Review

The Dual Role of Glutamatergic Neurotransmission in Alzheimer’s Disease: From Pathophysiology to Pharmacotherapy

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Abstract: Alzheimer’s disease (AD) is an age-related dementia and neurodegenerative disorder, characterized by Aβ and tau protein deposition impairing learning, memory and suppressing synaptic plasticity of neurons. Increasing evidence suggests that there is a link between the glucose and glutamate alterations with age that down-regulates glucose utilization reducing glutamate levels in AD patients. Deviations in brain energy metabolism reinforce the development of AD by hampering glutamate levels in the brain. Glutamate is a nonessential amino acid and the major excitatory neurotransmitter synthesized from glucose. Alterations in cerebral glucose and glutamate levels precede the deposition of Aβ plaques. In the brain, over 40% of neuronal synapses are glutamatergic and disturbances in glutamatergic function have been implicated in pathophysiology of AD. Nevertheless, targeting the glutamatergic system seems to be a promising strategy to develop novel, improved therapeutics for AD. Here, we review data supporting the involvement of the glutamatergic system in AD pathophysiology as well as the efficacy of glutamatergic agents in this neurodegenerative disorder. We also discuss exciting new prospects for the development of improved therapeutics for this devastating disorder.

Keywords: glutamate; NMDA; AMPA; metabotropic receptors; EAAT1/2; therapeutic targets; glucose; ageing; amyloid-β; tau; AD

1. Introduction

Alzheimer’s disease (AD) is the most common and prevalent neurodegenerative disease with memory dysfunction and cognitive impairment, affecting nearly 46.8 million people worldwide, as reported by the World Health Organisation. AD is characterized by extracellular deposition of amyloid-β (Aβ) senile plaques and intracellular accumulation of neurofibrillary tangles (NFTs) [1]. Aβ is a short peptide that is produced from amyloid precursor protein (APP), a type I integral membrane glycoprotein which undergoes cleavage by both amyloidogenic and non-amyloidogenic
pathways [2]. Amyloidogenic pathway produces soluble APPβ (sAPPβ) fragment, Aβ and APP intracellular domain (AICD) through sequential cleavage of APP by β-secretase and γ-secretase; non-amyloidogenic pathway generates soluble APPα (sAPPα), P3 peptide and AICD by α-secretase and γ-secretase [3]. Out of all Aβ species, soluble oligomeric Aβ1-42 is considered as the most neurotoxic product obtained after cleavage of APP [4]. Aβ was first identified in the extracellular component and later studies confirmed its presence in neuronal intracellular regions such as the endosome [5], endoplasmic reticulum [6], and trans-Golgi network [7]. Aβ in mitochondria reacts with proteins impairing oxidative phosphorylation and increasing reactive oxygen species (ROS) that damage the neuronal membrane [8–10].

Aβ peptides are involved in cognitive dysfunction by inducing synaptotoxicity through Aβ aggregation. Aβ species can be found at the synapse as low-molecular-weight (LMW) dimers, trimers and tetramers and high-molecular-weight (HMW) oligomers [11]. HMW Aβ oligomers have greater binding affinity in hippocampal neuronal synapses when compared to LMW Aβ oligomers [12]. However, LMW Aβ oligomers induce more cognitive dysfunction and HMW Aβ oligomers cause a transient decrease in cognitive functions [13]. Nevertheless, HMW oligomers can dissociate into LMW species impairing synaptic functions [14] and in contrast, dissociation of Aβ oligomers into monomers in vivo could reduce Aβ pathology and synaptotoxicity [15]. Aβ oligomers target the excitatory synapses with greater affinity and alter the structure and functions of the synapses [16].

Tau is a microtubule-associated protein (MAP) engaged in the stability of microtubules in neurons and also regulates synaptic function [17]. Hyperphosphorylation of tau results in the formation of NFTs, which is a major pathological hallmark of AD. Tau phosphorylation acts as an indicator of aberrant activities of kinases and phosphatases in AD [18]. In dendrites, hyperphosphorylation of tau forms fibrils, which appear as neuropil threads and as NFTs in axon and somatodendritic section of neurons [19,20]. Tau protein undergoes phosphorylation by proline-directed protein kinases (PDPKs) or non-proline-directed protein kinases (non-PDPKs) [21]. PDPKs include Cyclin-Dependent Kinase-5 (Cdk-5), Glycogen synthase kinase-3 (GSK-3), and extracellular signal-related protein kinase (ERK). The irregular activity of Cdk-5 in AD causes tau hyperphosphorylation, loss of dendritic spines and deterioration of synaptic plasticity [22]. Non-PDPKs comprise of protein kinase A (PKA), Casein kinase 1 (CK1), and Casein kinase 2 (CK2) [18]. Among the kinases identified to be responsible for tau hyperphosphorylation, GSK-3β plays an important role in the pathological changes of tau protein in AD [23]. Data collected in humans show increased activation of GSK-3β in early-stage AD [24], while a consistent inhibition was observed in late-stage AD [25,26], thus suggesting that GSK-3β-mediated tau phosphorylation is among the earliest events during the progression of the pathology. Increasing evidence shows that tau in dendrites plays a key role in Aβ-induced detrimental effects. Of note, tau knockout mice showed a decrease in extrasynaptic N-methyl-D-aspartate (NMDA) receptor activity in the hippocampus contributing to neuroprotective effects [27]. Accumulation of Aβ plaques in synapse and the infiltration of tau into dendritic spines reduce excitatory glutamatergic synaptic transmission leading to cognitive impairments [28].

In the central nervous system (CNS), glutamate is the primary excitatory neurotransmitter acting on both ionotropic and metabotropic receptors. It is at the crossroad between multiple metabolic pathways and plays an important role in the functions of learning and memory. The activity of glutamatergic neurons is compromised in AD due to the destruction of synapse and neuronal death and its deficit can influence memory, cognition and behaviour, including cortical and hippocampal processing [29,30]. On the other hand, the pathological accumulation of glutamate can induce neurotoxicity due to time-related exposure, over-stimulating the post-synaptic response causing an increase in the entry of Ca$^{2+}$ into neurons [31]. Since currently available therapies of AD include cholinesterase inhibitors, NMDA partial antagonist memantine, more information about AD-related changes in glutamate neurotransmission would be highly relevant to better understand its mechanisms of action and to optimize the treatment [32,33]. In fact, treatment using memantine has improved cognition, behaviour, global function but the degree of efficacy remains to be fully determined.
Thus, the present review will extensively cover recent findings on the dysregulation of glutamatergic signaling in AD and will highlight the molecular mechanisms through which the modulation of glutamatergic receptors might exert beneficial effects in AD treatment.

