Aging and Disease
www.aginganddisease.org
Volume 6, Number 2; 131-148, April 2015
http://dx.doi.org/10.14336/AD.2014.0423

Review Article

The Role of the Tripartite Glutamatergic Synapse in the Pathophysiology of Alzheimer's Disease

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[Received March 14, 2014; Revised April 22, 2014; Accepted April 23, 2014]

ABSTRACT: Alzheimer's disease (AD) is the most common form of dementia in individuals over 65 years of age and is characterized by accumulation of beta-amyloid (Aβ) and tau. Both Aβ and tau alter synaptic plasticity, leading to synapse loss, neural network dysfunction, and eventually neuron loss. However, the exact mechanism by which these proteins cause neurodegeneration is still not clear. A growing body of evidence suggests perturbations in the glutamatergic tripartite synapse, comprised of a presynaptic terminal, a postsynaptic spine, and an astrocytic process, may underlie the pathogenic mechanisms of AD. Glutamate is the primary excitatory neurotransmitter in the brain and plays an important role in learning and memory, but alterations in glutamatergic signaling can lead to excitotoxicity. This review discusses the ways in which both beta-amyloid (Aβ) and tau act alone and in concert to perturb synaptic functioning of the tripartite synapse, including alterations in glutamate release, astrocytic uptake, and receptor signaling. Particular emphasis is given to the role of N-methyl-D-aspartate (NMDA) as a possible convergence point for Aβ and tau toxicity.

Key words: Beta-amyloid, tau, Alzheimer's disease, excitotoxicity, glutamate, NMDA, astrocytes, tripartite synapse

Alzheimer's disease (AD) affects one in every nine adults age 65 and older and is the sixth leading cause of death in the United States [1]. By 2025, the number of individuals 65 years of age and older with AD is expected to reach 7.1 million, and this number is projected to reach 13.8 million people by 2050 [1]. AD is characterized by progressive memory loss, decline in cognitive skills, and adverse behavioral changes [2]. Biologically, AD is characterized by an abundance of extracellular amyloid plaques comprised of insoluble beta-amyloid (Aβ), and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein [3]. The third major feature of AD is an alteration of neuronal connections, eventually leading to massive neuron loss throughout the brain.

The best correlate of memory deficits in AD patients, however, is not Aβ plaque burden or neurofibrillary tangles, but synapse loss [4]. Similarly, synaptic dysfunction is observed prior to neuron loss in mouse models of AD and coincides with the onset of memory deficits [5, 6]. Emerging evidence suggests early cognitive decline in AD may result from a dysregulation of excitatory glutamatergic neurotransmission by soluble Aβ, leading to synaptic alterations and tau phosphorylation [e.g., 7].

Glutamate, the major excitatory neurotransmitter, is responsible for many of the brain's functions including cognition and memory [8, 9]. Glutamate is believed to contribute to hippocampal-dependent learning and memory through long-term potentiation (LTP) [10], a

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ISSN: 2152-5250

long-lasting strengthening in signal transmission between two neurons that results from their synchronous stimulation [11, 12]. Although beneficial at low levels, high concentrations of extracellular glutamate can lead to cell death through excessive activation of glutamate receptors, a process referred to as excitotoxicity [13]. Even at normal concentrations of glutamate, excitotoxicity can ensue if abnormalities in the glutamate receptors occur, such as tau-induced alterations in the phosphorylation of N-methyl-D-aspartate receptors (NMDARs) [14].

Excitotoxicity is linked to several neurodegenerative disorders, including AD [15], and occurs when uncontrolled glutamate release surpasses the capacity of astrocytic clearance mechanisms, leading to an overabundance of extracellular glutamate and excessive activation of extrasynaptic N-methyl-D-aspartate receptors (E-NMDARs) [16]. Because glutamatergic neurotransmission occurs mainly within the confines of the tripartite synapse, focus will be given to the ways in which these components of the synapse become deregulated during AD, with particular emphasis on consequences for E-NMDAR activation.

