


# Amyloid Beta-Related Alterations to Glutamate Signaling Dynamics During Alzheimer's Disease Progression

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Caleigh A. Findley<sup>1,2</sup>, Andrzej Bartke<sup>3</sup>, Kevin N. Hascup<sup>1,2,4</sup>  and Erin R. Hascup<sup>1,2</sup> 

## Abstract

Alzheimer's disease (AD) ranks sixth on the Centers for Disease Control and Prevention *Top 10 Leading Causes of Death* list for 2016, and the Alzheimer's Association attributes 60% to 80% of dementia cases as AD related. AD pathology hallmarks include accumulation of senile plaques and neurofibrillary tangles; however, evidence supports that soluble amyloid beta ( $A\beta$ ), rather than insoluble plaques, may instigate synaptic failure. Soluble  $A\beta$  accumulation results in depression of long-term potentiation leading to cognitive deficits commonly characterized in AD. The mechanisms through which  $A\beta$  incites cognitive decline have been extensively explored, with a growing body of evidence pointing to modulation of the glutamatergic system. The period of glutamatergic hypoactivation observed alongside long-term potentiation depression and cognitive deficits in later disease stages may be the consequence of a preceding period of increased glutamatergic activity. This review will explore the  $A\beta$ -related changes to the tripartite glutamate synapse resulting in altered cell signaling throughout disease progression, ultimately culminating in oxidative stress, synaptic dysfunction, and neuronal loss.

## Keywords

$\alpha 7$  nicotinic acetylcholine receptors ( $\alpha 7nAChRs$ ), amyloid oligomers, synaptic dysfunction, excitotoxicity, mild cognitive impairment, N-methyl-D-aspartic acid (NMDA)

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## Introduction

The glutamatergic synapse, referred to as the tripartite synapse, involves three elements: presynaptic neurons, postsynaptic neurons, and astrocytes. There are several different synaptic components expressed on both neurons and astrocytes in the glutamate synapse, as summarized in Table 1. These components include two types of glutamate receptors that exist on these synaptic elements: metabotropic and ionotropic. Metabotropic glutamate receptors (mGluRs) are present on both presynaptic and postsynaptic neurons (Revet et al., 2013) and involve three different groups of receptors: Group I (mGluR1 and mGluR5), Group II (mGluR 2 and 3), and Group III (mGluR4, mGluR6, mGluR7, and mGluR8; Petralia et al., 1996; Rudy et al., 2015). Group I mGluRs are Gq-coupled and are expressed postsynaptically, depolarizing the postsynaptic neuron upon stimulation (Petralia et al., 1996; Ferraguti and

Shigemoto, 2006; Revett et al., 2013). Groups II and III mGluRs are Gi/o-coupled inhibitory autoreceptors and are expressed both pre- and postsynaptically (Petralia et al., 1996; Rudy et al., 2015), leading to inhibition of presynaptic glutamate release or postsynaptic

<sup>1</sup>Department of Neurology, Center for Alzheimer's Disease and Related Disorders, Neuroscience Institute, Southern Illinois University School of Medicine, Springfield, IL, USA

<sup>2</sup>Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, IL, USA

<sup>3</sup>Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, IL, USA

<sup>4</sup>Department of Molecular Biology, Microbiology & Biochemistry, Southern Illinois University School of Medicine, Springfield, IL, USA

### Corresponding Author:

Erin R. Hascup, Department of Neurology, Center for Alzheimer's Disease and Related Disorders, Neuroscience Institute, Southern Illinois University School of Medicine, P.O. Box 19628, Springfield, IL 62794-9628, USA.  
Email: ehascup@siumed.edu



**Table 1.** Brief Overview of Glutamatergic Synapse Components: Localization and Function.

Glutamate synapse components	Localization	Function	References
VGluT	Presynaptic neuron	Packaging glutamate into vesicles	Takamori et al., 2000; Fremeau et al., 2001, 2004
Glutaminase	Presynaptic neuron	Synthesizes glutamate from glutamine	Revett et al., 2013
$\alpha 7nAChR$	Both neurons and glia	Soluble $A\beta$ binding (in low concentrations) triggers $Ca^{2+}$ -dependent release of glutamate from the presynaptic neuron, as well as stimulation of the postsynaptic neuron	Wang et al., 2000b; Gahring et al., 2004; Magdesian et al., 2005; Puzzo et al., 2008; Mura et al., 2012; Hascup and Hascup, 2016
mGluR Group II/III	Pre- and postsynaptic neuron	$Gi/o$ -coupled receptor; inhibition of presynaptic release of glutamate or inhibition of postsynaptic response to stimulation	Ambrosini et al., 1995; Petralia et al., 1996; Ferraguti and Shigemoto, 2006; Rudy et al., 2015
mGluR Group I	Postsynaptic neuron	$Gq$ -coupled receptor; depolarizes neuron upon binding of glutamate and results in $Ca^{2+}$ release from intracellular stores	Petralia et al., 1996; Ferraguti and Shigemoto, 2006; Revett et al., 2013
AMPA	Pre- and postsynaptic neuron	Presynaptically promotes the formation of synapses. Postsynaptically depolarizes the neuron upon glutamate binding	Wisden and Seeburg, 1993; Isaac et al., 2007; Rudy et al., 2015
NMDA	Postsynaptic neuron	Contains a magnesium block that is removed upon depolarization of postsynaptic membrane, allowing for $Ca^{2+}$ influx into the neuron	Calabresi et al., 1992; Wisden and Seeburg, 1993; Pandis et al., 2006; Parsons et al., 2007; Rudy et al., 2015
GLT-1 (EAAT1)/GLAST (EAAT2)	Astrocytes	Clearance of glutamate from the synapse by uptake into astrocytes	Lehre et al., 1995; Revett et al., 2013
GS	Astrocytes	Conversion of glutamate to glutamine so that it may be transported back to the presynaptic neuron	Norenberg and Martinez-Hernandez, 1979; Parsons et al., 2007; Revett et al., 2013

Note. Outline of glutamate neuronal and astrocytic components and their functions in glutamatergic neurotransmission.

$\alpha 7nAChR$  =  $\alpha$ -7 nicotinic acetylcholine receptor; AMPA =  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAAT = excitatory amino acid transporter; GLAST = glutamate aspartate transporter; GLT-1 = glutamate transporter-1; GS = glutamine synthetase; mGluR = metabotropic glutamate receptor; NMDA = N-methyl-D-aspartic acid; VGluT = vesicular glutamate transporter.

excitation (Ambrosini et al., 1995; Ferraguti and Shigemoto, 2006).

