HIGH SCHOOL EDITION
Journal of Student Research

Volume 13 Issue 1 (2024)

The Role of Astrocytes in the Relationship Between Amyloid-ß Accumulation and Synaptic Dysfunction in Alzheimer's Disease

Afsheen Fatima

ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disorder and is the most common cause of dementia worldwide. The disease is characterized by the accumulation of Amyloid-ß plaques, aggregation of tau protein resulting in neurofibrillary tangles, and the dysfunction of neuronal synapses, all of which lead to cognitive impairment and memory loss. Although previous research has focused more on the neuronal aspect of Alzheimer's disease, recent research has implicated the role of glial cells, most notably astrocytes, to have a significant impact on the disease's pathogenesis. Astrocytes are the most abundant type of glial cell in the central nervous system and are important in maintaining neuron homeostasis through their various functions in gliotransmission, phagocytosis, and synaptic regulation. The main objective of this review is to examine the role of astrocytes in Alzheimer's disease, specifically in the relationship between Amyloid-ß accumulation and synaptic dysfunction. After reviewing the literature, it can be concluded that Amyloid-ß accumulation induces several changes in astrocytic functions that promote the malfunction of synaptic transmission, thus resulting in synaptic dysfunction in Alzheimer's Disease. As there has been no cure or highly efficient treatment for Alzheimer's disease thus far, further research into the role of astrocytes in the relationship between Amyloid-ß accumulation and synaptic dysfunction in the disease could provide alternative pathways and targets for therapeutic treatment.

Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia worldwide. AD is a neurodegenerative disorder that extensively affects areas of the cerebral cortex and hippocampus resulting in clinical symptoms of progressive cognitive impairment and memory loss. Other symptoms that can be seen in AD include impairment and changes to mood and behavior, loss of ability to communicate and complete everyday tasks, and withdrawal from social interaction. The severity of these symptoms varies based on the stage of AD with preclinical AD being the earliest and least severe, to mild cognitive impairment (MCI), and finally AD dementia (Chun & Lee, 2018). AD symptoms can also be affected by other non-neuronal cells, most notably by astrocytes. Astrocytes are the most abundant type of glial cell found in the central nervous system (CNS). Astrocytes maintain structural, metabolic, and guidance support for neurons in the CNS and have been implicated in having a major role in the pathogenesis of several neurodegenerative disorders including AD (Acosta et al., 2017).

The two main types of AD are familial early-onset and sporadic late-onset. Sporadic late-onset, which typically occurs in those who are 65 years or older, comprises the majority of AD cases (95%) and is associated with environmental factors or aging (Masters et al., 2015). Familial early-onset, which makes up less than 5% of AD cases, is associated with inherited genetic mutations of AD-related proteins including the amyloid precursor protein (APP), presenilin 1 (PS1) and PS2. All of these genes are involved in the accumulation of Amyloid-ß (Aß), a key characteristic of AD pathology.

Molecular AD pathology is characterized by the abnormal formation of insoluble forms of extracellular Aß plaques and the aggregation of the highly-phosphorylated protein tau within intracellular neurofibrillary tangles (NFTs) (refs). Aß is formed through the proteolytic cleavage of APP, a protein associated with the formation of toxic Aß peptides, by the enzymes γ-secretases and ß-secretases, which include PS1 and PS2, often resulting in the formation of the isoforms Aß42 and Aß40. Aß42 is considered to be toxic as it exhibits amyloidogenic characteristics making it more prone to Aß aggregation. Mutations in the genes APP, PS1, and PS2 have been shown to increase the Aß42 to Aß40 ratio, thus furthering the rate of Aß aggregation and increasing neuronal cell toxicity (De Mena et al., 2020). The amyloid hypothesis claims that the formation of extracellular Aß plaques is the main cause of AD (Selkoe & Hardy, 2016). However, recent studies have found that non-Aß factors such as tau, a protein that stabilizes neuronal structure, and apolipoprotein E (APOE) accumulation, a protein that metabolizes fats, are also a significant part of AD pathogenesis (Morris et al., 2014). Nonetheless, Aß accumulation is still a substantial factor in AD pathology. Aß accumulation first forms soluble Aß oligomers before depositing as Aß fibrils and eventually Aß plaques (Chen et al., 2017). It has been shown that Aß fibrils contribute significantly to neuronal death and memory loss in AD, however, recent studies have revealed that soluble Aß oligomers may have a more damaging effect on neurons. Recent studies have also revealed that soluble Aß forms, like Aß oligomers and peptides, play an important role in the proinflammatory activation of primary microglia, the resident immune cells of the CNS (Sondag et al., 2009). Aß oligomers and peptides have also been shown to induce the release of astrocytic proinflammatory mediators leading to further synaptic dysfunction in neurons (Matos et al., 2008).