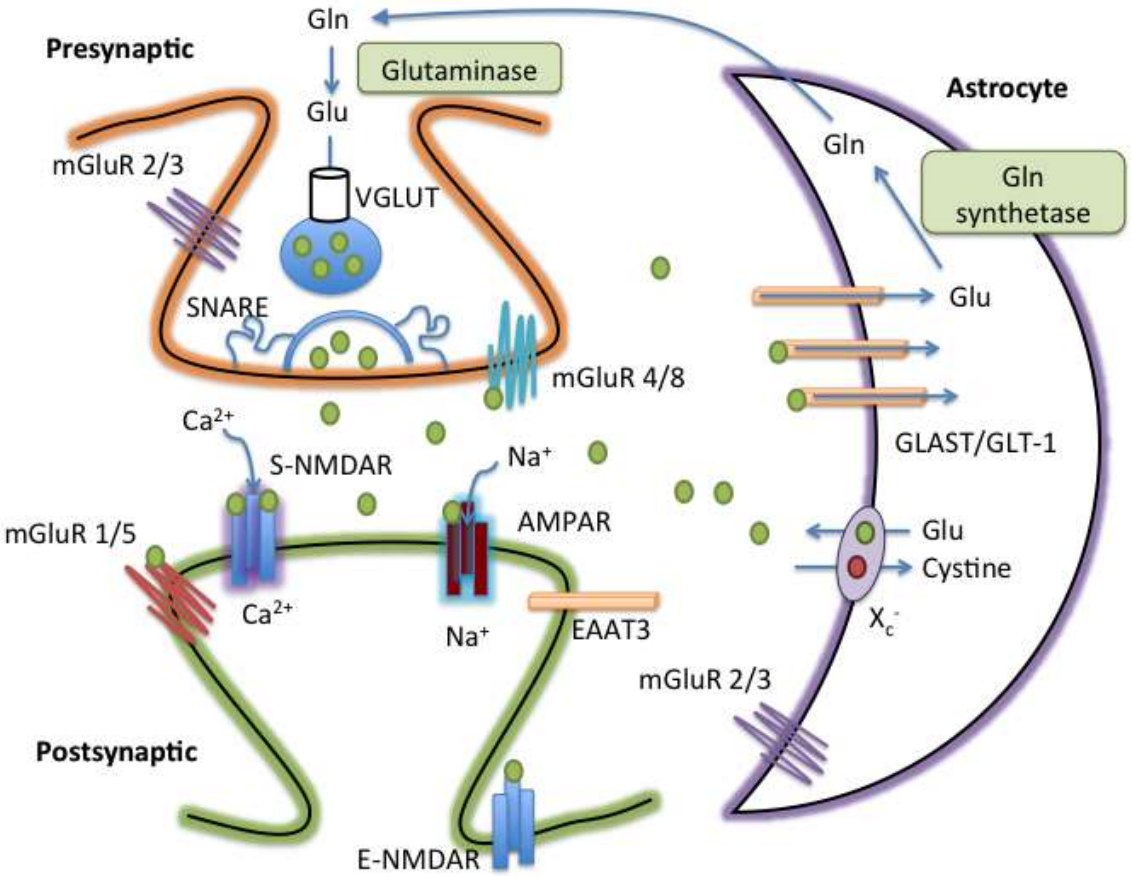

Figure 1. The tripartite glutamate synapse. In the presynaptic neuron, glutamine (Gln) is converted to glutamate (Glu) by glutaminase and packaged into synaptic vesicles by the vesicular glutamate transporter (VGLUT). SNARE complex proteins mediate the fusion of vesicles with the presynaptic membrane. Astrocytes also release glutamate via the cystine-glutamate antiporter (X_c^-). Following release into the extracellular space, glutamate binds to presynaptic (mGluR2/3 and mGluR4/8), synaptic (S-NMDAR and AMPAR) and peri-/extra- synaptic (mGluR1/5 and E-NMDAR) glutamate receptors. Glutamate is cleared from the synaptic space through excitatory amino acid transporters (EAATs) on neighboring astrocytes (GLAST and GLT-1) and, to a lesser extent, on neurons (EAAT3). Glutamate is converted to glutamine by glutamine synthetase within the astrocyte before being transported to presynaptic neurons, thereby completing the glutamate-glutamine cycle.

Table 1. Primary locations and functions of metabotropic glutamate receptors in the tripartite synapse.

mGluR Group	Subtype	Glutamate Receptor Affinity (EC_{50}) [178]	Location*	Function*
Group I	mGluR1	9	Postsynaptic [179]	Enhances excitability, synaptic plasticity, LTP/LTD [180, 181]
	mGluR5	10	Astrocytes [182]	Elevates intracellular calcium [183, 184]
Group II	mGluR2	4	Presynaptic	Inhibition of presynaptic glutamate [185]; LTD [186]
	mGluR3	3	Astrocytes [187]	Inhibition of cystine/glutamate antiporter [26]
Group III	mGluR4	5	Presynaptic [188]	Inhibition of presynaptic glutamate [189]
	mGluR7	1000	Astrocytes [190]	Increases glutamate uptake [187]
	mGluR8	2.5 [191]		

* Though these receptors are located elsewhere and have additional functions, this table describes the most described, and believed to be primary, locations and functions of these receptors as they relate to the tripartite synapse.

The Tripartite Glutamate Synapse

The term "tripartite synapse," proposed twenty years ago to describe communication between neurons and astrocytes [17], encompasses a presynaptic terminal, a postsynaptic spine, and an astrocytic process (Figure 1). Within the tripartite synapse are multiple sites that regulate extracellular glutamate levels and are sensitive to AD-related pathology. Below, the normal physiological processes regulating extracellular glutamate are briefly described, followed by descriptions of how these targets are deregulated in AD.

Glutamate can be synthesized de novo from glucose through the Krebs/tricarboxylic acid cycle [18] or through recycling of glutamate by the astrocyte-neuronal, glutamate-glutamine cycle. In the glutamate-glutamine cycle, glutamate is synaptically released and taken up by surrounding astrocytes, where it is converted to glutamine, a non-neuroexcitatory amino acid, and transferred back to neurons for conversion to glutamate [19]. Glutamate is then packaged presynaptically into synaptic vesicles by vesicular glutamate transporters (VGLUTs). Though VGLUTs were once thought to be found in astrocytes, more recent evidence suggests that VGLUTs are not expressed in astrocytes, at least in the mouse brain [20]. Following presynaptic neuronal depolarization, calcium channels open, permitting the influx of calcium and triggering the fusion of vesicles with the membrane, resulting in the exocytosis of glutamate into the synapse [21, 22]. However, glutamate release is not limited to presynaptic neurons. Astrocytes also exhibit calcium-dependent glutamate release [23, 24] and release glutamate via the cystine-glutamate antiporter (Xc-) [25], a sodium-independent anionic amino acid transporter that exchanges a molecule of glutamate into the extrasynaptic space in exchange for a molecule of cystine transported into astrocytes [25, 26].