2. Glucose Levels Affect Glutamate Content in AD

AD patients commonly suffer from other co-morbidities (stress, depression, diabetes, renal disease, etc.) that increase the complexity of AD pathogenesis [34–40]. Among all the co-morbidities, diabetes remains the most prevailing and significant risk in developing AD [41–46]. Familial AD patients exhibit alterations in the cerebral glucose metabolism before the manifestation of amyloid plaques that might be the causative reason for AD development [47,48].

Glucose is the main energy substrate for the brain cells (glial cells and neurons). It is now well established that aberrations in cerebral glucose utilization, glycolysis and oxidative metabolism are associated with cognitive dysfunction in AD [43,48–51]. There is a particular pattern of regional brain glucose hypometabolism in AD affecting the parietal and temporal cortices, where the glucose deficit is on the order of 20–25% compared to age-matched, cognitively normal controls [52]. Many studies indicate that presymptomatic brain glucose hypometabolism can be present long before the threshold of cognitive symptoms of AD and could therefore potentially be contributing to the development and/or progression of both the cognitive decline and the neuropathological hallmarks associated with AD. To this regard, although a neuropathological link has not yet been fully demonstrated in humans, increasing evidence in transgenic mouse models of AD suggests that various experimental approaches to diminishing brain glucose supply all drive Aβ overproduction [53]. Moreover, both type-2 diabetes and its associated brain insulin resistance were proposed to favour tau hyper-phosphorylation in AD, although the molecular mechanisms are still unclear [51,54,55].

During the course of time, glucose alterations in the brain have a detrimental effect on the glutamatergic system due to an imbalance in glutamate availability. Neurons and glial cells work in tight cooperation in the glutamate/glutamine cycle and this cycle is connected with the energy metabolism, and, in turn, with the availability of glucose to the brain. Glutamate can be converted into α-ketoglutarate and vice-versa and serves as a substrate in the tricarboxylic acid (TCA) cycle. Research on APPswe/PSEN1dE9 mice showed that prior to amyloid plaque deposition, brain energy metabolism is affected leading to changes in glucose metabolism, reduced TCA cycle activity, decreased adenosine triphosphate (ATP) synthesis in isolated mitochondria were observed demonstrating that alterations in cerebral energy metabolism precede the amyloid plaques formation [56]. The conversion of glutamate to glutamine by the enzyme glutamine synthetase requires ATP and it has been estimated that 70% of the signaling energy comes from the oxidation of glucose [57]. Therefore, impairment in glucose metabolism impacts the glutamate receptor-mediated signal pathway leading to initial stages of memory impairment observed in patients affected by AD [58,59]. Figure 1 describes how alterations in cerebral glucose levels affect glutamate output leading to neuronal death in AD.
Figure 1. Presynaptic terminals release glutamate activating ionotropic receptors on postsynaptic neurons. In normal condition, N-methyl-D-aspartate (NMDA) NR2A activation induces increase in calcium levels favouring induction of long-term potentiation (LTP) through metabolic pathways (extracellular signal-related protein kinase (ERK), CaMK II, cyclic adenosine monophosphate response element-binding protein (CREB)). Excess glutamate left is taken up by astrocytes through EAAT2 converting into glutamine and glutamate by glutamine synthetase and glutaminase respectively (black arrows). The synthesized glutamate is transported into vesicles by VGlut1/2. Conversely in Alzheimer’s disease (AD), Aβ oligomers interfere with NMDA receptors increasing the spillover of glutamate (red arrows) to extrasynaptic sites activating NMDA NR2B receptors increasing excess calcium levels inhibiting prosurvival pathways. Imbalance in glutamate/glutamine cycle (black-dashed arrows) is also reported in the figure.

3. Glutamatergic System

3.1. Glutamate/Glutamine Cycle

Glutamate is a nonessential amino acid that does not cross the blood–brain barrier and is extensively distributed throughout the CNS. Glutamate is produced in neurons, and glial cells from the precursor’s glucose, α-ketoglutarate [60]. The concentration of glutamate in the synaptic cleft at resting condition is about 0.6 μM [61] and it goes to above 10 μM during presynaptic neuronal depolarisation, where overstimulation is prevented by the rapid and efficient removal from the extracellular space [62]. Glutamate is released into synapse from presynaptic neurons, leading to its uptake and activation of glutamatergic receptors. After receptor activation, the excess amount of glutamate is taken up by astrocytes through their excitatory amino acid transporters (EAAT) 1, and 2. In glial cells, glutamate is converted into glutamine in the presence of glutamine synthetase. Glutamine is a non-neuroactive molecule, which is released into extracellular space and lacks the ability to react with glutamate receptors [63]. Presynaptic neurons recover the glutamine and convert it into glutamate by the action of phosphate-activated glutaminase (PAG) [64]. Glutamate is transported into synaptic vesicles through the activity of vesicular glutamate transporters 1 and 2 (VGLUT1/2). This complete glutamate/glutamine cycle was established in the 1970’s and is described in Figure 1 [65,66].

Perturbations of the glutamate/glutamine cycle could cause excitotoxicity through the tonic activation of glutamate receptors, leading to an influx of Ca²⁺ that, in turn, can cause cell death by necrosis and apoptosis. In particular, the perturbation may be due to the inactivation of EAAT1/2...
or glutamine synthetase, which would increase the concentration of glutamate in the synaptic cleft, causing over-excitation [67,68].