Synaptic dysfunction has been proven to be a key characteristic in AD pathology. Synapses are the basic unit of information transduction among neurons in the brain. Synapses mainly form between axons and dendrites and are made up of a presynaptic neuron (signal transmitter), synaptic cleft (gap between neurons), and a postsynaptic neuron (signal receiver) as modeled by Figure 1 (Südhof, 2018). Receptors involved in synaptic functioning include metabotropic glutamate receptors type 5 (mGluR5) and N-Methyl-D-Aspartate (NMDA) receptors. The mGluR5 receptor is a G-protein coupled receptor that plays a key role in neuronal Calcium release.

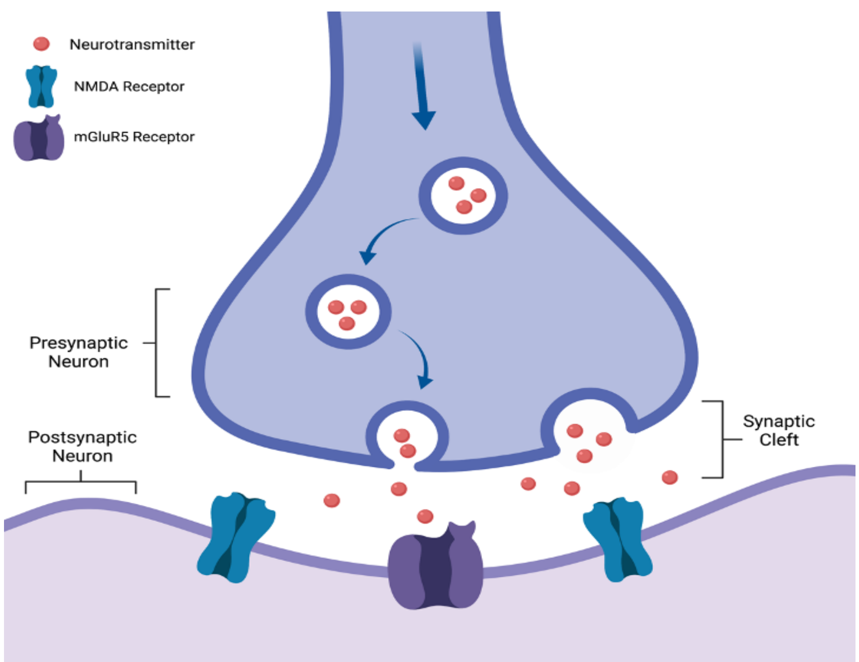

Figure 1. Depiction of the basic structure of the synapse with the presynaptic neuron, synaptic cleft, and Postsynaptic neuron. Neurotransmitters are entering the NMDA and mGluR5 receptors through the synaptic cleft.