The ionotropic glutamate receptors are expressed both pre- and postsynaptically (Wisden and Seeburg, 1993; Rudy et al., 2015) and include  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), *N*-methyl-*D*-aspartic acid receptors (NMDAR), and kainate receptors. AMPARs function presynaptically to promote synapse and spine formation (Isaac et al., 2007). On the postsynaptic side, all three ionotropic receptors are expressed (Wisden and Seeburg, 1993; Rudy et al., 2015). AMPARs are bound by glutamate and lead to membrane depolarization, while NMDARs have a magnesium block which is released upon membrane depolarization. This results from either high-frequency stimulation inducing  $\text{Na}^+$  influx through AMPARs or disinhibition of GABAergic synapses (Parsons et al., 2007), which then opens the NMDAR ion channel (Calabresi et al., 1992; Pandis et al., 2006; Parsons et al., 2007). In fact, AMPARs and NMDARs are colocalized on the postsynaptic membrane because of the cooperation required between the two receptors in response to membrane depolarization (Takumi et al., 1999; Antal et al., 2008). The opening of NMDARs results in  $\text{Ca}^{2+}$  influx into the postsynaptic neuron and, along with Group I mGluRs, increases intracellular  $\text{Ca}^{2+}$  (Chen et al., 2002; Hardingham et al., 2002; Hardingham and Bading, 2003; Verkhratsky and Kirchhoff, 2007; Yamin, 2009; Zhang et al., 2016). NMDA interacts with glutamate such that the NR2 subunit of the NMDA receptor binds glutamate, with NR2A and NR2B subtypes mediating excitotoxicity in cultured cortical neurons (von Engelhardt et al., 2007). The NR2 subunit is expressed both synaptically (NR2A) and extrasynaptically (NR2B; Rudy et al., 2015). Extrasynaptic NMDARs (E-NMDARS) are activated only by high concentrations of glutamate, unlike synaptic NMDARs (S-NMDARS) that are located closer to the synaptic cleft and are activated by presynaptic glutamate release (Groc et al., 2009; Newpher and Ehlers, 2009; Rudy et al., 2015). Both E-NMDAR stimulation and NMDA/mGluR-mediated  $\text{Ca}^{2+}$  influx constitute important factors in soluble amyloid beta ( $\text{A}\beta$ )-mediated neurotoxicity as explored further in this review.

Glutamate is synthesized from glutamine by glutaminase in the presynaptic neuron (Revett et al., 2013), and then transported to the synaptic terminals where vesicular glutamate transporter-1/2 (VGluT-1/2) packages glutamate into vesicles, which release glutamate upon neuronal depolarization (Takamori et al., 2000; Fremeau et al., 2001, 2004). Glutamate clearance from the synapse is carried out through high-efficiency excitatory amino acid transporters (EAATs) located primarily on astrocytes. Glutamate transporter-1 (GLT-1) and glutamate aspartate transporter (GLAST) allow for uptake

of glutamate into astrocytes (Lehre et al., 1995), where glutamate is then converted into glutamine by glutamine synthetase (GS) and transported back to the presynaptic neuron (Norenberg and Martinez-Hernandez, 1979). This is referred to as the glutamate/glutamine cycle (Revett et al., 2013), a critical regulation point for the glutamatergic system to terminate receptor signaling while preventing excess accumulation of synaptic glutamate potentially leading to excitotoxicity (Olney et al., 1997). As well, dysregulation of glucose metabolism can potentially impact glutamate synthesis in the glutamate/glutamine cycle (Knight et al., 2014), underlining the importance of this regulatory cycle for learning and memory (Valladolid-Acebes et al., 2012; Hascup et al., 2019a).

## Alterations in Glutamatergic Signaling Throughout Alzheimer's Disease Progression

### *The Relationship Between $\text{A}\beta$ and Glutamate*

Alzheimer's disease (AD) is characterized by excitotoxic levels of extracellular glutamate alongside accumulation of soluble  $\text{A}\beta$  and hyperphosphorylated tau protein leading to neuronal cell death (Hiruma et al., 2003; Kopeikina et al., 2012). Evidence shows that soluble  $\text{A}\beta$  accumulation results in synaptic failure, potentially through modifications to the glutamatergic system (Walsh et al., 2002; Wang et al., 2002; Barghorn et al., 2005; Cleary et al., 2005; Selkoe, 2008; Ferreira and Klein, 2011; Wilcox et al., 2011). Early stages of the disease show an increased excitability of pyramidal neurons (Grutzendler et al., 2007; Šišková et al., 2014; Hascup and Hascup, 2015) and an upregulation of glutamatergic presynaptic boutons as observed in mild cognitive impairment (MCI; Bell et al., 2007) and in mouse models of AD (Hascup et al., 2019a). Several studies have noted hyperactivity in the hippocampus of MCI patients (Bell et al., 2007; Miller et al., 2008; O'Brien et al., 2010; Huijbers et al., 2015) with familial history of AD (Okonkwo et al., 2014) and elevated  $\text{A}\beta$  deposition (Huijbers et al., 2015) also contributing to excitability. In fact, hyperactivity at baseline, as detected by functional magnetic resonance imaging, is associated with increased severity of cognitive decline (Miller et al., 2008; O'Brien et al., 2010; Huijbers et al., 2015).

Along with increased excitability, morphological changes in dendritic structure of hippocampal pyramidal neurons have been noted (Grutzendler et al., 2007; Šišková et al., 2014), with specific responsiveness to amyloid plaques (Masliah et al., 1993; Ovsepian et al., 2018). Whole-cell patch clamp recordings of CA1 pyramidal neurons in  $\text{A}\beta\text{PP/PS1}\Delta\text{E9}$  (APP/PS1; RRID:

MMRRC\_034832-JAX) mice show reductions in length, branching, and surface area of dendrites while also displaying a localized hyperactivity effect and increased synaptic integration that is attributed to the changes in dendritic structure (Šišková et al., 2014). Similar morphological changes appear in the PSAPP double transgenic mouse model (Tg2576 RRID: IMSR\_TAC:1349; PSEN1 (M146L): RRID: IMSR\_JAX:033255) and post-mortem AD brain samples (Grutzendler et al., 2007).

Later stages of AD show markedly decreased glutamatergic activity in stark juxtaposition to earlier hyperactivity. The APP/PS1 AD mouse model shows increased stimulus-evoked glutamate release at younger ages, which then steadily decreases with age and A $\beta$  accumulation (Minkevičienė et al., 2008; Hascup and Hascup, 2015; Hascup et al., 2019b). Busche et al. (2012) also note increased glutamatergic hyperactivity in young APP<sub>swe</sub>/PS1<sub>G384A</sub> double transgenic mice (APP<sub>swe</sub>: RRID: MGI: 3665286; PS1<sub>G384A</sub>: RRID: MGI: 4819108), with hyperactive neurons preferentially surrounding amyloid plaques. Such findings are observed in AD patients, with a decrease in presynaptic glutamatergic boutons and glutamate signaling noted in later disease stages (Bell et al., 2007; Miller et al., 2008; O'Brien et al., 2010). This could result in chronically elevated glutamate levels eventually leading to inhibition of axonal transport and neurodegeneration through A $\beta$  accumulation and increased Ca<sup>2+</sup> intracellular concentrations (Hiruma et al., 2003; Stutzmann, 2005).