Once in the extracellular space, glutamate can bind to ionotropic (iGluR) or metabotropic (mGluR1-8) receptors [27, 28]. The iGLuRs include N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (KA) [29]. iGLuRs are ligand-gated ion channels that mediate the majority of excitatory neurotransmission and synaptic plasticity [27, 30, 31]. Within each class, receptors have distinct functional properties that arise from the homo-oligomeric, or hetero-oligomeric, assembly of distinct subunits into cation-selective tetramers [32-36].

Both AMPA and KA receptors are involved in fast synaptic transmission; glutamate binding to these receptors results in a conformational change and sodium influx [37, 38]. In contrast, NMDA receptors do not participate in fast synaptic transmission. At resting potential, the NMDA receptor channel is blocked, in a voltage-dependent manner, by magnesium. Removal of magnesium requires depolarization of the postsynaptic neuron, which typically occurs after glutamate binds AMPA or KA receptors, leading to an influx of sodium [39-41]. In addition, NMDA receptors require the binding of glutamate, as well as a co-agonist, glycine or D-serine, to open the ion channel [42-44]. If both ligands (glutamate and a co-agonist) bind while the postsynaptic neuron is in a depolarized state, NMDA channels will open, permitting calcium to enter the cell [45]. Because NMDA receptors require concomitant presynaptic (release of glutamate) and postsynaptic (depolarization) activities, NMDA receptors detect the coincidence of two events and are sometimes referred to as coincidence detectors. In addition, NMDA receptors have a higher permeability to calcium than AMPA or KA receptors [46, 47]. The increased influx of calcium triggers secondary messenger systems leading to the establishment of LTP, a process believed to underlie learning and memory [10]. Overactivation of NMDA receptors, however, leads to an excess of intracellular calcium, which initiates a series of events leading to cell death [48-50], a process described in detail in the next section.

The mGLuRs are G-protein coupled receptors with a seven putative trans-membrane spanning domain [51]. This large domain selectively binds glutamate and activates second messenger systems [52-55], resulting in a modulatory role in the central nervous system (CNS) function of neuronal excitability and neurotransmitter release. Unlike fast synaptic transmission of ionotropic receptors, mGLuRs are involved in slow synaptic transmission and are subdivided into 3 groups, Groups I, II, and III, on the basis of signal transduction pathways and pharmacological profiles [53] (see Table 1). Group I mGluRs are positively coupled to phospholipase C [56], whereas Groups II and III mGluRs are negatively coupled to adenylyl cyclase [57-60]. All three groups of mGLuRs, with the exception of mGluR 6, play a role in regulating hippocampal function.

Regulation of extracellular concentrations of glutamate is essential. Over-stimulation can erode synaptic regulation, leading to alterations in learning and memory, and more concerning, neurodegeneration throughout vulnerable networks [61]. Because there are no extracellular enzymes to degrade glutamate, the only way to terminate glutamate signaling, and to keep extracellular glutamate levels low, is through uptake of glutamate by one of five sodium-dependent excitatory amino acid transporters (EAATs) [62]. Only EAAT1 and EAAT2, also referred to as GLAST and GLT-1, respectively, are expressed in rodent brains [62]. GLAST and GLT-1 are primarily responsible for glutamate uptake and are located on astrocytes [63, 64]. EAAT3 is present on postsynaptic neurons in the in the CA1 region of the hippocampus and the granular layer of the dentate gyrus, and its uptake of glutamate is sodium dependent [65]. Whereas GLAST and GLT-1 are found only in the brain, EAAT3 can also be found in the intestines, kidney, liver, and heart [66]. CNS expression of EAAT3 is relatively low compared to that of GLT and GLAST [67]. EAAT4 is expressed primarily in the cerebellar Purkinje cells, while EAAT5 is found in retinal neurons and is involved in visual processing [68].

When uncontrolled glutamate release surpasses the capacity of astrocyte clearance mechanisms, or when the function or expression of EAATs is decreased, excessive activation of glutamate receptors can occur, a process referred to as excitotoxicity. Of particular relevance to the process of excitotoxicity are NMDA receptors.

Synaptic vs. Extrasynaptic NMDARs

NMDARs are essential mediators of synaptic plasticity and transmission [10]. There are seven NMDA receptor subunits (NR1, NR2A-D, and NR3A-B) forming heteromeric complexes containing NR1 subunits and a combination of NR2 and/or NR3 subunits. NR1 and NR3 bind to glycine [69], whereas NR2 binds to glutamate [70]. Because NR3A is restricted to expression during development [71] and NR3B is restricted to brain regions not involved in early stages of AD (i.e., the somatic motor neurons of the brainstem and spinal cord [72]), focus will be given to NR1/NR2 complexes. Likewise, NR1/NR2 complexes play an important role in learning and memory [73], as well as in excitotoxicity [74], and are abundantly located in the hippocampus, one of the first regions affected in AD [75-77].

NMDA receptors can be found synaptically, perisynaptically, or extrasynaptically [78]. Synaptic NMDA receptors (S-NMDARs) are activated by presynaptic glutamate release [79], whereas perisynaptic NMDA receptors are located 200-300 nm from the postsynaptic density [80] and are activated only by high glutamate concentrations [78]. Extrasynaptic NMDA receptors (E-NMDARs) are located on the spine neck, dendritic shaft, or soma [81] and also require high glutamate concentrations [78]. In addition, many E-NMDARs are adjacent to glia [82] Thus, it is possible

that astrocytic release of glutamate may result in activation of E-NMDARs.