3.2. EAATs

EAATs take up the synaptic glutamate at synapse and terminate the glutamatergic transmission. Five mammalian EAAT isoforms (EAAT1–5) have been identified and EAAT1 and 2 are expressed mainly in astrocytes, while EAAT3, 4, and 5 are expressed in neurons [69–71]. However, EAAT2 is most significant in glutamate homeostasis and its dysfunction leads to glutamate-mediated toxicity and neuropathology in AD [67,68]. Electrophysiological studies confirm that 90–95% of extracellular glutamate is taken up by EAAT2 in astrocytes that modulate glutamate transmission and supply glutamate to other adjacent neurons [72]. Blockade with dihydrokainic acid (DHA), a selective inhibitor of EAAT2 [73] resulted in extended excitatory NMDA receptor-mediated synaptic current [74]. In astrocytes, glutamate undergoes oxidative metabolism producing ATP indicating that the glutamate transported via EAAT2 produces energy [75]. EAAT2 plays a vital role in cognitive functions [76], and its contribution to disease pathology is observed through the loss of EAAT2 protein and functions in AD patients [67]. Intriguingly, EAAT2 mRNA levels are not decreased in AD patients but the decline of EAAT2 protein levels indicates disturbances in the post-transcriptional process [68].

Moreover, mutation of APP/presenilin-1 in mice leads to a partial loss of EAAT2 expression, suggesting the imperative role of glia in AD pathology [77,78]. Moreover, the induction of Aβ1-42 leads to mislocalization of EAAT2 in glia, reducing the clearance of glutamate in the synaptic cleft [79]. EAAT2 undergoes impaired oxidation in AD patients and Aβ-treated rat cortical synaptosomes cultures [80]. In AD pathogenesis, lipid peroxidation in the neuronal membrane after Aβ deposition releases 4-Hydroxy-2-noneal (HNE), a neurotoxic peptide that promotes the generation of ROS modifying the structure and functions of EAAT2 [80,81]. HNE is an electrophilic aldehyde that reacts covalently with cysteine, lysine, and histidine residues of EAAT2 impairing its functions. This leads to an increase in glutamate concentration at the synaptic cleft triggering excitotoxicity mediated neurodegeneration [80,82]. Nonetheless, loss of EAAT2 function increases the activity of insulin-degrading enzymes in the liver, suggesting that the loss of EAATs causes insulin/protein kinase B signaling abnormalities in AD [83]. These findings suggest that EAAT2 loss/dysfunction associated with AD pathology and EAAT2 could be used as a therapeutic target for neuroprotection in glutamate-mediated excitotoxicity.

3.3. Ionotropic Receptors

Ionotropic glutamate receptors are ligand-gated ion channels that mediate fast excitatory transmission. They include three kinds of subfamilies named for their original selective agonists: NMDA, α-amino-3-hydroxy-5-methyl-4isoxasolepropionic acid (AMPA) and kainate [84]. Table 1 lists the receptor family members, subunits, signal pathway and relevant physiological function.
Table 1. Overview of glutamatergic receptors mainly involved in the pathophysiology and pharmacotherapy of AD.

| IONOTROPIC RECEPTORS | Subunits | Ions | Localization | Characteristic Functions | References |
|----------------------|----------|------|--------------|--------------------------|------------|
| NMDA                 | GluN1    | Ca^{2+}, Na^+ | Postsynaptic neuron; GluN2B is primarily extra-synaptic | GluN1 is obligatory glycine binding subunit; Mg^{2+} block is removed upon depolarization for ion influx | [33,85–90] |
|                      | GluN2A   |      |              |                          |            |
|                      | GluN2B   |      |              |                          |            |
|                      | GluN2C   |      |              |                          |            |
|                      | GluN2D   |      |              |                          |            |
|                      | GluN3A   |      |              |                          |            |
|                      | GluN3B   |      |              |                          |            |
| AMPA                 | GluA1    | Ca^{2+}, Na^+ | Presynaptic and postsynaptic neuron | Activation of presynaptic AMPA receptors results in a modulation of PKA activity; AMPA receptors depolarization in postsynaptic compartment leads to influx of Ca^{2+}, Na^+ ions activating NMDA receptors | [91–93] |
|                      | GluA2    |      |              |                          |            |
|                      | GluA3    |      |              |                          |            |
|                      | GluA4    |      |              |                          |            |

| METABOTROPIC RECEPTORS (mGluRs) | Groups | Receptors | G protein | Localization | Characteristic Functions | References |
|---------------------------------|--------|-----------|-----------|--------------|--------------------------|------------|
|                                 | Group 1 (Excitatory) | mGlu1 | Gq | Primarily postsynaptic | Involved in mediating LTP and LTD; Enhances excitability and synaptic plasticity | [90,94–97] |
|                                 |        | mGlu5    |           |              |                          |            |
|                                 | Group 2 (Inhibitory) | mGlu2 | Gi | Primarily presynaptic | mGluR2/3 receptors main function is to inhibit the release of glutamate. These receptors are activated by non-vesicular, extra-synaptic glutamate that is released by astrocytes in exchange for cystine | [90,94,97–100] |
|                                 |        | mGlu3    |           |              |                          |            |
|                                 | Group 3 (Inhibitory) | mGlu4 | Gi | Pre- and postsynaptic | Inhibit the release of presynaptic glutamate; Inhibit NMDA activity and prevent neurotoxicity | [90,94,97,101,102] |
|                                 |        | mGlu6    |           |              |                          |            |
|                                 |        | mGlu7    |           |              |                          |            |
|                                 |        | mGlu8    |           |              |                          |            |

3.3.1. NMDA Receptors

NMDA receptors are heterotetramers identified with seven different subunits such as one GluN1 subunit, four GluN2 subunits (GluN2A, GluN2B, GluN2C and GluN2D), and two GluN3 subunits (GluN3A and GluN3B) [103]. NMDA receptors comprise of two GluN1, two GluN2 or GluN3 subunits in some cases [104] and GluN1, is considered as an obligatory subunit. In addition to their synaptic localization, NMDA receptors are also found at extrasynaptic sites. In particular, extrasynaptic NMDA receptors are located on dendrites or on non-perisynaptic parts of the spine and require high glutamate concentrations in order to be activated [105]. These NMDA receptors are characterized by favoring the GluN2B subunit which, when excessively stimulated, contributes to pro-death signalling [106]. Moreover, extrasynaptic NMDA receptors are involved in the regulation of Aβ production and thus in the neuropathology of AD [107].

The activation of NMDA receptors is controlled by glutamate, D-serine or glycine binding and release of Mg^{2+} block after membrane depolarization [108]. NMDA receptors are permeable for Na^+, K^+, and highly permeable for Ca^{2+} that acts as a secondary messenger to stimulate intracellular signaling cascades such as Ca^{2+}/calmodulin-dependent kinase II (CaMKII), ERK activation, and phosphorylation of cyclic adenosine monophosphate response element-binding protein (CREB), which are involved in
inducing long-term potentiation (LTP) [109]. LTP induction promotes the growth of dendritic spines and the recruitment of AMPA receptors [110].