In particular, NMDA plays a central role in synaptic performance as NMDA receptor activation can induce either long-term potentiation (LTP), a process associated with synaptic strengthening, or long-term depression (LTD), a process associated with synaptic deterioration (Alifragis & Marsh, 2018). Synaptic plasticity describes the ability of synapses to strengthen or weaken over time in response to changes in their activation making them a key component of learning and memory. Both LTP and LTD are factors that affect synaptic plasticity with LTP enhancing synaptic strength and LTD depressing it. Studies have shown that aberrant functioning of synapses via synaptic loss and deregulation are associated with cognitive decline and memory loss in AD patients (Chen et al., 2019). Synaptic dysfunction in AD occurs as a result of the malfunction of certain synaptic mechanisms including receptor activation, gliotransmitter release, and presynaptic and postsynaptic regulation (Chen et al., 2019). Additionally, Aß has also been shown to contribute to synaptic dysfunction as studies have proven that Aß oligomers bind to synaptic sites to regulate the activation of NMDA, mGluR5, and other synaptic membrane receptors (Li & Selkoe, 2020).

Astrocytes play a role in the regulation of synaptic transmission between neurons via their proximity to synapses and their release and reuptake of gliotransmitters. Astrocytes in the CNS are closely associated with synapses allowing them to monitor and alter synaptic function and modulate synaptic activity through their gliotransmitter abilities (Chung et al., 2015). Astrocytes can release several gliotransmitters including glutamate, GABA, ATP, and D-Serine (refs). Studies on AD mouse models have revealed that astrocyte gliotransmission, the process of neuroactive chemicals being released from astrocytes, is impaired in AD, causing excessive GABA release into the extracellular space in the brain, thus resulting in the inhibition of glutamate release and neuronal activity alongside memory impairment (Harada et al., 2016). Recent studies have also shown that the Ca2+-dependent release of the gliotransmitter D-serine from astrocytes has been shown to control NMDAR, the receptor of NMDA, dependent synaptic plasticity in excitatory synapses (Henneberger et al., 2010). These findings indicate a crucial role of astrocytic gliotransmission in impairing synaptic transmission in AD. Furthermore, during injury, disease, and other toxic conditions, astrocytes become reactive and undergo morphological and metabolic changes in a process called astrogliosis. In acute models of astrogliosis, astrocytes have been found to increase their expression of genes involved in protein synthesis and antioxidant defense in response to neurodegeneration (Das et al., 2020). Astrogliosis occurs at a rapid pace in AD in response to the formation of NFTs and Aß accumulation. Soluble Aß oligomers cause astrogliosis to occur at higher rates, effectively furthering AD pathogenesis (Sturcher-Pierrat & Staufenbiel, 2006).

As astrocytes are the most abundant glial cells in the CNS, impairment in their relationship with Aß accumulation and synaptic dysfunction can further promote neuronal degeneration in AD (Figure 2). This review aims to analyze the different roles of astrocytes in the relationship between Aß accumulation and synaptic dysfunction, and how this is relevant in AD pathogenesis.