Activation of S-NMDARs, which predominantly contain the NR2A subunit, mediates neuronal survival and resistance to trauma via their anti-apoptotic and antioxidant effects [16, 83]. In contrast, activation of E-NMDARs (predominately containing the NR2B subunit) is associated with neurotoxicity by stimulating cell death pathways [16, 83]. S-NMDAR receptors primarily use D-serine, released by neighboring astrocytes, as their co-agonist [84], whereas E-NMDARs are believed to use glycine as their co-agonist [85]. The relative difference in co-agonist use by S-NMDARs and E-NMDARs might be explained by the differential localization of NR2A and NR2B subunits, respectively, as NR2B-containing receptors have a tenfold higher affinity for glycine than NR2A-containing receptors [70, 86]. Similarly, the localized release and astrocytic uptake of these co-agonists has also been hypothesized to explain the differences in co-agonist use by S-NMDARs vs. E-NMDARs (see [87, 88] for review). Further work is needed in this area, as a better understanding of the role of NMDAR co-agonists may have therapeutic implications.

The pathways triggered by E-NMDARs are not directly related to calcium overload; even after triggering equivalent calcium concentrations, the downstream events for synaptic and extrasynaptic receptors differ ([16] and see [15] for review) and are often in direct opposition to one another. One particularly relevant example for AD includes the differential effects on CREB (cyclic cAMP response element binding protein), a transcription factor essential for the conversion of short to long-term memory [89-91]. S-NMDARs activate CREB [16], whereas E-NMDARs inactivate CREB, and this inactivation dominates over the effects of S-NMDAR activation [16, 92].

Alterations in CREB activity are not only important for learning and memory but also for neuroprotection. Increases in CREB signaling following activation of S-NMDARs result in increased expression of brain-derived neurotrophic factor (BDNF) [16], essential for neuronal survival [93]. S-NMDAR activation also suppresses apoptotic signaling and increases antioxidant defenses. For example, activation of S-NMDARs suppresses forkhead box O (FOXO), a transcription factor involved in the regulation of oxidative stress and the modulation of genes involved in apoptosis [94].

Many of the signaling pathways activated by E-NMDARs are in direct antagonism to those activated by S-NMDARs. As with CREB activity [16], the extracellular signal-regulated kinase (ERK1/2) pathway is bidirectionally modulated by S-NMDARs and E-NMDARs, with E-NMDARs exerting a dominant ERK shutoff pathway [95]. Because ERK is crucial in memory consolidation and synaptic plasticity [96], shutoff of this pathway represents another way in which E-NMDAR activation is detrimental to learning and memory. Similarly, the suppression of FOXO activity by S-NMDAR signaling is opposite to that observed following E-NMDAR activation; E-NMDAR activation increases FOXO activation, leading to excitotoxic cell death [97].

In addition to the direct antagonism of S-NMDAR pathways, activation of E-NMDARs also affects pathways not involved in S-NMDAR signaling. For example, S-NMDAR activation does not affect calpain activity, whereas E-NMDAR stimulation invokes calpain-mediated cleavage of striatal enriched tyrosine phosphatase (STEP) into an inactive form [98]. This inactive form of STEP is unable to dephosphorylate its substrates, including the stress-activated protein kinase, p38, and the Src kinase family member, Fyn, leading to an overactivation of these substrates following STEP cleavage. Activation of p38 is closely linked with cell death [99]; however, the consequences of increased Fyn activity are less clear and only recently recognized. One consequence of increased Fyn activity is an increase in the surface expression of NR2B [98]. Fyn phosphorylates the Tyr1472 residue of the NR2B subunit, leading to exocytosis of NMDAR complexes to neuronal surfaces [100]. When E-NMDAR stimulation inactivates STEP, STEP can no longer deactivate Fyn, leading to increased Fyn activity and exocytosis of NR2B receptors [101]. In addition, STEP dephosphorylates the Tyr1472 residue, promoting internationalization [102]. Thus, inactivating STEP leads to decreased endocytosis and increased exocytosis of NR2B receptors [101]. This increase in NR2B-containing receptors may then lead to an increase in E-NMDAR signaling, thereby creating a self-perpetuating, feed-forward loop of excitotoxicity.

Increased activation of E-NMDARs may also mediate tau pathology in AD. Increased activation of NR2B-containing receptors induces tau phosphorylation, while blockade of NR2B receptors prevents this phosphorylation [103]. Likewise, blockade of extrasynaptic NR2B receptors abolishes tau-mediated cytotoxicity in a cell culture system [104]. Memantine, used to treat AD, preferentially blocks E-NMDARs at low doses, while sparing normal synaptic activity [105]. Memantine treatment reduces tau phosphorylation [106] and excitotoxicity [107] while increasing memory functioning [108]. The following sections will provide evidence that glutamate can accumulate extracellularly to reach pathological levels as the tripartite synapse becomes deregulated in AD.