Studies attempting to characterize disease cell signaling and pathology in human AD typically use post-mortem tissue due to logistical difficulties in obtaining tissues and data from patients in earlier disease stages. Such limitations hinder study of earlier cell signaling changes, although there are some methods currently used to examine glutamate in live patients. Of note, studies using proton magnetic resonance spectroscopy (1H MRS) and glutamate chemical exchange saturation transfer (GluCEST) show decreased overall glutamate concentration in APP/PS1 mice and AD patients (Rupsingh et al., 2011; Haris et al., 2013). The hippocampus was specifically noted as having a large decrease in glutamate concentration, and as previously discussed, the hippocampus is especially vulnerable to A $\beta$  accumulation. The CA1 region is particularly susceptible to disease-related neuronal loss (West et al., 1994; Hof et al., 2003) and shows decreased stimulus-evoked glutamate with age in APP/PS1 mice (Hascup et al., 2016). This supports that the decrease in total concentration observed may be a consequence of neuronal loss resulting from excitotoxicity, as opposed to decreased glutamate concentration in the hippocampus.

These findings display a flexibility in glutamatergic characterization such that it is specific to the disease stage. The paradoxical nature of glutamate signaling in

AD petitions for a deeper look into the individual impact on glutamatergic synaptic components throughout disease progression. Modifications in expression of synaptic elements could lead to alterations in cell signaling, allowing for excitotoxic conditions to grow and building the foundation for cognitive decline.

### *Neuronal Glutamate Synaptic Component Changes in AD*

Individual changes in glutamatergic synaptic components underlie the altered glutamate release observed throughout disease progression. As mentioned previously, earlier stages are marked with elevated glutamate release that eventually increases glutamate concentrations in and around the synapse. Evidence supports that this starts presynaptically, with A $\beta$  and VGluT1 colocalizing on glutamatergic synaptic boutons and preferentially accumulating in these terminals (Sokolow et al., 2012). This coincides with elevated expression of VGluT1 in mouse models of AD, supporting increased vesicle trafficking of glutamate (Hascup et al., 2019a). Several studies have also shown a downregulation of VGluT1 expression in AD (Kashani et al., 2008; Canas et al., 2014; Rodriguez-Perdigon et al., 2016), but only VGluT2 downregulation in MCI subjects (Kashani et al., 2008), supporting that VGluT1 levels are not downregulated until later stages of AD. This expression pattern matches that of glutamate release such that initially more glutamate is packaged into vesicles for release, contributing to an increase in extracellular glutamate levels into a toxic range.

Postsynaptically, the impact of A $\beta$  accumulation on AMPA/NMDA receptors has been well documented. Bath application of A $\beta$  reduces both the amplitude and frequency of AMPA postsynaptic currents in CA1 pyramidal neurons (Parameshwaran et al., 2007). Neuronal cell cultures taken from the cortex and hippocampus of Tg2576 transgenic AD mice show decreased expression of the GluR1 AMPA subunit as A $\beta$  concentrations increased (Almedia et al., 2005). A decrease in GluR1 and GluR2/3 expression has also been observed in post-mortem AD entorhinal cortex (Yasuda et al., 1995), although GluR2/3 is expressed presynaptically as well. In the hippocampus, ionotropic glutamate receptor AMPA subunit-4 expression is downregulated in sporadic AD (Jacob et al., 2007), along with decreased AMPA binding in the CA1 (Dewar et al., 1991). It is arguable that the decrease in AMPA binding may be due to decreased GluR1 surface expression caused by decreased expression of synaptic calcium-calmodulin II (CaMKII) as seen in APP/PS1 mice (Gu et al., 2009). The decreased release of stimulus-evoked glutamate mentioned earlier could also account for this decrease in binding (Hascup and Hascup, 2015). In cell culture, GluA1 expression is upregulated in APP knockout corticohippocampal

neurons supporting that  $A\beta$  directly impacts expression levels of AMPA subunits (Martinsson et al., 2019). Interestingly, GluR2 has been shown to be upregulated in incipient AD patients (Williams et al., 2009), supporting that AMPA expression may follow the same cycle of early upregulation and then subsequent downregulation with AD progression. Early upregulation is likely a response to increased presynaptic glutamate stimulation, but overtime, chronic excessive stimulation leads to desensitization and internalization of the AMPA receptor (Esposito et al., 2013).

NMDA receptors are a cornerstone in the relationship between  $A\beta$  accumulation and glutamate toxicity.  $A\beta_{42}$  preferentially binds to glutamatergic neurons expressing NR1 or NR2B NMDA subunits compared with other subunits (Lacor et al., 2007).  $A\beta_{42}$  can stimulate glutamate release, potentially through  $\alpha 7$  nicotinic acetylcholine receptors ( $\alpha 7nAChR$ ; discussed later), to activate E-NMDARs (Talentova et al., 2013). This can result in long-term potentiation (LTP) inhibition (Li et al., 2011; Kervern et al., 2012) and contribute to synaptic spine loss (Talentova et al., 2013). This  $A\beta$ -mediated increase in glutamate concentration leads to endocytosis and decreased surface expression of NR1 and NR2B (Snyder et al., 2005). Downregulated NMDA subunit expression in the hippocampus has been observed in several postmortem studies in human AD subjects (Hynd et al., 2004a, 2004b; Jacob et al., 2007).

NMDARs are believed to mediate soluble  $A\beta$ -induced cell death such that persistent activation of NMDA from excessive glutamate release leads to selective neuronal death from chronic excitotoxicity (Butterfield and Pocernich, 2003). E-NMDARs allow for  $Ca^{2+}$  entry into the cell (Zhang et al., 2016), which causes increased dendritic calcium-induced calcium release from ryanodine receptors, thus increasing intracellular  $Ca^{2+}$  concentrations (Goussakov et al., 2010). In fact, MCI patients show increased expression of ryanodine receptor 2 (Bruno et al., 2012), which would allow for further NMDA-mediated increases in intracellular  $Ca^{2+}$  concentrations. Overtime, this can eventually result in toxic  $Ca^{2+}$  levels leading to depolarization of the mitochondrial membrane, free radical production, and cell death. (Hardingham et al., 2002; Hardingham and Bading, 2003; Bezprozvanny and Mattson, 2008; Zhang et al., 2016). Along with this, E-NMDAR-mediated  $Ca^{2+}$  influx activates cAMP-regulatory element binding protein (CREB) shut off pathways (Hardingham et al., 2002). CREB plays a central role in long-term memory (Yin and Tully, 1996; Barco et al., 2003; Tully et al., 2003), and downregulation results in memory impairment (Xiong et al., 2013; Zhang et al., 2014). Thus, increased intracellular  $Ca^{2+}$  levels resulting from E-NMDAR stimulation contributes to both cognitive decline and neuronal loss in AD pathology.

