβ and tau work together, regardless of their accumulation in plaques and tangles, to bring healthy neurons to a diseased state, and that such distinctive toxic properties of Aβ require the presence of tau [5]. Cognitive impairments in AD are closely related to synaptic plasticity, in which NMDAR plays a crucial role [6]. Excitatory glutamatergic neurotransmission via NMDAR is crucial for synaptic plasticity and neuronal survival. However, excessive NMDAR activity causes excitotoxicity and promotes cell death, which underlies the potential mechanism of neurodegeneration that occurs in AD [7]. The main factors influencing NMDAR signaling in AD are glutamate availability and modulation of NMDAR channel functions [7].

**Beta Amyloid and NMDAR**

In Alzheimer's Disease (AD), the "cascade hypothesis" of amyloid beta (Aβ) postulates an initiating event of amyloidosis with subsequent accumulation of tau protein preceding subsequent brain atrophy and cognitive suppression [8]. From studies using methods such as amyloid-PET and florbetapir-PET, it was known that beta-amyloid deposition occurs selectively first in the cerebral cortex, starting from the temporo-basal and fronto-medial regions and sequentially affecting the primary sensorimotor regions and the medial temporal lobe. It was followed by the hippocampal regions, then the striatum, basal forebrain, thalamus, and finally the brainstem and cerebellar nuclei [9-11]. Beta-amyloid deposition in the medial parietal cortex appears to be the first stage of AD development, although Tau protein aggregates in the medial temporal lobe precede beta-amyloid deposition in cognitively healthy elderly people [12]. Beta-amyloid is produced by endoproteolysis of the amyloid precursor protein (APP), which is achieved by sequential cleavage of APP by groups of enzymes called b- and g-secretases [13]. Aβ is formed as a monomer but is easily aggregated to form multimeric complexes.

The initial amyloid hypothesis postulated that the accumulation of beta-amyloid in the brain is the main factor determining the pathogenesis of AD. Cell studies and animal experiments have confirmed that oligomeric, soluble Aβs, rather than insoluble amyloid plaques, have a toxic effect [14,15]. Thus, according to the modified hypothesis of the amyloid cascade, soluble oligomeric forms of Aβ-b induce a neurodegenerative triad [4].

The Aβ peptide was first identified as a component of extracellular amyloid plaques in the mid-1980s. Currently, a large number of studies have proved the presence of intracellular beta-amyloid in neurons [13]. Studies also show that beta-amyloid is produced intracellularly in the compartments of the endosome [16-21], ER (endoplasmic reticulum) [22,23], and the trans-Pole of K. Golgi -in neurons [18]. Secreted beta-amyloid, which forms the extracellular pool of beta-amyloid, can be absorbed by cells and internalized into intracellular pools. Aβ binds to the nicotinic acetylcholine receptor with high affinity, which leads to internalization of the receptor and accumulation of beta-amyloid intracellularly [7,19]. In addition to nicotinic receptors, internalization of beta-amyloid has been reported via LRP (Low-density lipoprotein receptor related protein) [20], RAGE (scavenger receptor for advanced glycation end products) [21], and NMDAR [24]. The uptake of beta-amyloid was completely blocked by NMDAR antagonists, which indicates the involvement of this receptor in the re-uptake of the peptide [25].

Cognitive function ultimately depends on synaptic plasticity, where LTP is associated with synaptic growth and LTD is associated with synapse loss. Aβ is associated with inhibition of LTP (increased synaptic transmission between two neurons that persists for a long time – the main component of synaptic plasticity) [26] and activation of LTD (decreased efficiency of neuronal synapses – their depression) [27,28]. During LTD induction, a strong and prolonged release of glutamate from the presynaptic terminal activates AMPA receptors, and subsequent depolarization removes the blockade of the Mg channel of NMDAR and provides an influx of Ca. This strong activation of NMDARs triggers Ca/calmodulin-dependent protein kinase II (CaMKII), an indirect signaling cascade that ultimately leads to increased synaptic strength.