Though NMDA receptors maintain synaptic plasticity and survival of neurons, excess activation of NMDA receptors leads to excitotoxicity, neurodegeneration and cell death. The increase in Ca\(^{2+}\) levels activates catabolizing enzymes like calpain I [111], phospholipases [112] and arachidonic acid metabolism [113] resulting in a surge of reactive oxygen and nitrogen species leading to neuronal cytoskeleton collapse and membrane degeneration [114]. Moreover, elevated Ca\(^{2+}\) may also activate protein kinases, which lead to hyperphosphorylation of ubiquitin and tau [115,116]. Thus, modulation of NMDA receptor functions is beneficial in AD by regulating glutamate availability and altering NMDA receptor signaling [117].

### 3.3.2. Interaction between NMDA Receptors and A\(\beta\)

A\(\beta\) peptides exist as monomers, dimers, trimers, tetramers, dodecamers, oligomers and protofibrils [118]. Studies confirm that soluble A\(\beta\) and oligomeric A\(\beta\) exert more toxic effects than insoluble amyloid plaques [119,120]. In the hippocampus and cortex, the brain region mainly affected by A\(\beta\) pathology in human, GluN2A and GluN2B are the predominant subunits with vital functions in synaptic plasticity [121]. Elevated A\(\beta\) peptides inhibit LTP leading to the shift of NMDA receptor-dependent signaling cascades to long-term depression (LTD) [110]. Therefore, the accumulation of A\(\beta\) oligomers disrupts the synaptic transmission leading to early cognitive deficits [122]. A\(\beta\)-induced LTD is caused by blocking glutamate uptake at glial cells, increasing glutamate levels in the synaptic cleft. Besides, A\(\beta\) peptides also enhance glutamate release from presynaptic neurons [123] and astrocytes [124]. Thus, an increase in glutamate level activates extra-synaptic GluN2B containing NMDA receptors, which cause a modest increase in postsynaptic Ca\(^{2+}\) triggering LTD and, in turn, leading to synaptic impairment due to the collapse of dendritic spines damaging synapse growth and plasticity [110,125]. In particular, a high level of Ca\(^{2+}\) activates p38 mitogen-activated protein kinases (MAPKs), GSK3\(\beta\) and c-Jun N-terminal kinase (JNK) pathways that are involved in cell death signaling and tau hyperphosphorylation [105,126,127]. The increase in cytosolic Ca\(^{2+}\) is rapidly taken up by mitochondria to prevent cytosolic Ca\(^{2+}\) overload. The excess levels of Ca\(^{2+}\) in mitochondria result in the generation of ROS and nitric oxide, inhibition of ATP synthesis, mitochondrial permeability transition pore (mPTP) opening, release of cytochrome c, activation of caspases and lead to apoptosis [128–130]. Moreover, A\(\beta\) also initiates a spectrum of neuroinflammation by activating microglia that plays a detrimental role in the expression of pro-inflammatory cytokines like interleukins and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) influencing neurodegeneration as shown in Figure 2 [131–133].

Several studies have demonstrated that A\(\beta\) is also able to modulate the expression of NMDA receptors and vice versa. In this regard, an in vivo study shows that a low-level activation of the NMDA receptor increases A\(\beta\) production, while the higher activation of the NMDA receptor decreases A\(\beta\) production [134]. A\(\beta\) oligomers also seem to bind the surface tyrosine kinase receptor namely the Ephrin ligand-receptor (EphB2), which maintains the integrity of NMDA receptors. Loss of NMDA receptor functions and reduction in LTD are noticed after EphB2 degradation that resulted in a decrease in NMDA receptor surface localization [135]. AD mouse models and post-mortem analysis of the prefrontal cortex in AD patients displayed an increase in expression of striatal-enriched protein tyrosine phosphatase 61 (STEP61). A\(\beta\) interacts with NMDA receptor reducing their surface expression through A\(\beta\)-induced NMDA receptor internalization by STEP61 through dephosphorylation of the GluN2B subunit at Tyr-1472 [136–138]. A\(\beta\) oligomers also react with cellular prion protein (PrPc) altering the NMDA receptor function through two known potential mechanisms [139]. Primarily, A\(\beta\) oligomer interacts with PrPc receptor activating Fyn, a tyrosine kinase phosphorylating GluN2B enhancing NMDA receptor function before dephosphorylation of GluN2B by increased levels of STEP61. Secondarily, A\(\beta\) chelates copper ions abrogating the binding of PrPc to NMDA receptors and inhibiting their activity thereby, producing large nondesensitizing steady-state NMDA receptor currents and neurotoxicity [140].
3.3.3. Interaction between NMDA Receptors and Tau

Tau is an axonal protein engaged in the stability of microtubules and is a major component in NFT. Tau protein mis-localizes from axon to dendritic spines after phosphorylation resulting in synaptic impairment and LTP deficits [141]. NMDA receptor stimulation and Aβ deposition induce tau phosphorylation. Enhanced overexpression of tau phosphorylation may increase NMDA receptor transmission that could facilitate to LTD. NMDA receptor-dependent tau phosphorylation is reversible but Aβ-induced tau phosphorylation is not reversible if the Aβ exposure persists for more than five days [142]. Tau protein is involved in the activation of the NMDA receptor mediated by Fyn, a tyrosine kinase that phosphorylates GluN2B subunit at Tyr1472 stabilizing interaction with cellular prion protein (PrPc) altering the NMDA receptor function through two known potential mechanisms [139]. Primarily, Aβ/PrPc-mGlu5 combination leads to AMPA internalization. Excess increase in levels of Ca2+ in mitochondria results in the generation of reactive oxygen species (ROS) and NO, inhibition of ATP synthesis, mitochondrial permeability transition pore (mPTP) opening, release of cytochrome c, activation of caspases and leading to apoptosis. In addition, Aβ also initiates a spectrum of neuroinflammation by activating microglia that plays a detrimental role in the expression of pro-inflammatory cytokines like interleukins and tumor necrosis factor-α (TNF-α) influencing neurodegeneration. (red arrows indicate “increase”).