Furthermore, soluble  $A\beta$  acts through NMDAR to activate nicotinamide adenine dinucleotide phosphate oxidase leading to induction of reactive oxygen species (ROS; Kishida and Klann, 2006) and release of arachidonic acid (Shelat et al., 2008). The influx of  $Ca^{2+}$  from NMDAR activation is required for ROS formation (De Felice et al., 2007). Although NMDA production of ROS is a necessary element for LTP (Kishida and Klann, 2006),  $A\beta$  stimulates an excessive ROS induction from NMDARs, leading to oxidative damage and synaptic failure (De Felice et al., 2007; Shelat et al., 2008). In fact, elevated ROS levels contribute to impairment of LTP (Serrano and Klann, 2004) and spatial learning (Nicolle et al., 2001) with age. NMDA activation also increases nitric oxide (NO) synthesis (Garthwaite et al., 1989) in a  $Ca^{2+}$  (Law et al., 2001) and postsynaptic density-95 dependent manner (Sattler et al., 1999). The 3xTg-AD (RRID: MMRRC\_034830-JAX) mouse model shows significant increases in NMDA-mediated NO concentration peaks in the CA1 at earlier disease stages, which then substantially decreased with age (Dias et al., 2016), an effect that could underlie the changes in glutamate cell signaling seen throughout disease progression. Furthermore, inducible nitric oxide synthase (iNOS) mediates  $A\beta$ -induced LTP inhibition (Wang et al., 2004), while soluble  $A\beta$  works through both NMDA and NOS to increase oxidative stress (Parks et al., 2001). However, NO can in turn inhibit NMDAR action (Manzoni et al., 1992), which could play a role in decreased NMDAR activity in later stages of AD. Even with increasing neurotoxicity, NOS+ neurons in the hippocampus are relatively spared (Hyman et al., 1992), supporting a complicated relationship between NO and glutamate such that NO provides some neuroprotection while also contributing to the consequences of excitotoxicity.

Studies performed in primary cortical neuron cultures have shown seemingly opposing results on NMDA modulation of APP processing. NMDA (50  $\mu M$ ) treatment showed both induction of Kunitz protease inhibitory domain (KPI)-APP neuronal expression promoting production of  $A\beta_{42}$  (Lesné et al., 2005), and increases in  $\alpha$ -carboxyterminal fragment levels, supporting enhancement of nonamyloidogenic  $\alpha$ -secretase cleavage (Hoey et al., 2009). Interestingly, the increase in  $\alpha$ -carboxyterminal fragment levels was not observed in isolated E-NMDARs, supporting that this is solely an S-NMDAR effect (Hoey et al., 2009). Furthermore, Lesné et al. (2005) used a longer NMDA incubation period (24 hr) to create an excitotoxic environment, as would be observed with chronic E-NMDAR stimulation. Bordji et al. (2010) addressed these conflicting findings by isolating either S-NMDARs or E-NMDARs in primary cortical neuron culture. While S-NMDARs were shown to have no impact on KPI-APP neuronal expression,

E-NMDARs increased KPI-APP expression at the 12- and 24-hr time points. This E-NMDAR-mediated increase in KPI-APP expression was also found to be calcium-calmodulin dependent, supporting induction through NMDA-mediated  $\text{Ca}^{2+}$  entry into the neuron. Along with these findings, NMDA antagonists are capable of blocking  $A\beta_{42}$  uptake into hippocampal neurons (Bi et al., 2002) where  $A\beta$  can reduce axonal transport through an NMDA/glycogen synthase kinase-3 $\beta$  dependent mechanism (Decker et al., 2010). This further emphasizes the critical roles of E-NMDARs in AD, impacting both APP processing and  $A\beta_{42}$  internalization, and thereby establishing E-NMDARs as a central mediator to the neurotoxic effects of  $A\beta$ .

Autoradiography studies of postmortem brain tissue shows decreased binding to mGluRs and decreased mGluR/neuronal density ratio (Dewar et al., 1991; Albasanz et al., 2005). This effect was associated with a decrease in mGluR1 expression, which continuously declines with AD progression (Albasanz et al., 2005). Interestingly, another study found mGluR2, which is primarily expressed presynaptically, to be upregulated in AD (Lee et al., 2004). mGluR2 protects against excitotoxicity by inhibiting presynaptic glutamate release (Buisson and Choi, 1995; Imre, 2007; Hascup et al., 2010; Quintero et al., 2011; Hascup et al., 2019b) and has been shown to directly activate extracellular signal-regulated kinase (ERK) in a phosphoinositide 3-kinase (PI3K)-dependent manner (Ferraguti et al., 1999). ERK impacts CREB phosphorylation and promotes cell survival (Lu and Xu, 2006; Lee et al., 2009) but also phosphorylates tau which can contribute to aberrant hyperphosphorylation resulting in neurofibrillary tangles (Lee et al., 2009). These findings support that while this mechanism may initially be neuroprotective (Bond et al., 2000), over time, it may contribute to disease pathology.

### *Astrocytic Glutamate Component Changes in AD*

Astrocytes play a key role both in the tripartite glutamatergic synapse and in AD pathogenesis (Rudy et al., 2015). Reactive astrocytes are known to associate with senile plaques in AD mouse models and human tissue (Verkhatsky et al., 2010; Rodríguez-Arellano et al., 2016), leading to astrogliosis in the hippocampus and cortex characterized by increased expression of glial fibrillary acidic protein (GFAP; Nagele et al., 2004; Olabarria et al., 2010; Hascup et al., 2019a). This response is triggered by damaged neuronal signals, referred to as damaged-associated molecular patterns, and  $A\beta$  plaque deposition (Verkhatsky et al., 2010) leading to increased release of proinflammatory factors such as interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor- $\alpha$  (Morales et al., 2014). Continuing induction of astrocytic

response leads to chronic inflammation that results in cell damage (Streit et al., 2004).

Glutamate clearance from the synapse is hindered in AD through decreased uptake into astrocytes. This is supported by decreased expression of both GLT-1 and GLAST in the hippocampus (Cassano et al., 2012) that appears prior to plaque deposition (Schallier et al., 2011). In later stages, GLT-1 expression is markedly decreased around plaques (Hefendehl et al., 2016). Expression of GLT-1 may be directly impacted by  $A\beta$  through lipid peroxidation and 4-hydroxynonenal modification as a result of oxidative stress (Butterfield et al., 2002). This change in GLT-1 expression contributed to spatial learning deficits in earlier stages (6 months old) but did not cause a significant deviation in cognitive performance in 9-month-old APP/PS1 mice lacking one GLT-1 allele (Mookherjee et al., 2011). This effect is also observed with decreased expression of EAAT-2 (the human GLT-1 equivalent) in postmortem AD cortex (Scott et al., 2011) as well as EAAT-1 (GLAST) reduction in the hippocampus (Jacob et al., 2007). Again, this reduction was specifically noted in the vicinity of senile plaques (Jacob et al., 2007; Hefendehl et al., 2016), supporting elevated basal glutamate surrounding plaques in both mouse and human models. Interestingly, several disease-specific splice variants of EAAT2 exist that reduce the glutamate transport capacity of EAAT2 in AD postmortem tissue (Scott et al., 2011). This may offer an additional avenue for excitotoxicity, whereby glutamate transporters are both downregulated and have decreased functional glutamate clearance.