In contrast, moderate activation of NMDARs causes a moderate increase in postsynaptic Ca and triggers phosphatase-mediated

**Table 1. The main deterministic and risky AD genes.**

<table>
<thead>
<tr>
<th>Genes</th>
<th>Locus</th>
<th>Function normal</th>
<th>Involvement in AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenilin - 1 (PS-1)</td>
<td>Xp. 14</td>
<td>Processing of amyloid precursor protein and Aβ formation</td>
<td>Cause of early onset of AD</td>
</tr>
<tr>
<td>Presenilin-2 (PS-2)</td>
<td>Xp. 1</td>
<td>Processing of amyloid precursor protein and Aβ formation</td>
<td>Cause of early onset of AD</td>
</tr>
<tr>
<td>APP (amyloid precursor)</td>
<td>Xp. 21</td>
<td>Regulates synaptic function</td>
<td>Cause of early AD</td>
</tr>
<tr>
<td>onset Apolipoprotein E4</td>
<td>Xp. 19</td>
<td>Transport CS</td>
<td>is a risk factor for AD</td>
</tr>
</tbody>
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LTD [29]. Activation of synaptic NMDARs and a significant increase in [Ca] are required for LTP, whereas internalization of synaptic NMDARs, activation of perisynaptic NMDARs, and a decrease in [Ca] increase is required for LTD. LTP induction promotes the selection of AMPA receptors and the growth of dendritic spines, while LTD induces spines depression and synaptic loss [30]. Pathologically elevated Aβ can indirectly cause partial blocking of NMDAR and shift the activation of NMDAR-dependent signaling cascades towards pathways involved in LTD induction and synaptic loss [31,15]. This model is consistent with the fact that Aβ worsens LTD [26,32] and stimulates LTD [33,34,27]. Although the mechanisms underlying Aβ -induced LTD are not yet fully elucidated, they may involve desensitization of receptors [35] or internalization and subsequent destruction of dendritic spines [36,37].

Beta-amyloid modulates NMDARs-related responses; pre - exposure to Aβ reduced the NMDA-induced increase in [Ca] and pre - exposure to NMDA reduced the Aβ response. In addition, simultaneous exposure to Aβ plus NMDA synergistically increased [Ca] levels, an effect mediated by GluN2B-containing NMDARs [38]. Accumulated data indicate that glutamate receptors are dysregulated by Aβ oligomers, which leads to a violation of glutamatergic synaptic transmission, which corresponds to an early cognitive deficit. Theoretically, there are several potential roles of the NMDA receptor in Aβ -related mechanisms [39] first, the function of the NMDA receptor may be an important downstream target of Aβ; second, NMDA receptors may be necessary for the action of Aβ on synaptic transmission and plasticity.

**Tau protein and NMDAR**

Tau is one of the main components of NFT, which is a pathological sign of AD. In a healthy brain, tau protein (tau) is an exclusively axonal protein involved in the assembly and stabilization of microtubules. In contrast, in the brain of AD, tau is hyperphosphorylated and forms fibrils that appear as neuritophilic filaments in dendrites and as NFTs in the somatodendritic compartment and axons. Strong evidence has been provided that the deposition of cerebral amyloid precedes cerebral tau pathology in familial autosomal dominant AD, while the appearance of NFT precedes Aβ pathology in the vast majority of affected regions in sporadic AD [40,41]. For the first time, the possibility that tau reduction altered Aβ levels or aggregation and disconnected the brain was excluded. Aβ depends on top-down pathogenic mechanisms [42].

Tau not only contributes to axonal structure by maintaining microtubule stability, but also plays an important role in regulating synaptic function. Tau is required for Fyn-mediated NMDAR activation in PSD [42]. Tau has been shown to be important for the induction of LTD [43], as well as BDNF-dependent morphological plasticity [44]. Fyn, a member of the Src tyrosine kinase family [45], can phosphorylate tau in its tyrosine 18 residue to produce pY18-tau [46] and can bind to tau via one or moreproline-rich (PxxP) motifs in tau [46-48]. Fyn phosphorylates the NMDAR subunit GluN2B in y1472 [49], which enhances the interaction between NMDARs and PSD-95 in PSD [50] and enhances the activity of GluN2B-containing NMDARs [51]. Some experiments have shown that tau is usually highly enriched in axons relative to dendrites [52], but in response to Aβ, tau is extensively redistributed into the somato-dendritic compartment [53,54]. Excess Fyn accompanies excess tau in dendrites in AD and increases the activity of NMDA receptors there, flooding the dendrites with harmful calcium levels. This calcium-induced excitotoxicity can damage postsynaptic sites and cause neuronal death. Some results have confirmed that glutamate-induced excitotoxicity is inhibited by a decrease in tau [41,42] and worsened by an overexpression of tau [55,56]. In turn, glutamate-induced excitotoxicity increases экспрессию tau expression [57,58] and its phosphorylation [57]. It has recently been reported that activation of extrasynaptic NMDA receptors induces Tau overexpression with simultaneous neuron degeneration and reduced neuronal survival [59].