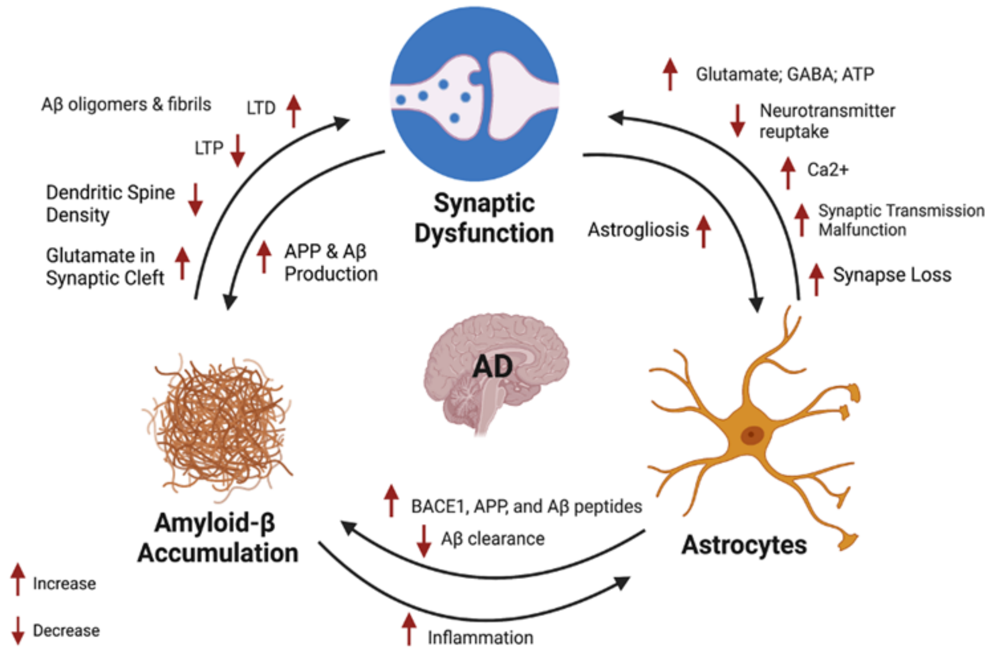

Figure 2. Representation of the relationship between Astrocytes, Amyloid-ß Accumulation, and Synaptic Dysfunction in AD. Aß accumulation causes decreased dendritic spine density and LTP induction alongside imbalances in neurotransmitter levels in the synaptic cleft, and LTD activation. Neurons and synapses are in turn sources of APP and Aß production. Astrocytes contribute to Aß accumulation by increased BACE1, APP, and Aß peptide production alongside decreased Aß clearance. Aß accumulation affects astrocytes by inducing inflammation. Astrocytes trigger synaptic dysfunction by causing synapse loss, synaptic transmission malfunction, Ca2+ increase, and excessive release and reuptake of the gliotransmitters glutamate, GABA, and ATP. Synaptic dysfunction affects astrocytes by increasing the rate of astrogliosis in AD, thus causing severe disparities in astrocytic functioning.

The Relationship Between Aß Accumulation and Synaptic Dysfunction in AD

Aß accumulation has been proven to have a significant role in modulating synaptic transmission both presynaptically and postsynaptically. Research has shown that soluble forms of Aß oligomers are more potent than other forms of Aß in causing synaptic dysfunction and impairment. Increased levels of soluble Aß oligomers have been shown to disrupt synaptic plasticity by inducing LTD in the CA1 region of the hippocampus, which is heavily involved in memory formation and retention, and decreasing glutamate reuptake in the synapse (Li et al., 2009). APP undergoes proteolytic cleavage resulting in the formation of Aß peptides. Aß peptides then start to aggregate to first form Aß oligomers, then Aß fibrils, and in the end ultimately form Aß plaques. Thus, APP has been shown to modulate neuronal excitability by depressing excitatory synaptic transmission (Kamenetz et al., 2003) and inducing post-synaptic depression (Mucke & Selkoe, 2012). Additionally, studies have shown that APP transgenic mice which contained the Swedish mutation (increases abnormal cleavage of APP) showed deficits in synaptic transmission and communication long before detectable signs of extracellular Aß plaque formation (Holcomb et al., 1999). These findings suggest that neuronal Aß peptide accumulation via APP cleavage can induce impairments in synaptic function early on in AD. Furthermore, increased levels of Aß42 induced by APP have been implicated in memory loss and cognitive decline in early forms of AD

(Alifragis & Marsh, 2018). All of these mechanisms involving APP processing and Aß accumulation thus result in impairments to the synaptic transmission of neurons in AD.