GS action upon glutamate is a critical component in preventing excitotoxicity (Verkhatsky and Kirchhoff, 2007; Rudy et al., 2015) but shows altered expression in AD (Robinson, 2001; Boyd-Kimball et al., 2005; Olabarria et al., 2011; Palmieri et al., 2017; Huang et al., 2016). In 3xTg-AD mice, GS+ astrocyte distribution mirrored that of GFAP+ distribution in the DG and CA1, but by 12 months of age, GS+ astrocyte cell counts decreased, and by 18 months of age, downregulation of GS expression in the hippocampus was observed (Olabarria et al., 2011). Human tissue taken from patients with advanced AD also shows a decrease in GS expression. Interestingly, less GS staining was observed clustering around plaques, unlike GFAP+ astrocytes (Robinson, 2001). This is possibly due to the level of neuronal loss experienced during advanced stages of AD (DeKosky and Scheff, 1990; Selkoe, 2002). GS is particularly vulnerable to oxidative modification (Boyd-Kimball et al., 2005) that makes it a potential target of  $A\beta$ -induced oxidative damage (Huang et al., 2016). Along with this, GS inhibition in activated microglia results in stronger induction of inflammatory markers which increases neuronal toxicity (Palmieri et al., 2017).

The evidence presented for both neuronal and astrocytic components of the tripartite glutamate synapse involvement in AD progression support that A $\beta$  can impact the glutamatergic system through various mechanisms. Changes in expression of each of the synaptic components lead to chronically elevated extracellular glutamate that becomes excitotoxic and underlies AD pathology.

### A $\beta$ - $\alpha$ 7nAChR Interactions

$\alpha$ 7nAChRs are expressed on both neurons and glia, with hippocampal immunostaining showing the highest density of  $\alpha$ 7nAChR-expressing neurons in the neuropil and  $\alpha$ 7nAChR-expressing glia in the distal regions of the stratum radiatum (Gahring et al., 2004). It has been well established in the literature that application of nicotine elicits glutamate release both *in vitro* and *in vivo* (Marchi et al., 2002; Lambe et al., 2003; Konradsson-Geuken et al., 2009). *In vivo* microelectrode array recording studies have shown nicotine-induced glutamate release in the prefrontal cortex of freely moving rats, that is attenuated with application of  $\alpha$ -bungarotoxin, an  $\alpha$ 7nAChR antagonist (Konradsson-Geuken et al., 2009). Soluble A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub> interact with nAChRs at these synapses (Wang et al., 2000a, 2000b) impacting glutamate release. A $\beta$  interacts with both  $\alpha$ 7 and  $\alpha$ 4 $\beta$ 2 nAChRs; however,  $\alpha$ 4 $\beta$ 2nAChR receptor binding requires a significantly higher concentration than  $\alpha$ 7nAChR (Wang et al., 2000b). Regarding differences between A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub>, A $\beta$ <sub>40</sub> was found to bind with less affinity and decreased potency compared with A $\beta$ <sub>42</sub> (Wang et al., 2000a; Dineley et al., 2002a). More specifically, A $\beta$ <sub>42</sub> binds with femtomolar affinity to the nicotine/acetylcholine (ACh)-binding pocket of  $\alpha$ 7nAChR (Wang et al., 2000b; Magdesian et al., 2005) and can elicit different responses dependent on A $\beta$  preparation and concentration used (Parri et al., 2011; Hascup and Hascup, 2016). High concentrations of A $\beta$  (nM- $\mu$ M) noncompetitively block hippocampal  $\alpha$ 7nAChRs in *in vitro* hippocampal cell culture and slices (Liu et al., 2001; Mura et al., 2012). Alternatively, low concentrations of A $\beta$  (fM-pM) have been shown to potentiate glutamate release (Puzzo et al., 2008; Mura et al., 2012; Hascup and Hascup, 2016) with some effects on aspartate and GABA release also observed *in vivo* (Mura et al., 2012). In fact, A $\beta$ -stimulated  $\alpha$ 7nAChR glutamate release from neurons and astrocytes can result in rising extracellular glutamate levels that can chronically activate E-NMDARs, thereby contributing to excitotoxicity (Rudy et al., 2015).

Lower concentrations of A $\beta$ <sub>42</sub> have been shown to enhance LTP and spatial memory performance in C57BL/6 mice (RRID: IMSR\_JAX:000664; Puzzo et al., 2008), while higher concentrations result in LTP deficits (Chen et al., 2006, 2010; Gu and Yakel, 2011).

The LTP-enhancing aspect of A $\beta$ <sub>42</sub> is not mediated by AMPA/NMDA receptors, as A $\beta$ <sub>42</sub> perfusion of hippocampal slices does not impact AMPA/NMDA receptor currents or amplitude frequency and distribution (Puzzo et al., 2008). This concentration-dependent action of A $\beta$  supports a transformation from excitation to inhibition of  $\alpha$ 7nAChRs as AD progresses, with A $\beta$  levels rising from picomolar to nanomolar levels (Näslund et al., 1994; Auld et al., 1998; Puzzo and Arancio, 2012). It should be noted that presynaptic  $\alpha$ 7nAChRs are known to interact with neighboring NMDARs such that the chronic inactivation of  $\alpha$ 7nAChR, resulting from desensitization by A $\beta$ , could result in enhanced NMDAR function (Lin et al., 2010). However, this increased presynaptic glutamate release may not evoke LTP enhancement as postsynaptic AMPA/NMDA receptors become desensitized and downregulated in the excitotoxic state associated with AD (Yasuda et al., 1995; Selkoe, 2002; Hynd et al., 2004a, 2004b; Parameshwaran et al., 2007).

Evidence of A $\beta$ <sub>42</sub> concentration-dependent  $\alpha$ 7nAChR modulation is further characterized through microelectrode array recordings in the hippocampus. Hascup and Hascup (2016) showed glutamatergic stimulation with local application of A $\beta$ <sub>42</sub> in hippocampal recordings from anesthetized C57BL/6 mice, an effect that was blocked with co-application of  $\alpha$ -bungarotoxin supporting involvement of  $\alpha$ 7nAChR. Interestingly, different responses to A $\beta$ <sub>42</sub> application were observed depending on the hippocampal subfield, with the CA1 and dentate gyrus responding most to lower concentrations of A $\beta$ <sub>42</sub> compared with the CA3. These findings mirror current knowledge of AD disease progression, with the CA1 showing the earliest increases in glutamate release in the APP/PS1 transgenic AD mouse model (Hascup and Hascup, 2015) and the earliest site of plaque deposition for the hippocampus in human AD patients (Thal et al., 2000; Shie et al., 2003).