**Some atypical types of NMDAR reception in AD**

**Presynaptic NMDARs:**

Traditionally, NMDARs are thought to be located on the postsynaptic membrane, while recent anatomical and physiological data suggest that they may also exist on presynaptic terminals. Presynaptic NMDARs (preNMDARs) can regulate presynaptic glutamate release, as well as alter synaptic transmission and plasticity [60-63]. Thus, the composition of the preNMDAR subunit is crucial for modulating where and how preNMDARs affect glutamate release. The subunit composition of preNMDARs shows strong variability; depending on the brain region, all four subunits of GluN2 (Glu2A-D) and GluN3A can be included [64].

The presynaptic GluN2B subunit has been found in many brain regions, such as the hippocampus [65-67], cerebellum [68], entorhinal cortex [69], somatosensory [70], and visual cortex [71]. Although it appears and peaks later in development [72,73], the GluN2A subunit can also be included in preNMDAR sites [74]. In cerebellar parallel fiber-Purkinje cell synapses, preNMDARs are predominantly diheteromeric GluN1/GluN2A [75]. In addition, the GluN2B and GluN3A subunits, probably combining to form the trigeteromeric GluN1/GluN2B/GluN3A, are essential preNMDARs in the developing visual cortex L2 / 3 [76,77].

preNMDARs have been reported to regulate both spontaneous and evoked release. Although the two forms of release were initially thought to use the same mechanism, emerging evidence suggests that preNMDARs control evoked and spontaneous release by different mechanisms. preNMDARs can control spontaneous release independently of Mg and Ca while regulation of evoked release depends on frequency, relying on the more traditional Mg-dependent pathway [78-81] showed that preNMDARs in L5 pyramidal cells regulate evoked and spontaneous release via the RIM1ab and jnk2-dependent pathways, respectively.

In addition, activation of preNMDARs is necessary for the induction of LTD [82,79], but it is noteworthy that the roles of preNMDARs change during development. Induction of LTD in the pyramidal visual cortex cells of young mice (up to postnatal 20 days) requires presynaptic activation, whereas in older mice, LTD induction requires postsynaptic activation of NMDARs [60]. In contrast to these results, [83] shows that in
the somatosensory cortex of 2 - to 3-week-old rats and mice, it is postsynaptic rather than preNMDARs processes that are necessary for the induction of LTD. This contradictory result may be caused by different observed brain regions. Not only being essential for LTD induction, preNMDARs are also involved in LTP induction [84,85] reported that preNMDARs play a key role in LTP induction in mouse corticostriatal synapses. Activation of preNMDARs induces BDNF secretion through amplification of Ca signals in axonal terminals, which indicates that preNMDARs are just as important as postsynaptic NMDARs in LTP induction [85].

Bell et al. (2007) [86] found that subjects with moderate cognitive impairment show a paradoxical increase in glutamatergic presynaptic density, which then depletes and decreases with disease progression. These results showed that neurite degeneration and reduced presynaptic terminal density окончаний negatively affect neurotransmission and cognitive function in the later stages of AD. While some progress has already been made, much remains to be done to clarify the exact functions and molecular mechanisms of preNMDARs.