Figure 2. Schematic representation of AD pathophysiology involving Aβ, extrasynaptic NMDA Glu2NB, mGlu5 and role of activated microglia. Activation of NMDA Glu2NB receptors increases calcium levels inducing p35 to p25 cleavage mediated by calpain and p25 is activates cdk-5 enhancing DARPP-32 phosphorylation eventually leading to AMPA receptor internalization. Increase in Aβ levels activates Cdk-5 that plays a major role in Golgi fragmentation and tau phosphorylation leading to dissociation of tau from microtubules. Furthermore, Cdk-5 mediates phosphorylation of signal transducer and activator of transcription 3 (STAT3), which increases β-site APP cleaving enzyme 1 (BACE1) transcription resulting in an increase of Aβ content. Moreover, Aβ-PrPc-mGlu5 combination leads to AMPA internalization. Excess increase in levels of Ca2+ in mitochondria results in the generation of reactive oxygen species (ROS) and NO, inhibition of ATP synthesis, mitochondrial permeability transition pore (mPTP) opening, release of cytochrome c, activation of caspases and leading to apoptosis. In addition, Aβ also initiates a spectrum of neuroinflammation by activating microglia that plays a detrimental role in the expression of pro-inflammatory cytokines like interleukins and tumor necrosis factor-α (TNF-α) influencing neurodegeneration. (red arrows indicate “increase”).
3.3.4. AMPA Receptors

AMPA receptors mediate fast and excitatory synaptic neurotransmission in the brain. AMPA receptors are composed of tetrameric assemblies of two dimers having subunits GluA1-GluA4 [147]. AMPA receptors are expressed both in neural and glial cells, their tight control at synapse maintain synaptic plasticity. Aberrant trafficking of AMPA receptors impairs learning and memory [148].

3.3.5. Interaction between AMPA Receptors and Aβ

AMPA receptors trafficking at the synapse is an important mechanism in inducing synaptic plasticity. Aberrant movement of AMPA receptors towards and away from synapse leads to impairment in learning and memory [148]. AD pathogenesis involves deviations in AMPA receptor trafficking pathways. Aβ plays an important role in promoting AMPA receptor endocytosis leading to synaptic depression [125]. Aβ induces p35 to p25 cleavage mediated by calpain in the hippocampus. P25 is a Cdk-5 activating peptide involved in the pathological action of Aβ [149]. P25/Cdk-5 activity is increased by Aβ that enhances phosphorylation at Thr-75 of dopamine-and cyclic adenosine monophosphate-regulated neuronal phosphoprotein (DARPP-32), which inhibits PKA activity [150]. Moreover, Aβ dephosphorylates Thr-34 of DARPP-32, which eventually leads to AMPA receptor internalization due to loss of GluA1 phosphorylation at Ser-845 [151]. Consistent with these findings, inhibition of p25 generation in 5xFAD transgenic mice rescues LTP and memory deficits [149]. In addition, activation of Cdk-5 demonstrated to increase Aβ production [152] and further studies revealed that Cdk-5 mediated phosphorylation of signal transducer and activator of transcription 3 (STAT3), which increases the transcription of β-site APP cleaving enzyme 1 (BACE1) [153], consequently resulting in an increase of Aβ generation as shown in Figure 2 [154]. Elevated Aβ levels stimulate Cdk-5 activity, which plays a major role in Golgi fragmentation [155] and tau phosphorylation leading to dissociation of tau from microtubules in AD [156].

Aβ prevents activation of Ca²⁺/CaMKII and their accumulation causes deviations in the redistribution of CaMKII from synapse to cytosol, preventing AMPA receptors insertion into the plasma membrane [151,157]. CaMKII has multiple roles in mediating AMPA receptor transmission and potentiating synaptic transmission through GluA1 phosphorylation at Ser-831 that increases AMPA receptor channel conductance, to facilitate AMPA receptor synaptic recruitment by TCR Gamma Alternate Reading Frame Protein (TARP), stargazin phosphorylation and potentiating Ras-ERK pathway [158–160]. APPswe transgenic mice and cultured neurons with Aβ exposure displayed consistent results confirming that AMPA receptor response decreases due to the redistribution of CaMKII [161].

3.4. Metabotropic Receptors

mGlu receptors are G protein-coupled receptors (GPCRs) classified into three subtypes containing eight mGlu receptors and are responsible for modulating and fine-tuning the synapse [162]. Group I mGlu receptors contain mGlu1 and mGlu2, which are linked to polyphosphoinositide (PI) hydrolysis and negatively coupled with K⁺ channels [163]. Group II mGlu receptors consist of mGlu3, mGlu5 and Group III comprise of mGlu4, mGlu6, mGlu7 and mGlu8. Group II and III negatively regulate adenylate cyclase but activate MAPKs and PI-3-kinase pathways [164,165].

All mGlu receptor subtypes are present in neurons, while mGlu3 and mGlu5 receptors are found in astrocytes and microglial cells express mGlu2, mGlu3 and mGlu5 receptors [166]. Table 1 lists the receptor family members, subunits, signal pathway and relevant physiological function.

3.4.1. mGlu5 Receptors

mGlu5 receptors have been implicated in neurodegenerative diseases like Alzheimer’s, Parkinson’s and Huntington’s disease [167]. Memantine, a non-competitive NMDA receptor antagonist failed to attenuate Aβ-induced glutamate levels suggesting the involvement of other receptors [168]. Recent studies
have demonstrated that mGlu5 but not mGlu1 mediates synaptotoxic signaling [169]. mGlu5 receptors are highly expressed in the brain cortex and hippocampal regions that play a preponderance role in cognition and hence assumed that mGlu5 receptors are involved in synaptotoxic effects of AD pathogenesis mediated by oligomeric forms of Aβ1-42 [170–172]. Deleterious effects of Aβ oligomers on mGlu5 receptors include receptor overactivation, intracellular Ca²⁺ accumulation, receptor clustering, impaired homeostasis and synaptic disruption [173,174].

mGlu5 receptors are linked to the extra-synaptic GluN2 subunit of the NMDA receptor and involved in regulating neuronal excitability possibly through Homer/PSD95/Shank protein complex [172,175,176]. mGlu5 receptors display peri-synaptic localization at the post-synaptic membrane [177], regulating neuronal excitability of ionotropic glutamate receptor channels [178,179]. Genetic deletion, antagonists and pharmacological blockade of mGlu5 receptors suppress excitotoxic degeneration and are found to be neuroprotective [180–183]. Moreover, mGlu5 receptor gene transfer into hippocampal cornu ammonis 1 (CA1) resulted in neurodegeneration, and in contrast, silencing mGlu5 receptors has shown protective effects in CA3 region of transgenic mice [184].