Disruptions in neuronal synaptic plasticity is an early pathological symptom of AD that can indicate cognitive decline. Synaptic plasticity is mainly regulated by the amount of active AMPA receptors (AMPARs) and NMDARs receptors at the synapse. Both AMPARs and NMDARs regulate LTP and LTD induction, the major forms of synaptic plasticity that underlie cellular mechanisms of learning and memory. Oligomeric Aß peptides have been shown to activate extrasynaptic NMDARs mainly composed of the glutamate subtypes GluN2B, which interacts with proteins in synaptic plasticity resulting in the blockage of LTP (Kervern et al., 2012). It was also revealed that Aß oligomers switched the direction of synaptic plasticity to favor synaptic depression under high-frequency conditions. In order to activate synaptic NMDARs for LTP, a large increase in Ca^{2+} is needed while the activation of synaptic NMDARs for LTD requires a slight increase in Ca^{2+} levels. Soluble Aß oligomers reduce NMDAR-mediated calcium influx levels in hippocampal neurons by blocking Ca2+ transmission resulting in the suppression of LTP and onset of LTD (Figure 3) (Liang et al., 2017). All of the mechanisms described above either enhance LTD, impair LTP, or do both. However, it should be noted that these observations are all seen in Aß oligomers not Aß monomers.

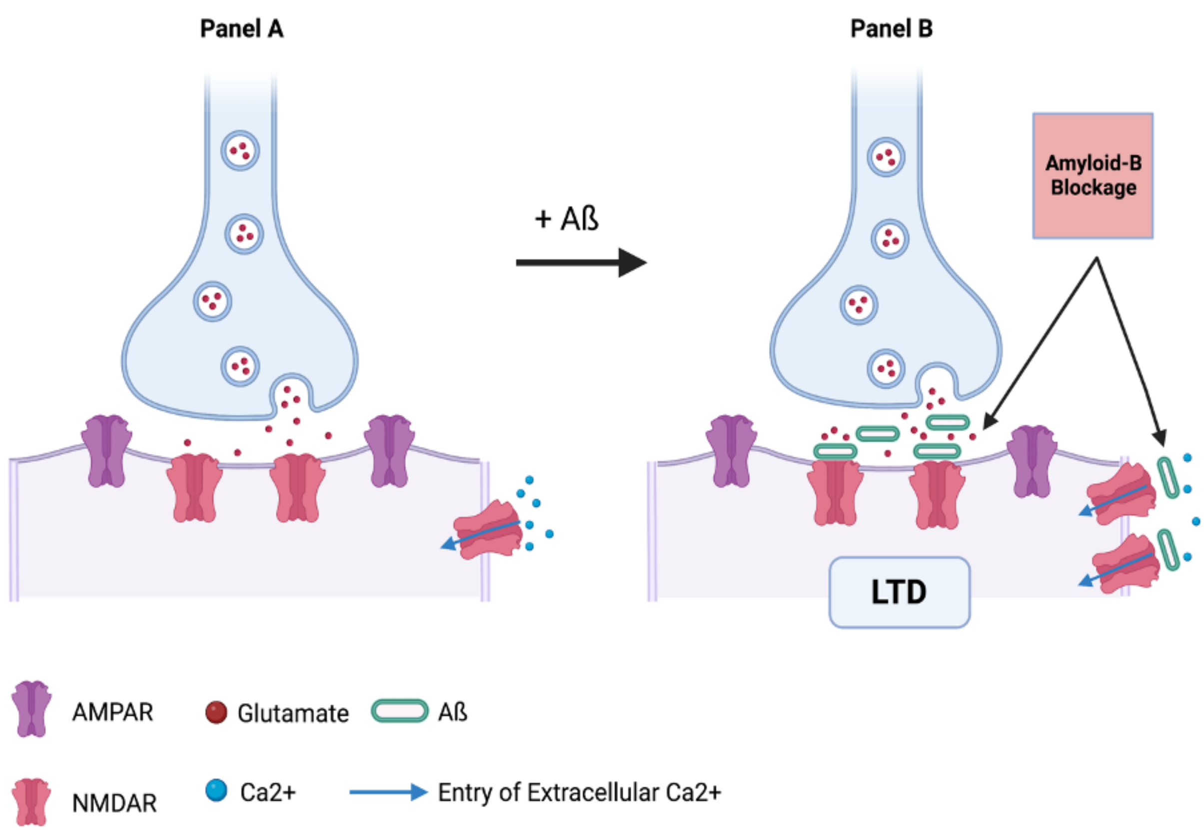

Figure 3. Depicts the change in synaptic transmission once Aß is added. The synapse on the left shows normal glutamate and Ca^{2+} transmission without Aß. The synapse on the right indicates what occurs when Aß is added into the synaptic cleft. Aß is blocking both glutamate and Ca^{2+} from binding to NMDAR receptors resulting in a decrease of both glutamate and extracellular Ca^{2+} entry into the synapse. The decrease in glutamate and Ca2+ levels then triggers LTD.