Glial NMDARs:

While neuronal NMDARs are widely studied, they are also expressed in many non-neuronal cells, including astrocytes. Astrocytic NMDA receptors are poorly understood compared to neuronal receptors. Emerging dataindicate that astrocytic NMDARs have pronounced structural and functional properties, including weak susceptibility to Mg blockade and lower Ca permeability [87]. NMDAR expression and function in astrocytes was demonstrated in cultured astrocytes in the mouse neocortex [88-91]. All seven identified NMDAR subunits (GluN1, GluN2A-D, and GluN3AB) were detected in primary human astrocytes. Increasing data indicate that astrocytes express NMDARs with a three-heteromeric configuration combining GluN1, GluN2C, or D and the GluN3 subunit [92,93]. Glutamate and QUIN can activate astrocytic NMDARs, which in turn increases Ca influx and induces a signaling cascade [46]. It has been established that astrocytic functional NMDARs are able to respond to neuronal glutamatergic input, which is accompanied by dynamic intracellular Ca elevation, triggering gliotransmitter-mediated regulation of synapse function [94-96]. Astrocytic NMDARs may also be involved in neuroinflammatory processes, as well as contribute to morphological transformations characteristic of reactive astrogliosis, and mediate the release of proinflammatory cytokines [97-99]. In particular, astrocytic NMDARs may contribute to AD due to their role in promoting glutamate excitotoxicity [46]. Our studies have shown that A-b-induced early synaptotoxicity can be enhanced after treatment with blockade of astrocytic GluN2A and GluN2B, and nerve growth factor (BDNF) can act as a mediator in synaptoprotection of astrocytic GluN2 activation [91]. In the co-culture system, it was found that pretreatment of astrocytes with 1 mM or 10 mM NMDA to activate GluN2A or GluN2B before exposure to Aβ 1-40-40 prevented the introduction of Aβ PSD-95 and a decrease in synaptophysin. Whereas blockade of astrocytic GluN2A with TCN-201 or GluN2B with ifenprodil: respectively, both exacerbated the synaptotoxic effects of Aβ.

In addition, NMDARs are also expressed by oligodendrocyte line cells as mediators of intracellular Ca accumulation, which leads to reduced oligodendrocytic survival and white matter damage [100-102]. The dominant force underlying NMDA-induced currents in mature oligodendrocytes is actually increased extracellular K+ released when neuronal or astrocytic NMDARs are activated. An increased level of oligodendrocytic Ca will be gated by the transient receptor potential of the cationic channel (TRP) al [103]. NMDAR of oligodendrocyte progenitor cells (OSCs) can also contribute to myelination. Activation of NMDARs in OPC cultures increased migration [60], core protein expression [104], and differentiation [60].

Rather surprisingly, a recent study showed that NMDARs are present in primary cultures of microglia from the cerebral cortex and hippocampus of mice [105], and exposure to NMDAR co-agonists resulted in induced internal currents and an intracellular increase in Ca sensitive to inhibition by the non-competitive NMDAR channel blocker MK801 [106,107]. Activation of NMDAR in microglia leads to significant phosphorylation of ERK1 / 2. Phosphorylation of ERKs, namely nmdar, interacts with mitogen-activated protein kinase, and signaling via MAPK depends on CaM and NCS1 in neurons, whereas signaling via NMDAR in microglia depends only on CaM. NMDAR function was potentiated in microglia from transgenic APPSw;Ind mice, indicating that the NCS1–NMDAR interaction is relevant to receptor function in the microglia of a mouse model with AD [105].

Metabotropic NMDARs:

Считалось, что NMDAR-dependent synaptic plasticity was thought to be completely controlled by Ca influx, and elevated cytoplasmic [Ca] acts as a second messenger in the postsynaptic neuron. More recent data suggest that when glutamate binds, NMDARs can cause long-term changes in synaptic function in the absence of calcium conduction [107-110]. In other words, NMDAR can act as a metabotropic receptor and signal metabotropically, without the need for Ca influx through the channel. [107-110].

Conventional wisdom suggests that NMDARs trigger LTP through a high level of Ca influx, while the metabotropic receptor arises from synaptic depression induced by low-frequency stimulation (LFS), which is called NMDAR-dependent LTD [111,112]. Recent results have shown that glutamate binding alone is sufficient to induce conformational changes in NMDARs that trigger p38 MAPK signaling cascades, and, in turn, to induce LTD [107-109]. It is noteworthy that an increase in Ca can induce LTD; however, maintaining the initial level of intracellular Ca is necessary for metabotropic activation of NMDAR, which leads to synaptic depression [107].