A study demonstrated that Aβ could suppress LTP in normal mice but not in mice lacking PrPc [139], suggesting that mGlu5 could be a co-receptor for both PrPc and Aβ oligomers [185]. mGlu5 receptor interacts with amino acids 91-153 of PrPc and is influenced by mGlu5 receptor ligands. Aβ-PrPc-mGlu5 combination signals Fyn tyrosine kinase activation and E2F phosphorylation leading to synaptic loss [186,187]. Furthermore, this combination causes the redistribution of CaMKII leading to AMPA internalization [151]. Besides, other studies also indicate that PrPc is essential for the actions of Aβ in altering mGlu5 functions to regulate synaptic plasticity [188]. PrPc is found to be a potential receptor for Aβ oligomers greater than 150 kDa [189]. Aβ oligomers increase the interaction of the mGlu5 receptor with PrPc mediating Aβ-dependent synaptotoxicity [186]. In AD mice, the deletion of mGlu5 receptors reduces amyloid content and rescues from memory deficits [181]. However, it was also shown that PrPc is not required for Aβ-induced synaptic depression, spine density reduction and blockade of LTP [190]. Consequently, it is necessary to evaluate the interactions of Aβ-PrPc-mGlu5 and their involvement in inducing synaptic depression.

3.4.2. mGlu2/3 Receptors

mGlu2 receptors are located in presynaptic terminals of glutamatergic neurons inhibiting the release of glutamate and maintain glutamatergic transmission [94]. Meanwhile, mGlu3 receptors are present in the postsynaptic membrane and in glial cells [94,191]. mGlu3 receptor activation enhances neuroprotection by preventing glucose-induced oxidative injury through radical scavenging and antioxidant defence [192]. Selective activation of the mGlu2 receptor enhances neuronal vulnerability to Aβ, while dual activation of mGlu2 and mGlu3 receptors is protective against Aβ-induced neurotoxicity [193]. Therefore, a combination of mGlu2 receptor blockade and activation of the mGlu3 receptor could be used as a strategy in AD treatment [171]. mGlu receptors activation in microglia showed the controversial results that mGlu2 receptor activation intensifies myelin-induced neurotoxicity in cerebellar granule neurons, while neuroprotective effects are exerted by mGlu3 receptor agonist N-acetylaspartylglutamate (NAAG) [194]. Moreover, in astrocytes, mGlu3 receptor activation promotes non-amyloidogenic or α-cleavage of APP increasing sAPPα and inhibiting expression of β-secretase [195]. mGlu2 receptor activation induces microglial apoptosis [196], while another study shows that mGlu2 receptor mediates in Aβ clearance by microglia [197].

mGlu2 receptors are also involved in learning and cognition and its inhibition improved memory in AD rodent models [198,199]. mGlu2 receptor activation induces TNF-α mediating TNF receptor 1 and caspase-3 activation leading to microglial neurotoxicity [196]. Furthermore, upregulated levels of chromogranin-A peptide in AD after activation of group II metabotropic receptors results in microglial reactivity and neurotoxicity [200]. Of note, selective activation of mGlu2 receptor activation increases Aβ neurotoxicity while combined activation of mGlu2 and mGlu3 receptors found to be neuroprotective in the presence of astrocytes due to the release of Transforming growth factor
β1 (TGF-β1) mediated by glial mGlu3 receptors [193]. TGF-β1 seems to play an imperative role in deploying synaptic plasticity and memory transition from early LTP to late LTP [201]. Moreover, TGF-β1 exerts neuroprotective and anti-inflammatory effects stimulating microglia in the clearance of Aβ peptides [202]. The connection between TGF-β1 gene polymorphism and AD strengthens the role of TGF-β1 in memory and neuroprotective functions [171]. Reduction in type-II TGF-β1 receptors and dysfunction in TGF-β1 signaling leads to neurodegeneration and AD pathology in mice [203,204].

mGlu3 receptor binds to peptide transmitter NAAG, the third most prevalent neurotransmitter after glutamate and gamma-aminobutyric acid (GABA) [205,206]. NAAG synthetase I (NAAGSI) mediates the synthesis of NAAG in neuronal cells. The glial enzyme, glutamate caboxypeptidase II (GCPII), converts NAAG into N-acetylaspartate (NAA) and glutamate, which gets transported into glial cells [206]. GCPII inhibitors increase the extracellular concentration of NAAG and the drugs that increase the NAAG levels are pro-cognitive in object recognition test [207]. Treatment with GCPII inhibitors, ZJ43 (N-[[1S]-1-Carboxy-3-methylbutyl]amino]carbonyl]-L-glutamic acid) and 2-(phosphonomethyl) pentanedioic acid (2-PMPA) improved cognition in mice. In aged triple transgenic mice, ZJ43 reversed the cognitive deficit and 2-PMPA improved short-term novel object recognition test in 9-month old AD mice [208]. NAAG is co-released along with glutamate into the synapse, while NAAG is released perisynaptically activating presynaptic mGlu3 receptors that inhibit further release of glutamate to prevent excitotoxicity and to reduce disease pathogenesis. Besides, mGlu3 receptor activation by NAAG also stimulates the release of TGF-β1 [206].