$\alpha$ 7nAChRs open upon nicotine binding, allowing a Ca<sup>2+</sup> influx into the presynaptic neuron (Gray et al., 1996). Similarly, binding of soluble A $\beta$  to the  $\alpha$ 7nAChR triggers an influx of Ca<sup>2+</sup> into the presynaptic neuron (Dineley et al., 2001, 2002a; Dougherty et al., 2003) and has been shown to activate the ERK/mitogen-activated protein kinases pathway (Dineley et al., 2001; Bell et al., 2004; Abbott et al., 2008; Young et al., 2009) in a P13K-dependent manner (Bell et al., 2004) which in turn impacts the phosphorylation of CREB (Dineley et al., 2001). Intraperitoneal injection of  $\alpha$ 7nAChR selective agonist A-582941 resulted in increased ERK 1/2 and CREB phosphorylation that improved behavioral performance on delayed matching to sample titration, inhibitory avoidance, and social recognition (Bitner et al., 2007). However, in the Tg2576 mouse model, CREB was found to be upregulated at 13 months of age and then downregulated by 20

months of age (Dineley et al., 2001). This supports that CREB activation mirrors the  $A\beta$ - $\alpha 7nAChR$  interaction such that CREB expression is enhanced in the early stages of AD when there are lower concentrations of  $A\beta$ , and then decreases with disease progression corresponding to  $A\beta$  accumulation.

The potentiation of glutamate release from  $A\beta$  activation of  $\alpha 7nAChR$  contributes to excitotoxicity while also resulting in rapid desensitization of the  $\alpha 7nAChR$  (Dineley et al., 2002b).  $A\beta_{42}$  and  $\alpha 7nAChR$  have been shown to form a complex that becomes internalized in the neuron and leads to cell lysis and plaque deposition (D'Andrea et al., 2001; Nagele et al., 2002; Deutsch et al., 2014; Godyń et al., 2016). In fact,  $A\beta$  accumulates at a faster rate in neuroblastoma cells transfected with  $\alpha 7nAChR$  (Nagele et al., 2002). The  $A\beta_{42}$ - $\alpha 7nAChR$  complex internalization leads to decreased surface expression of  $\alpha 7nAChR$  (Nagele et al., 2002), coinciding with upregulation of  $\alpha 7nAChR$  seen throughout AD progression (Hellström-Lindahl et al., 1999; Dineley et al., 2001, 2002b; D'Andrea and Nagele, 2006) supporting an  $\alpha 7nAChR$  compensatory mechanism for decreased surface expression. Interestingly, this chronic desensitization of  $\alpha 7nAChR$  has been shown to increase NMDAR surface expression (Lin et al., 2010), suggesting a complex compensatory response to accumulation of  $A\beta_{42}$ .

### Learning and Memory Consequences of Altered Glutamatergic Signaling

Glutamatergic dysfunction due to deregulation of synaptic components has phenotypic consequences in the form of decreased learning and memory performance. Presynaptically, reductions in VGLUT1 and VGLUT2 correlated with decline in cognitive status and disease duration in AD patients (Kashani et al., 2008). Cognitive ability is negatively correlated with glutamate presynaptic bouton density in MCI patients such that the increase in bouton density leads to decreased cognitive ability (Bell et al., 2007). Similarly, elevated hippocampal glutamate release negatively correlated with cognitive performance prior to cognitive decline in APP/PS1 mice (Hascup and Hascup, 2015). This is in stark contrast to cognitively normal patients that have a positive correlation (Bell et al., 2007), supporting a threshold in which increased glutamate signaling switches from stimulating to hindering cognition.

NMDA and mGluRs are both known to play vital roles in induction of LTP and long-term depression (LTD; Parameshwaran et al., 2007; Shankar et al., 2008). Soluble  $A\beta$  inhibits S-NMDARs that are required for LTP conduction (Collingridge and Bliss, 1995; Parsons et al., 2007). Treatment with (2R)-amino-5-phosphonovaleric acid (D-AP5), a selective NMDA

antagonist, impairs LTP *in vivo* supporting that the involvement of NMDARs in LTP (Davis et al., 1992). However, in GLT-1 knockout mice, the LTP impairment observed was reversed with application of D-AP5, supporting that both blockade and overactivation of NMDARs can interfere with LTP (Katagiri et al., 2001). This effect may be due to the involvement of E-NMDARs, whereby inhibition of E-NMDARs prevents  $A\beta$ -mediated LTP impairments (Li et al., 2011; Rammes et al., 2011). Memantine, an FDA-approved noncompetitive NR2 antagonist (Parsons et al., 1998) for treating AD has shown efficacy in improving Morris water maze performance (Barnes et al., 1996; Van Dam et al., 2005; Banerjee et al., 2006) and blocked  $A\beta$  inhibition of LTP in 3xTg-AD hippocampal slices (Parsons et al., 2009; Martinez-Coria et al., 2010). Thus, supporting that noncompetitive inhibition of NR2+NMDARs provides a counterbalance to both inhibition of S-NMDARs and overactivation of E-NMDARs, explored further in the next section. mGluRs are involved in both the  $A\beta$ -induced suppression of LTP and potentiation of LTD (Wang et al., 2004; Shankar et al., 2008; Rammes et al., 2011).  $A\beta$ -mediated LTP impairments can be blocked by inhibition of mGluR5 (Wang et al., 2004; Rammes et al., 2011). As NMDARs and mGluRs are mechanistically coupled, chronic stimulation of either can lead to synaptic failure as seen in AD (Rammes et al., 2011; Kervern et al., 2012). This failure is potentially due to  $Ca^{2+}$  dysregulation and dephosphorylation of CREB as both E-NMDARs and mGluR5 elevate intracellular  $Ca^{2+}$  (Chen et al., 2002; Hardingham et al., 2002; Hardingham and Bading, 2003; Verkhratsky and Kirchhoff, 2007; Yamin, 2009; Zhang et al., 2016). In addition, mGluR1 has been shown to be involved in synaptic plasticity and LTP in the CA1 (Neyman and Manahan-Vaughan, 2008; Rudy et al., 2015). Of note, agonism of mGluR1 and mGluR5 with 3-hydroxyphenylglycine potentiated NMDAR-induced neurotoxicity, juxtaposing the neuroprotective effects observed with mGluR2 agonism (Buisson and Choi, 1995; Tyszkiewicz and Yan, 2005) and further supporting a deleterious relationship between NMDAR and mGluRs upon LTP and excitotoxicity. Furthermore, mGluRs are required for soluble  $A\beta$ -mediated LTD enhancement (Shankar et al., 2008; Palop and Mucke, 2010; Um et al., 2013). Treatment with a similar Group I mGluR agonist, 3,5-dihydroxyphenylglycine, results in decreased AMPAR surface expression during LTD (Um et al., 2013), supporting another mechanism by which soluble  $A\beta$  impacts learning and memory signal conductance.