Consistent with this metabotropic signaling, some researchers have found that pre-NMDARs can control spontaneous release without the need for Mg and Ca, while evoked release was sensitive to Mg [78,80]. Pre-NMDARs promote transmitter release in part through protein kinase c signaling [78]. These data suggest that pre-NMDARs can signal metabotropically, and further support the assumption that evoked and spontaneous release occurs through various mechanisms [113,114]. Although some conclusions support an ion flux-independent mechanism
for NMDAR-dependent LTD [110,83], it has been challenged by some recent discoveries [115-117].

In addition, some studies have shown that astrocytic cells can also act through metabotropic NMDAR signaling pathways [118,119], which may involve phospholipase C-0 mediated Ca elevation in the endoplasmic reticulum and activation of Cd protein kinase [118], but much remains to be done to clarify this complex mechanism [87].

Early synaptic dysfunction in AD is associated with an increase in the level of A-b oligomers, which causes rapid NMDAR-dependent synaptic depression and loss of dendritic spines [76,63]. While some studies have shown that A-b -induced NMDAR-dependent synaptic depression does not require ion flow through the receptor [108] and is blocked by AP-5, but not by MK-801, it is suggested that the metabotropic effect of NMDARs contributes to A-b-induced synaptic dysfunction. This may be a common mechanism between metabotropic NMDAR-dependent LTD and A-b-induced synaptic depression [120].

Discussion.

Currently, there is reliable evidence (p<0.05) that synaptic dysfunction in Alzheimer’s disease is due to excessive synaptic Ca^2+ input in response to excessive NMDARs activation. Since other iGluRs are associated with triggering LTP and increasing the efficiency of neuroplasticity processes (AMPA in particular). It is also important to take into account the fact that areas affected by Alzheimer’s disease have mainly NMDARs receptors consisting of GluN2A and GluN2B subunits.

Excessive NMDAR activity causes excitotoxicity and promotes cell death, which underlies a potential mechanism of neurodegeneration that occurs in AD. It is known that deposits of beta-amyloid (A-b) and tau protein (tau) also play a role in the pathogenesis of early hereditary Alzheimer's disease.

Accumulated data indicate that glutamate receptors are dysregulated by A-b oligomers, which leads to a violation of glutamatergic synaptic transmission, which corresponds to an early cognitive deficit. Beta-amyloid, as a product of perverted synthesis, can also use NMDAR as a downstream target or even other iGluRs are associated with triggering LTP and increasing the efficiency of neuroplasticity processes (AMPA in particular). It is also important to take into account the fact that areas affected by Alzheimer's disease have mainly NMDARs receptors consisting of GluN2A and GluN2B subunits.

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Previously, activation of extrasynaptic NMDA receptors was also found to induce overexpression of tau protein with simultaneous neuron degeneration and reduced neuronal survival.

Various forms of NMDAR have been found to contribute to the development of Alzheimer's disease. In particular, astrocytic NMDARs may contribute to AD due to their role in promoting glutamate excitotoxicity. The NCS1–NMDAR interaction is relevant to receptor function in the microglia of a mouse model with Alzheimer's disease.

Typically, activation of preNMDARs induces BDNF secretion through amplification of Ca signals at axonal terminals, indicating that preNMDARs are just as important as postsynaptic NMDARs in LTP induction. However, in individuals with moderate cognitive impairment, glutamatergic presynaptic transmission processes were subsequently enhanced, which contributed to the activation of LTD and further neurodegeneration.

The metabotropic receptor arises from synaptic depression induced by low-frequency stimulation (LFS), which is called NMDAR-dependent LTD. This reaction is especially sharply caused by low-frequency stimulation of the extrasynaptic forms of NMDAR, which are dominated GluNby the GluN2B subunit. Their expression and incorporation into the receptors increases with age.

Thus, it is assumed that there are indeed two different forms of NMDAR-dependent LTD: one requires an ion flux, and the other does not. There are certain interactions between the A-b/tau protein oligomers and NMDAR, and it is possible that the relationship may be mutual.

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