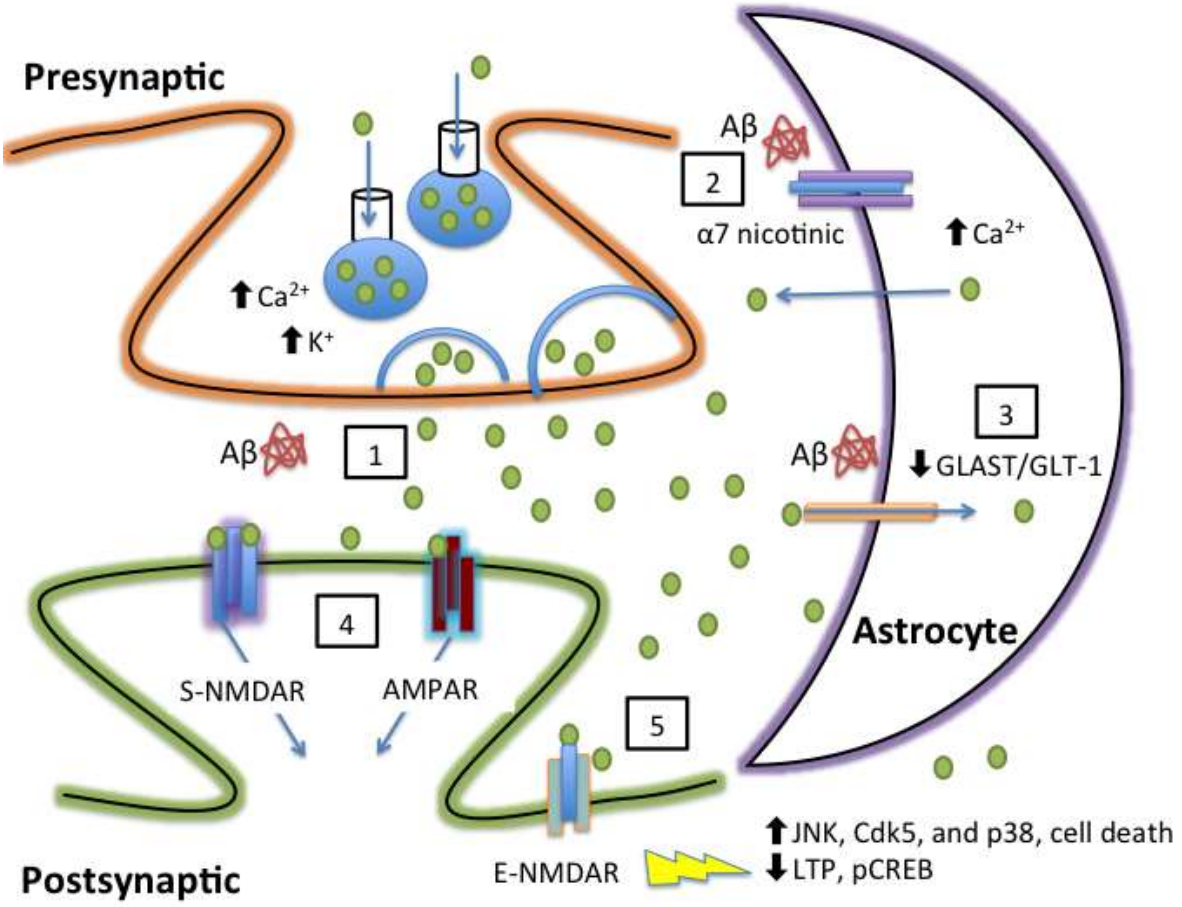

Figure 2. Aβ-mediated increases in extracellular glutamate and the resulting excitotoxicity. (1) Aβ increases presynaptic release of glutamate. (**2**) Aβ elevates astrocytic calcium via stimulation of astrocytic α7 nicotinic receptors, resulting in astrocytic glutamate release via an unknown mechanism. (**3**) Aβ decreases glutamate clearance from the synapse, thereby prolonging the duration of glutamate in the synapse and potentially resulting in the spread of glutamate to neighboring synapses. (**4**) Prolonged activation of S-NMDARs and AMPARs resulting from increased extracellular glutamate is predicted to cause desensitization and internalization of NMDA/AMPA, resulting in synaptic depression. (**5**) Glutamate spillover activates E-NMDARs, resulting in multiple deleterious downstream events, including an increase in tau kinase activity, cell death, and blockade of long-term potentiation (LTP) and CREB phosphorylation (pCREB).

Aβ and Excitotoxicity

Beta-amyloid (Aβ) has long been implicated in the pathogenesis of AD [109-113]. According to the original amyloid cascade hypothesis [114], the mismetabolism of the amyloid precursor protein (APP) results in increased amyloid plaque deposition (the insoluble deposits of extracellular Aβ) and a pathological cascade leading to neurofibrillary tangle formation and neuronal death. However, more recent studies have resulted in a reformulation of the amyloid cascade hypothesis with a shifted focus from amyloid plaques to increases in soluble oligomeric Aβ as the more likely initiating event in AD [115-120]. Aβ plaques and, in particular, soluble oligomers, have been tied to disruptions in glutamate synaptic transmission [5, 6, 121-124] and can result in excitotoxicity through several different routes, including stimulation of glutamate release, inhibition of glutamate uptake, and alteration of signaling pathways related to activation of glutamatergic receptors (Figure 2).

Aβ can increase glutamate release from neurons [125, 126] and astrocytes [127-129], resulting in abnormally high extracellular levels capable of activating the pathological E-NMDARs. Aβ25-35 (1 – 100 uM), a particularly toxic Aβ fragment, increases potassium-induced release of both aspartate and glutamate in cultured hippocampal neurons, an effect dependent on calcium; interestingly, basal release of glutamate and potassium-induced glutamate release is exacerbated in slices from aged rats exposed to Aβ25-35 compared to slices from young rats, suggesting one way in which aging might increase the risk for AD [125]. Soluble Aβ oligomers also promote extracellular accumulation of glutamate by increasing the release of presynaptic vesicles, resulting in increased postsynaptic activity [126]. This Aβ oligomer-induced release of glutamate is blocked by a sodium channel blocker (tetrodotoxin), an NMDAR antagonist (MK-801), or the removal of calcium from the extracellular medium, suggesting a dependence on excitatory neuronal activity [126].

Aβ has primarily been shown to stimulate glutamate release through its action on glia [127-129]. Picomolar concentrations of Aβ1-42 elevate astrocytic calcium via stimulation of astrocytic α7 nicotinic receptors, resulting in astrocytic glutamate release in rat hippocampal slices [127, 128]. As with the neuronal release of glutamate [130], the activation of E-NMDARs is a primary route by which downstream toxicity occurs; Aβ-induced astrocytic glutamate release increases E-NMDAR currents and decreases S-NMDAR currents, leading to synapse loss [128].