4. Therapeutics for AD

Drug discovery, research and development for AD are strenuous and challenging. Over hundreds of drugs have failed and, currently, there are 132 agents in clinical trials for AD treatment. Since 2003, no new drugs and no disease-modifying treatments (DMTs) have been approved for AD [209]. Current treatment of AD includes drugs targeting the cholinergic system such as donepezil, rivastigmine, galantamine; drug acting on the glutamatergic system like memantine and drugs that intervene both cholinergic and glutamatergic system namely Namzaric, a combination of memantine and donepezil [210]. Some of the therapeutic agents acting on the glutamatergic system are discussed below and listed in Table 2.

| Receptors | Drugs | Mechanisms | Key Findings | Preclinical and Clinical Studies/Approval Status | References |
|-----------|-------|------------|--------------|-----------------------------------------------|------------|
| NMDA      | Memantine | Non-competitive NMDAR antagonist | Improves cognition, Slow-down disease progression, Reduce tau phosphorylation | Approved by EMEA in 2002 and by USFDA in 2003 | [32,33,211–213] |
| Phenycycline | NMDAR antagonist | | Psychotomimetic | No clinical applications | [214] |
| Ketamine | Non-competitive NMDAR antagonist | | Psychotomimetic | No clinical applications | [214] |
| MK-801 (Dizocilpine) | Non-competitive NMDA blocker | | Cardiovascular side effects | No clinical applications | [214] |
| Nitromemantine | Selective inhibition of extrasynaptic NMDAR | | Ameliorates Aβ-induced synaptic loss | In vivo studies in α7nAChR-knockout, hAPP-J20/Tg, and 3× Tg AD mice | [124] |
4.1. Modulators of Ionotropic Receptors

The non-competitive NMDA receptor antagonist memantine has an inhibitory effect on NMDA receptor-mediated excitotoxicity, improves cognition, slows disease progression and reduces tau phosphorylation [32,33,211,226]. Phencyclidine, ketamine and MK-801 (dizocilpine) target NMDA receptors but their clinical applications are hampered due to severe side effects [214]. Memantine inhibits neuronal excitotoxicity by inhibiting extrasynaptic Ca²⁺ influx, improving symptoms in patients with moderate to severe AD [227]. However, memantine preferentially targets HMW Aβ-induced synaptotoxicity rescuing from both neuronal oxidative stress and transient memory impairment but unable to prevent LMW Aβ-induced persistent cognitive deficit [13]. An improved NMDA receptor antagonist nitromemantine protects neuronal synapses both in vitro and in vivo by selectively blocking the aberrant extrasynaptic activity over physiological synaptic NMDA receptor activity [124].
Uncaria rhynchophylla is a medicinal herb that contains oxindole alkaloid, rhynchophylline that restores LTP and alleviates Aβ-induced activation of extrasynaptic NMDA receptors. Rhynchophylline is a significant active compound that protects from deficits in spatial learning and memory induced by soluble Aβ oligomers. Moreover, rhynchophylline also prevents the hyperactivation of extrasynaptic NMDA receptors by reducing postsynaptic currents in AD mice [216]. Another medicinal plant Pulsatilla Chinensis contains a natural triterpenoid saponin compound anemoside A3 (AA3) that modulates synaptic connectivity and memory enhancement. AA3 increases serine phosphorylation of AMPA receptors subunit of GluA1 that is required for AMPA receptors trafficking at synapses. In the hippocampus, AA3 increases the expression of monoamine neurotransmitters and neurotrophin, a brain-derived neurotrophic factor. Furthermore, AA3 acts as a non-competitive NMDA receptor modulator protective against overexcitation and ischemic brain injury [217].

4.2. Modulators of mGlu Receptors

4.2.1. mGlu5 Receptor Modulators

mGlu5 receptor is coupled with heterotrimeric G protein Gaq/11 and its activation results in the release of intracellular Ca2+ that is linked to numerous neurodegenerative diseases [167]. Genetic deletion of mGlu5 receptor rescues cognitive decline and AD pathogenesis in APPswe/PS1E9 AD mouse model [181]. Besides, selective blockade of mGlu5 receptor activity with a negative allosteric modulator (NAM) 2-chloro-4-[2-[2,5-dimethyl-1-[4-(trifluoromethoxy)phe-nyl]imidazol-4-yl]ethynyl] pyridine (CTEP) improved cognition in AD mice [218]. CTEP rescues cognitive functions by decreasing Aβ levels through ZBTB16-mediated autophagy activation in APPswe/PS1E9 mice [228]. However, the efficacy of CTEP remains inconsistent with disease progression. In 15-month-old APPswe/PS1E9 mice, loss of CTEP efficacy is found after 36 weeks of treatment due to the abolished contribution of ZBTB16 and mammalian target of rapamycin (mTOR)-mediated signaling. This data suggests that the pathological role of mGlu5 receptors may shift during the course of disease progression and proper therapeutic strategies should be amended for beneficial outcomes [229].

Furthermore, the selective blockade of mGlu5 receptors with 3-((2-methyl-1,3-thiazol-4-yl)ethynyl) pyridine (MTEP) reversed the learning and memory deficits in AD mice by rescuing synaptic dysfunction [181,186]. A key finding suggests that the silent allosteric modulator (SAM) BMS-984923 was able to rescue the established memory deficits in AD mice with normal mGlu5 receptor signaling in APPswe/PS1E9 mouse model of AD. BMS-984923 is able to potentially inhibit mGlu5-PrPc interactions preventing Aβ-induced pathological signaling [219]. Moreover, mGlu5 receptors are also involved in regulating the release of inflammatory factors and ATP in non-neuronal cells such as microglia and astrocytes [230]. Non-selective group I/II mGlu receptor antagonist LY341495, reported to improve synaptic plasticity and blocking Aβ-enhanced long-term depression [224]. Moreover, pretreatment with mGlu1/5 receptor agonist, 3,5-dihydroxyphenylglycone (DHPG) also decreased Aβ-enhanced LTD [220]. mGlu5 receptor non-competitive antagonist SIB1757, prevented Aβ-induced reduction of NMDA receptors when neurons were pretreated with this molecule [173].

4.2.2. mGlu2/3 Receptor Agonist/Antagonists

mGlu2/3 receptor antagonists demonstrated pro-cognitive effects in the Morris water maze test [199], novel recognition test [231] and social recognition test [232]. Orthosteric mGlu2/3 receptor agonist like LY379268 exerts mGlu3 receptor signaling, protecting neurons through the production of TGF-β1 and glial cell line-derived neurotrophic factors (GDNF) [193,221–223]. Durand et al. (2017) showed that apart from mGlu3 receptor agonists, protective effects through astrocyte-derived neurophins, neuronal mGlu3 receptor activation also protects against Aβ-induced toxicity that disagrees with a previous report by Caraci et al., 2011. LY379268 injection upregulates brain-derived neurotrophic factor (BDNF) mRNA and protein levels in neurons of the cerebral cortex and hippocampus [233], group II mGlu receptor agonist (2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine (DCG-IV) increased BDNF
mRNA only in microglial cells [234], while another study found an increase in BDNF mRNA levels after treating cultured astrocytes with LY379268 [197]. mGlu2 receptor positive allosteric modulator (PAM), N'-4'-cyano-biphenyl-3-yl)-N-(3 pyridinylmethyl)-ethanesulfonamide hydrochloride (LY566332) has increased Aβ-induced neurodegeneration, while this effect is prevented by treatment with mGlu2/3 receptor agonist (2S,1'S,2'S)-2-(9-xanthylmethyl)-2-(2'-carboxycyclopropyl) glycine (LY341495) [193].