### Theories on the Paradoxical Nature of Glutamate in AD

The two-stage model theory was first set forth by Olney et al. (1997) describing two stages of NMDAR-mediated



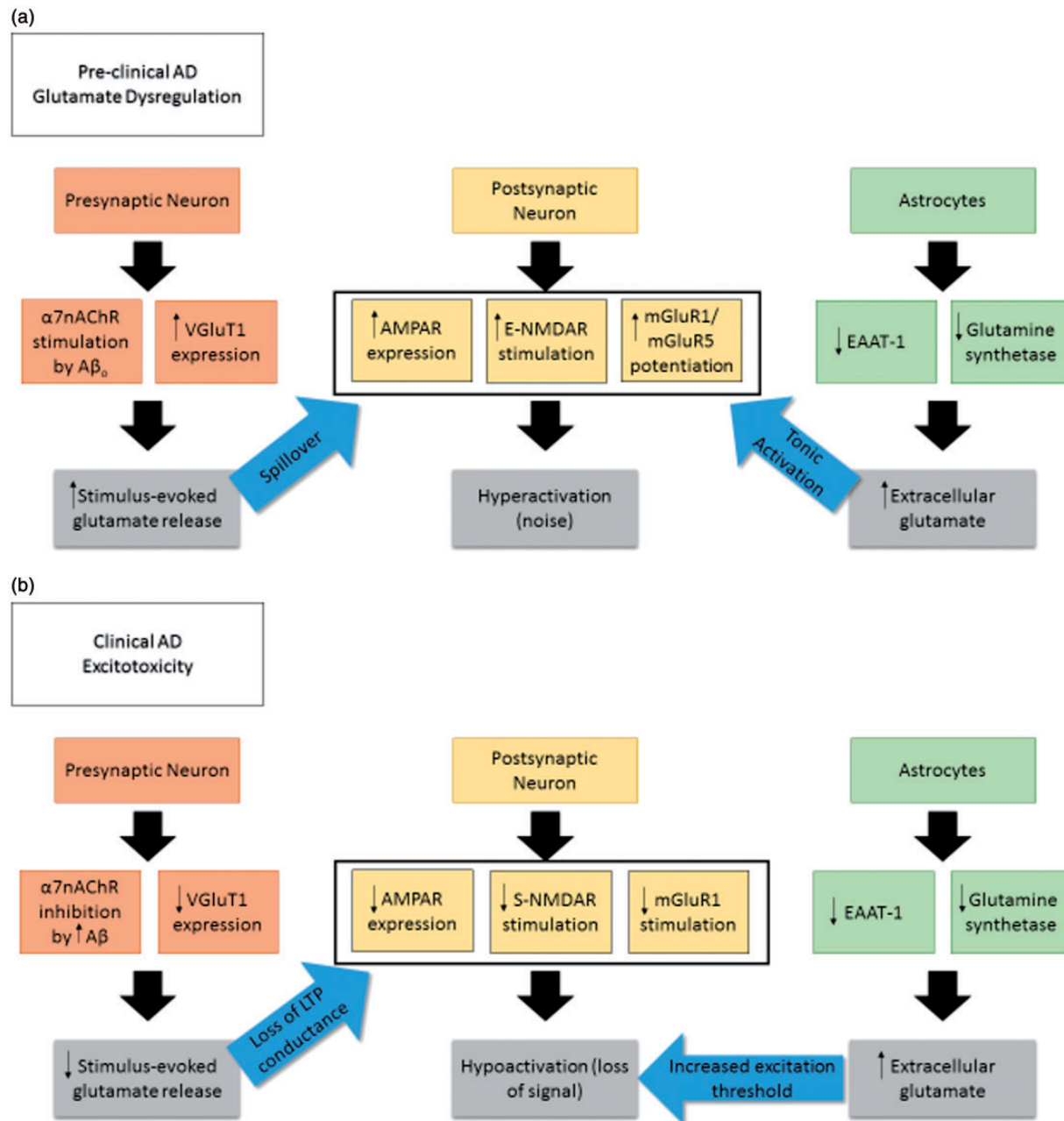
toxicity in AD pathology. The first stage, referred to as NRHyper, describes persistent activation of NMDA receptors. Chronic NMDAR stimulation then leads to the second disease stage, referred to as NRHypo, in which the NMDARs become hypoactive as a result of chronic overstimulation leading to inhibition of LTP conductance and cognitive decline. These disease stages are driven by soluble  $A\beta$  accumulation. During the NRHyper phase,  $A\beta$  potentiates glutamate release and increases NMDA activation and sensitivity to glutamate. This leads to partial membrane depolarization allowing tonic activation of NMDA receptors (Koh et al., 1990; Gray and Patel, 1995; Danysz and Parsons, 2012). This overstimulation subsequently results in an NRHypo state in which glutamatergic activation is depressed and synaptic components are downregulated. NMDARs become hypofunctional in normal brain aging; however, this is experienced to an extreme in AD possibly due to the increase hyperactivation state experienced in AD that precedes hypoactivation. NMDAR hypoactivation applies to NMDARs on GABAergic neurons as well, causing disinhibition of the glutamatergic system and resulting in increased extracellular glutamate concentrations and neuronal loss. This is expanded upon by the findings of Huijber et al. (2015) and the trait versus state hypothesis set forth by Aizenstein and Klunk (2015), describing two models of hippocampal activity such that some individuals have a *trait* of high levels of hippocampal activation prior to MCI and some experience hyperactivation as a *state* with MCI onset. Both models subsequently result in cognitive decline and support a period of hippocampal hyperactivation occurring before hypoactivation.

Similarly, Parsons et al. (2007) proposed the signal-to-noise ratio hypothesis. This hypothesis notes that in AD pathology, NMDAR is stimulated by glutamate for longer periods of time due to a hyperactive glutamatergic system (Buisson et al., 1992; Mitani et al., 1992). As such, this leads to tonic activation of NMDAR that generates increasing amounts of *noise*. This noise raises the threshold by which neuronal stimulation must pass to generate a stimulus-evoked *signal*. With disease progression, the increased noise eventually drowns out the signal, leading to learning and memory deficits seen in AD. This effect has been observed in our lab, with APP/PS1 mice showing a decline in stimulus-evoked glutamate and an increase in basal glutamate levels with disease progression, impacting spatial memory performance (Hascup and Hascup, 2015). This hypothesis is further elucidated with the proposed action of memantine, the noncompetitive NR2 antagonist, which shows fast unblocking kinetics dependent upon membrane potential. This characteristic allows memantine to quickly unblock the NMDAR during strong depolarization of the postsynaptic membrane and remain bound during tonic