Another way in which Aβ can increase extracellular concentrations of glutamate is by inhibition of astrocytic uptake, resulting in an increased duration of glutamate in the synaptic cleft [131-135]. In cultured astrocytes, surface expression of GLT-1, but not GLAST, is reduced following incubation with Aβ1-42 (500 nM) [133]. In the hippocampus of mice, however, the expression of both GLT-1 and GLAST is reduced following injection of Aβ1-40 (400 pmol/site) [135]. Similarly, GLT-1 and GLAST uptake activity is inhibited following the administration of either Aβ1-40 (5 μM) or Aβ1-42 (5 μM) to cultured astrocytes [132]; this decrease in transporter activity is due to a decrease in transporter expression resulting from Aβ-mediated phosphorylation/activation of astrocytic mitogen-activated protein (MAP) kinases, including ERK and JNK [132]. Altered activity of MAP kinase cascades results from the oxidative stress conditions induced by Aβ [132], and anti-oxidant pretreatment can prevent the Aβ-mediated decrease in astrocytic uptake of glutamate [133]. The ability of Aβ to almost double the amount of time required to clear synaptically released glutamate suggests Aβ may promote the spread of glutamate from one synaptic domain to the next [133]. Such a spread could potentially alter the activity of entire neuronal networks.

Inhibition of glutamate reuptake is not limited to astrocytes; in cultured microglia, Aβ25-35 (5 uM) treatment also increases extracellular glutamate concentration via the reverse glutamate transporter [129]. Recent work suggests the Aβ-mediated changes in glutamate uptake may further increase Aβ levels and cognitive impairment; mice lacking one allele for GLT-1 crossed with transgenic mice expressing mutations of APP and presenilin-1 (AβPPswe/PS1ΔE9) exhibited earlier memory deficits and an increase in Aβ42/Aβ40 compared to AβPPswe/PS1ΔE9 mice [136]. Alterations in GLT-1 have also been observed in mild cognitive impairment (MCI) and AD patients, with the severity of detergent-insoluble GLT-1 associated with disease progression [137].

Astrocytes not only maintain healthy glutamate levels, but also have the capacity to clear and degrade Aβ [138, 139]. Astrocytes express Aβ-degrading proteases, including neprilysin and insulin-degrading enzyme [140]. There is an age-related downregulation of these Aβ-degrading proteases [141], suggesting one way in which Aβ levels may increase with age. Of particular interest to the current review is recent work showing that MK-801 and ketamine, both non-competitive NMDAR antagonists, decrease the expression of neprilysin, but not insulin-degrading enzyme, resulting in decreased Aβ degradation [140]. Though the decreased neprilysin expression is associated with a reduction in p38 MAPK phosphorylation [140], the exact mechanism by which NMDAR antagonism decreases Aβ degradation is not known and warrants further investigation.

One consequence of increased Aβ release is an increase in glutamate spillover and activation of E-NMDARs [128, 130]. Accumulating evidence for the link among Aβ, glutamate excitotoxicity, and E-NMDARs has stemmed in part from the ability of various NMDAR antagonists to prevent or reverse Aβ-related damage to neuronal and glial cultures. Although many early studies investigating the role of Aβ in excitotoxicity used high concentrations of synthetic Aβ (upwards of 20 μM and higher than that found in healthy brains), recent work suggests the application of much lower Aβ concentrations also results in dramatic synapse loss, reactive oxygen species production, and cell death (e.g., [123, 142]). Even picomolar concentrations of Aβ incubated with organotypic hippocampal cultures results in perturbed NMDAR-dependent signaling and progressive loss of synapses and spines, whereas

blockade of NMDARs prevents the loss of hippocampal synapses [123]. A slightly higher concentration of oligomeric Aβ1-42 (1 μM) in cultured cortical neurons leads to activation of NADPH oxidase and a subsequent increase in reactive oxygen species production [142]. The reactive oxygen species trigger ERK1/2 activation and arachidonic acid release, effects reversed by a selective NMDAR antagonist, D-APV (10 μM), as well as memantine (5 μl) [142]. Aβ-induced activation of E-NMDARs also results in toxic levels of nitrous oxide and abnormally high levels of caspase-3 activity that contribute to synaptic spine loss as a result of excessive calcium influx [128].