4.3. EAAT2 Activators

EAAT2 impairment is implicated in excess glutamate accumulation at the synaptic cleft leading to neurodegeneration in AD. The compounds that increase the activity of EAAT2 may have therapeutic benefits and neuroprotection. To investigate the cognitive benefit of restored EAAT2 in APP_{Sw,Ind} mice, a novel translational activator (LDN/OSU-0212320) is used as a pharmacological approach that restored EAAT2 protein significantly with improved cognitive functions and reduced Aβ plaques [69]. In a virtual screening approach study, two molecules GT949 and GT951 were identified as PAM of EAAT2 in cultured cells that enhanced glutamate uptake showing neuroprotective properties [225].

5. Conclusions

Neurodegeneration as in AD is a multifactorial disease, which is why a general pathological mechanism and appropriate treatment have not been found, but various etiological hypotheses have been proposed in order to understand a little about the etiology of AD. To this regard, glutamate seems to play major roles in part because of its abundance in brain tissue and in part because it is at the crossroad of multiple metabolic pathways. In fact, glutamate is the major mediator of excitatory signals in SNC and both too much glutamate and too little glutamate are harmful. When this delicate balance is disrupted, the perturbations of glutamate neurotransmission have severe consequences, leading to the onset of AD. Although it has a pivotal role in the etiology of AD, the glutamatergic system offers many pharmacological tools and therapeutical targets in order to slow down the disease.

In this regard, antagonists of the NMDA receptor damper the excitotoxicity induced by glutamate in AD. Memantine and its combination with donepezil are approved by Food and Drug Administration to treat moderate to severe AD. However, these current medications are not able to completely rescue the brain cells from the damage of AD progression. Thus, there is a lot of need to focus on and develop some disease-modifying drugs that could slow the progression of AD. Some medicinal herbs contain active components, like rhynchophylline, and AA3, which restore LTP by inhibiting the activation of extrasynaptic NMDA receptor and enhance cognition by acting on AMPA receptors respectively. Moreover, mGlu2/3 ligands could be used as antagonists for AD treatment and mGlu5 receptor modulators rescue from cognitive decline. Of note, PAMs of EAAT2 could block glutamate-mediated excitotoxicity by increasing the glutamate clearance. Thus, it is clear that the future to treat AD is through a multi-drug and multi-model approach using combinations of potential drugs for the treatment. The lack of successful drug developments in AD has provided the opportunity to develop agents that could modify AD progression. Aiming at the glutamatergic system is one such target that could be beneficial in the treatment of AD by reducing glutamate levels rescuing from glutamate-induced excitotoxicity.

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### Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AA3 | Anemoside A3 |
| AD | Alzheimer’s disease |
| AICD | APP intracellular domain |
| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid |
| ATP | Adenosine triphosphate |
| APP | Amyloid precursor protein |
| Aβ | Amyloid-β |
| BDNF | Brain-derived neurotrophic factor |
| BACE1 | β-site APP cleaving enzyme 1 |
| CA1 | cornu ammonis 1 |
| CAMKII | Calmodulin-dependent kinase II |
| Cdk-5 | Cyclin Dependent Kinase-5 |
| CK1/2 | Casein kinase 1/2 |
| CNS | Central nervous system |
| CREB | Cyclic adenosine monophosphate response element binding protein |
| CTEP | 2-chloro-4-[2-[2,5-dimethyl-1-[4-(trifluoromethoxy)phe-nyl]imidazol-4-yl]ethynyl] pyridine |
| DARPP-32 | Dopamine and cyclic adenosine monophosphate-regulated neuronal phosphoprotein |
| DCG-IV | (2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine |
| DHA | Dihydrokainic acid |
| DHPG | 3,5-dihydroxyphenylglycone |
| EAATs | Excitatory aminoacid transporters |
| EphB2 | Ephrin ligand receptor |
| ERK | Extracellular signal-related kinase |
| GABA | Gamma-Aminobutyric acid |
| GCPII | Glutamate caboxypeptidase II |
| GDNF | Glial cell line-derived neurotrophic factors |
| GPCRs | G protein-coupled receptors |
| GSK3β | Glycogen synthase kinase 3-β |
| HMW | High-molecular-weight |
| HNE | 4-Hydroxy-2-noneal |
| JNK | c-Jun N-terminal kinase |
| LTD | Long-term depression |
| LTP | Long-term potentiation |
| LMW | Low-molecular-weight |
| mTOR | mammalian Target of Rapamycin |
| MAP | Microtubule associated protein |
| MAPK | Mitogen-activated protein kinase |
| mPTP | mitochondrial permeability transition pore |
| MTEP | 3-(2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine |
| NAA | N-acetylaspartate |
| NAAG | N-acetylaspartylglutamate |
| NAAGS-I | NAAG synthetase I |
| NAM | Negative allosteric modulator |
| NFTs | Neurofibrillary tangles |
| NMDA | N-methyl-D-aspartate |
| Non-PDPKs | Non-proline-directed protein kinases |
| PAG | Phosphate-activated glutaminase |
| PAM | Positive allosteric modulator |
| PSD95 | Postsynaptic density protein 95 |
| PDPKs | Proline-directed protein kinases |
| PI | Polyphosphoinositide |
PKA Protein kinase A
PrPc Cellular prion protein
ROS Reactive oxygen species
SAM Silent allosteric modulator
sAPPα Soluble APPα
sAPPβ Soluble APPβ
STAT3 Signal transducer and activator of transcription 3
STEP61 Striatal-enriched protein tyrosine phosphatase 61
TARP TCR Gamma Alternate Reading Frame Protein
TCA Tricaboxylic acid
TGF-β1 Transforming growth factor β1
TMD Transmembrane domain
TNF-α Tumor necrosis factor-α
VGLUT1/2 Vesicular glutamate transporters 1 and 2
2-PMPA 2-(phosphonomethyl) pentanedioic acid

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