stimulation. In fact, recovery from memantine blockade is shown to be even faster in the presence of higher synaptic glutamate concentrations (Clements et al., 1992). Memantine benefits both S-NMDARs and E-NMDARs in LTP such that LTP conductance is not hindered at the synapse but chronic stimulation of E-NMDARs is blocked, ultimately helping to alleviate excitotoxic effects. This is seen with memantine improvements in LTP induction and Morris water maze performance as discussed earlier (Barnes et al., 1996; Van Dam et al., 2005; Banerjee et al., 2006; Parsons et al., 2009; Martinez-Coria et al., 2010). Of note, memantine has also showed efficacy in reducing  $A\beta$  production brought on by E-NMDAR prolonged activation (Bordji et al., 2010), as well as reducing the levels of both soluble  $A\beta$  and insoluble  $A\beta$  plaques in 3xTg-AD mice (Martinez-Coria et al., 2010) and blocking soluble  $A\beta$ -induced oxidative stress (De Felice et al., 2007). As such, memantine shows modulation of  $A\beta$ -and-glutamate-induced neurotoxicity giving support to the idea that noise created by extracellular glutamate overpowers stimulus-evoked glutamate signals in AD.

In clinical trials, memantine was shown to reduce cognitive deficits in mild to severe AD patients (Winblad and Poritis, 1999; Reisberg et al., 2003; Peskind et al., 2006). A meta-analysis of memantine trials also revealed efficacy in treating patients with moderate to severe AD (Winblad et al., 2007). However, the weak procognitive effects observed in AD patients treated with memantine (McShane et al., 2006; Schneider et al., 2011) may be due to the disease stage when treatment was initiated. If memantine treatment is initiated too late in disease progression, neuronal loss may be too severe to yield procognitive effects. As such, post hoc analysis of nine clinical trials of memantine show delay of clinical worsening in moderate to severe AD patients (Hellweg et al., 2012). Danysz and Parsons (2012) argue that starting treatment in the prodromal stage of AD would allow for memantine-induced neuroprotection, which could yield more promising clinical results and further delay cognitive decline.

In addition, NMDARs are not the only components that modulate the signal-to-noise ratio. mGluRs are multifaceted due to their G-protein and NMDAR coupling and as such are also a vital mediator in LTP. Riedel (1996) has argued that mGluRs are responsible for the initial setup of the signal-to-noise ratio to allow for efficient plasticity. Pretraining injection of mGluR agonists leads to nonspecific activation of Group I mGluRs, generating an increase in noise and preventing memory formation. Groups II and III mGluRs then act as mediators to reduce noise and allow for signal conductance and memory formation. This initial organization of the signal-to-noise ratio is impacted at the mGluR level in AD pathology, as mentioned earlier with mGluR1 and mGluR5 potentiating NMDA-induced neurotoxicity and



**Figure 1.** Changes in glutamatergic synapse component expression and signaling with AD progression. (a) Preclinical AD upregulation of several neuronal components contributing to hyperactivation and building the foundation for excitotoxicity. (b) Clinical AD is characterized by hypoactivation of the glutamatergic system, possibly a consequence of the earlier preclinical stage. This results in cognitive deficits due to signal-to-noise ratio imbalance.

AD = Alzheimer's disease;  $\alpha 7$ nAChR = alpha-7 nicotinic acetylcholine receptor;  $A\beta_o$  = amyloid beta oligomer; VGLuT1 = vesicular glutamate transporter 1; AMPAR =  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; E-NMDAR = extrasynaptic N-methyl-D-aspartic acid receptor; mGluR = metabotropic glutamate receptor; S-NMDAR = synaptic N-methyl-D-aspartic acid receptor; EAAT = excitatory amino acid transporter.

then experiencing a downregulation in expression in later disease stages (Buisson and Choi, 1995; Albasanz et al., 2005), following a similar hyper- to hypoactivation trend. This initial noise generation overpowers the inhibitory modulation of mGluR2, despite its upregulation in

early AD (Buisson and Choi, 1995). However, our laboratory recently demonstrated that prodromal treatment with the mGluR Group II agonist LY379268 does not offer long-term procognitive benefits in APP/PS1 mice (Hascup et al., 2019b).

Furthermore, our laboratory and others have reported a relationship between  $A\beta$  and glutamate mediated by  $\alpha 7nAChR$  stimulation that contributes to increases in glutamate release (Puzzo et al., 2008; Mura et al., 2012; Hascup and Hascup, 2016), generating a large amount of signal. This relationship changes as AD progresses and  $A\beta$  increases in concentration and plaque formation such that we see an opposite impact through  $\alpha 7nAChR$  in which glutamate release is inhibited and thus contributes to overall hypoactivation (Liu et al., 2001; Mura et al., 2012). Interestingly,  $\alpha 7nAChR$  desensitization leads to increased NMDAR surface expression and enhanced function (Lin et al., 2010), and both pathways modulate  $A\beta$  toxicity such that  $\alpha 7nAChR$  and E-NMDARs lead to  $A\beta_{42}$  internalization (D'Andrea et al., 2001; Bi et al., 2002; Nagele et al., 2002; Deutsch et al., 2014; Godyń et al., 2016), and E-NMDARs lead to increased amyloidogenic processing (Bordji et al., 2010). In addition, nicotine-mediated enhancement of LTP is both NMDA and mGluR5 dependent (Welsby et al., 2006), and because  $A\beta_{42}$  binds to the same pocket as nicotine, it follows that mGluR5 may potentiate both NMDA and  $\alpha 7nAChR$ -induced excitotoxicity. Other pathways previously discussed in this review also result in toxic  $Ca^{2+}$  intracellular levels and modulation in CREB expression that result in neuronal cell loss. This interaction between multiple glutamatergic pathways emphasizes the breadth of  $A\beta$  modulation of the glutamatergic system to generate neurotoxicity as outlined in Figure 1.

## Conclusion

Taken together, the presented evidence supports a signal-to-noise ratio imbalance occurring in AD pathology.  $A\beta$  modulates several parts of the tripartite glutamatergic synapse that culminates in an excitotoxic environment. The excitation threshold at which glutamate signals must surpass for learning and memory increases while also undergoing an overall dampening of the glutamatergic system. Loss of signal detection due to persistently elevated synaptic and extrasynaptic glutamate levels leads to the hallmark symptoms of cognitive deficits and eventual neuronal loss in AD disease progression.

## Summary

Glutamatergic transmission displays stark changes throughout AD progression. Earlier stages are characterized by upregulation of synaptic components contributing to increased glutamate signaling. Later stages exhibit hypoactivation possibly due to cell damage and neuronal loss, subsequently resulting in cognitive decline.

## Author Contributions

All authors were involved with the article preparation and editing.


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## ORCID iD

Kevin N. Hascup  <https://orcid.org/0000-0001-6604-1874>

Erin R. Hascup  <https://orcid.org/0000-0003-1037-0809>

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