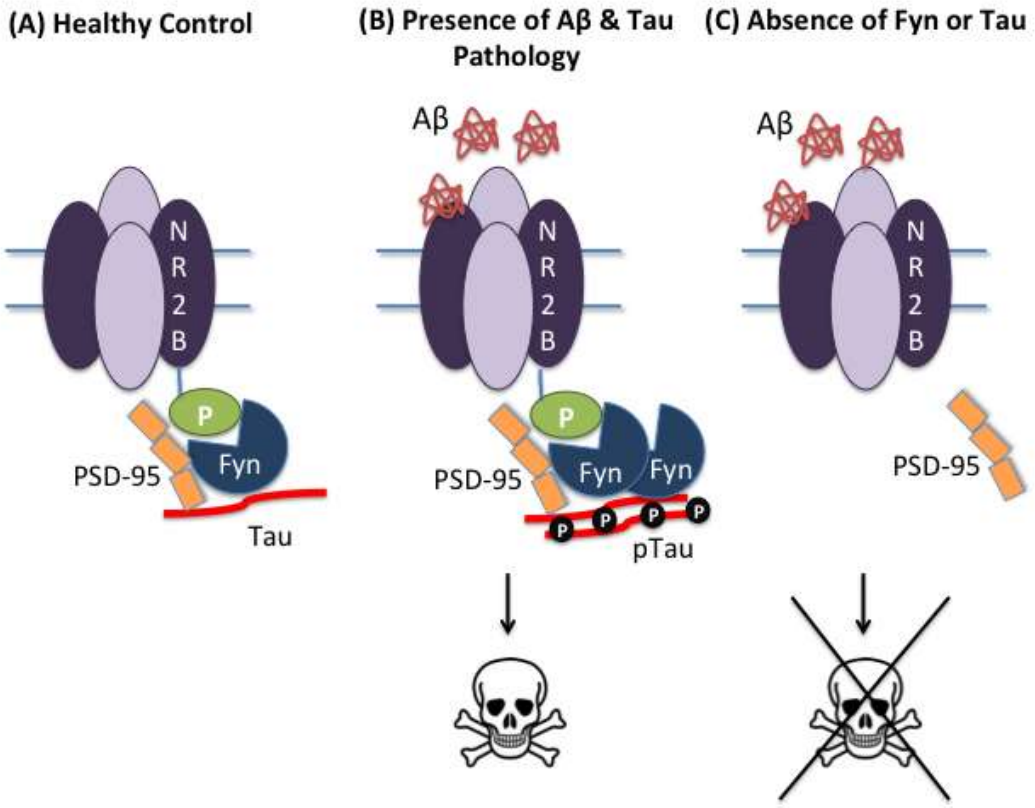

Figure 3. Tau-mediated excitotoxicity. (A) In healthy neurons, tau transports Fyn to the dendritic spine where Fyn, a tyrosine kinase that phosphorylates the NR2B receptor subunit Tyr[1472], stabilizes the NR2B:PSD95 complex. (B) In the presence of Aβ and/or hyperphosphorylated tau (ptau), stabilization of the NR2B:PSD95 complex enhances glutamatergic excitotoxicity. (C) Removal of tau or Fyn prevents glutamatergic excitotoxicity mediated by Aβ.

Aβ oligomers can shift the activation of NMDAR-dependent signaling pathways toward those involved in the impairment of LTP and the induction of long-term depression (LTD), effects observed in both neuronal cultures and in vivo [121-124, 143-147]. The mechanism by which Aβ impairs LTP has yet to be completely elucidated, but it may involve the extreme permeability of the membrane to calcium and subsequent reactive oxygen species production [144], effects potentially mediated by E-NMDARs and mGluR5 activation. Application of Aβ1-42 (1 - 100 nM) to cultured hippocampal slices results in blockade of LTP, an effect prevented by inhibition of E-NMDARs with memantine [143] or inhibitors of pathways downstream of E-NMDAR activation, including JNK, Cdk5, and p38 inhibitors [146]. Because mGluR5 receptors are

mechanistically coupled to NMDARs, NMDA excitotoxicity can be mediated by mGluR5 activity, creating a positive feedback loop whereby activation of one potentiates the activity of the other [148, 149]. Inhibition of mGluR5 activity prevents the block of LTP induced by Aβ [143, 146] and is neuroprotective against Aβ [150-153].

In addition to decreasing LTP, Aβ can also induce LTD [124, 147, 154]. For example, the addition of soluble Aβ1-42 (500 nM - 2μM) to hippocampal slices results in enhanced LTD that is induced by low-frequency stimulation [154]. The exact mechanism by which Aβ induces LTD has not yet been elucidated, though the necessity of the mitogen-activated protein kinase, p38, has been suggested by some [154], but not all, studies [124]. Similarly, there is not a consensus as to whether Aβ-mediated LTD is NMDAR-dependent. Some studies contend that Aβ-mediated LTD is mGluR-, but not NMDAR-, dependent [154]; addition of a non-selective Group I/II mGluR antagonist, LY341495 (10μM), enhances Aβ-mediated LTD, whereas application of an NMDAR antagonist, D-AP5 (50 μM), has no effect [154]. However, it has been noted that whether Aβ-enhanced LTD is mediated by mGluR or NMDAR activity depends not only on the induction protocol used, but also on the dose of AP5 (50 vs 100 uM) [124].

Thus, the Aβ-mediated increase in glutamate resulting from increased glutamate release, either from presynaptic neurons or astrocytes, is predicted to initially activate S-NMDARs. However, prolonged activation may result in desensitization and ultimately synaptic depression, possibly via internalization of NMDA/AMPA receptors. The increased levels would also spillover to activate E-NMDARs, resulting in LTD and blockade of LTP. Finally, the Aβ-mediated decreases in glutamate clearance may result in the spread of glutamate to neighboring synapses, thereby altering neuronal network activity.

The link between Aβ and glutamate excitotoxicity has been firmly established in the literature. However, only in the last decade has the role of tau in glutamate excitotoxicity been examined. The essential role of tau in mediating Aβ toxicity, as well as tau's direct effects on glutamate dysregulation, will be explored below.

Tau and Excitotoxicity

Although historically studied less than Aβ, tau has also been implicated in glutamate excitotoxicity and synaptic dysfunction (Figure 3). The role of tau in glutamate excitotoxicity is established in part by findings that NMDAR antagonists prevent tau-mediated cell death [e.g., 104]. Much like with Aβ, soluble tau, as opposed to tangles, is the more toxic species [155, 156] and can cause synaptic dysfunction independently of Aβ (see [157] for review). For example, we have shown that tau phosphorylation results in mislocalization of tau from axons to dendritic spines, resulting in decreased expression of AMPA receptors and LTP deficits; preventing tau phosphorylation prevented mislocalization and rescued LTP deficits [155].

A particularly interesting topic of late, however, is the notion that tau mediates or enables Aβ's excitotoxic effects [e.g., 14, 158]. Tau necessity was first shown in 2002 when primary cultured neurons from tau knockout mice were shown to be resistant to Aβ exposure [159], but it was not until 2007 that this effect was confirmed in vivo by crossing APP transgenic mice with tau knockout mice [158]. Since this time, NMDARs, or more specifically the NR2B-PSD95-Fyn complex within dendritic spines, has been identified as a convergence point for tau, glutamate, and Aβ [7, 160].

Fyn is a tyrosine kinase that phosphorylates the NR2B receptor subunit Tyr1472, thereby stabilizing its interaction with PSD95, a scaffolding protein in dendritic spines [161]. Stabilization of the NR2B:PSD95 complex enhances the glutamatergic excitotoxicity induced by Aβ [14]. Overexpression of Fyn exacerbates Aβ-related cognitive deficits and premature lethality [162, 163], whereas Fyn ablation protects against Aβ toxicity [163]. Tau mediates this process via its binding and transport of Fyn to dendritic spines [14]. Tau reductions, or expression of tau fragments that cannot transport Fyn to dendritic spines, prevent the memory deficits and network excitability caused by Aβ [14, 160], an effect attributed to a reduction in postsynaptic targeting of Fyn [14].

Until recently, tau was believed to be restricted to axons under physiological conditions, and to mislocalize to the somatodendritic regions only during pathological events [155]. However, more recent evidence suggests physiological tau does localize to dendritic spines [14, 164] where it binds not only Fyn but also the PSD95-NMDA receptor complex [164]. This binding, however, is phosphorylation dependent; NMDA receptor activation increases tau phosphorylation of tau, at GSK3β-dependent sites – PHF-1, AT8, and AT180 – leading to a decrease in tau's affinity for PSD95 and an increase in tau's interaction with Fyn. Tau's increased affinity for Fyn is believed to lead to a transient increase in synaptic Fyn and hence to a temporary increase in NMDA receptor activation before tau-Fyn leaves the PSD95-NMDA receptor complex [164].

Tau phosphorylation also increases NMDA receptor transmission and facilitation of LTD [164]. Noteworthy

is the finding that NMDA receptor-dependent phosphorylation of tau is transient, whereas tau phosphorylation after 5 days of Aβ exposure is not [164]. Because tau phosphorylation increases facilitation of LTD [164] and LTD leads to AMPA receptor endocytosis [165], this prolonged tau phosphorylation observed after Aβ exposure might explain the endocytosis of AMPA receptors induced by Aβ oligomers [166], though this has yet to be definitively shown.

Although the investigation into the role of tau in glutamate excitotoxicity is a relatively nascent field, it warrants attention in that tau likely serves as a mediator of Aβ-induced neuronal death [7, 14, 106, 167-169] and can induce synaptic dysfunction independently (see [157] for review). Similarly, it is becoming clear that extrasynaptic NR2B receptors play a prominent role in mediating this interaction between Aβ and tau [7, 14, 164]. Recent work suggests Aβ-induced neuronal death, as well as tau phosphorylation via GSK3β, is mediated by NR2B- but not NR2A- containing receptors [7]. Blockade of NR2B receptors, or removal of tau, prevents Aβ-induced neuronal death [7]. However, tau may not be necessary for all of Aβ's effects; Aβ-induced dendritic spine loss occurs via a pathway involving NR2A-containing NMDARs and is tau-independent [7]. Thus, further elucidation of tau-dependent and tau-independent pathways is needed, as well as a better understanding of which NMDA receptors mediate the various pathological effects produced by Aβ.

Future Directions

Though the role of the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease has become much clearer in recent years, several questions still remain. Whether the network dysfunction characteristic of AD is due in part to an Aβ-mediated spread of glutamate from one synaptic domain to the next is still unknown. Reports that early Aβ deposition occurs preferentially in regions of high neuronal activity [170] and that secretion of Aβ is driven by synaptic activity [e.g., 171] suggests diffusion of extracellular glutamate to neighboring synapses could facilitate the spread of Aβ pathology. Similarly, recent work suggests presynaptic glutamate release is sufficient to drive tau release into the extracellular space [172]. Thus, glutamate-mediated exocytosis of tau may indicate one mechanism for the trans-synaptic spread of tau pathology associated with synaptic activity. A better understanding of the role of glutamate in the trans-synaptic spread of pathology could facilitate our understanding of risk factors for AD. For example, aging, the greatest known risk factor for AD, is associated with a decline in glutamate transporters and uptake [173, 174], leading to higher levels of extracellular glutamate [175]. This age-related increase in extracellular glutamate results in greater activation of extrasynaptic NMDARs [176, 177] and could potentially be permissive for the spread of Aβ and tau pathology through vulnerable networks.

Conclusions

The studies reviewed here indicate the glutamatergic system, particularly E-NMDARs, play a critical role in the synaptic dysfunction and neuronal death triggered by both Aβ and tau. Improving our understanding of these alterations will hopefully lead to the development of therapeutics needed to prevent or attenuate these pathological processes. A greater understanding of the role of excitotoxicity in the pathogenesis of AD would not only inform therapeutic design for AD but also a host of other acute and chronic diseases with excitotoxicity as a core feature.

Acknowledgements

The project described was supported by the National Institute of General Medical Sciences, U54GM104942, and the Alzheimer's Association, NIRG-12-242187 (MNR). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or Alzheimer's Association.

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