Aß accumulation can lead to the weakening of dendritic spines and synaptic loss, leading to LTD induction and LTP inhibition in AD. Dendritic spines are the part of the synapse that function as the center of synaptic strength and help transmit electrical signals to other neurons. Decreases in dendritic spine density can represent decreases in synaptic plasticity and strength for neurons. LTP promotes the growth of the dendritic spine while LTD induces dendritic spine shrinkage (Kullmann & Lamsa, 2007). Aß oligomers have been shown to trigger dendritic spine density reduction in hippocampal pyramidal neurons via the induction of LTD as seen in Figure 4 (Liu et al., 2004). Additionally, studies have revealed that Aß oligomers inhibit LTP in excitatory synapses through the blockage of NMDAR receptors, resulting in decreased dendritic spines, consequently causing interferences in the memory and behavior of adult mice (Figure 4)(Kervern et al., 2012). Furthermore, a recent study showed that Aß oligomers surrounding Aß plaques were associated with a phenotype of postsynaptic density shrinkage and synaptic loss. The study hypothesized that the plaques acted as a reservoir of soluble Aß oligomers, resulting in synaptic loss and toxicity in the cerebral cortex (Koffie et al., 2009).

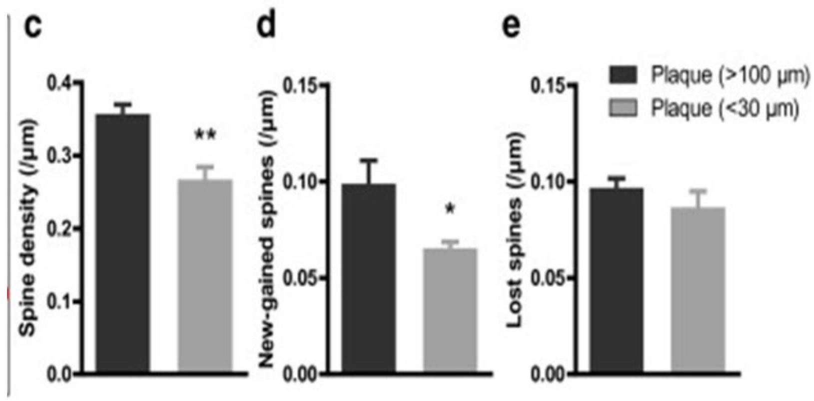

Figure 4. Indicates the decrease of dendritic spine density after AB is added (From Dorostkar et al., 2015).

Soluble Aß oligomers can also affect the activation of NMDARs and LTD induction by increasing glutamate levels. Glutamate is a major excitatory neurotransmitter that mediates the intensity of synaptic signaling between neurons. Aß oligomers block neuronal glutamate uptake at synapses leading to increased glutamate levels in the synaptic cleft and LTD induction (Li et al., 2009). This reaction occurs because increased glutamate causes the initial activation of NMDARs but also results in the desensitization of the receptors, thus limiting calcium influx during repeated synaptic stimulation that could induce synaptic strength. As there is now significantly more glutamate than NMDAR receptors are equipped to handle, synaptic depression occurs. Furthermore, a study showed that neurons that were briefly exposed to Aß peptides increased their LTP, while higher concentration of Aß peptides or longer exposure of Aß peptides to the neurons resulted in decreased excitatory postsynaptic potential and inhibited LTP (Puzzo et al., 2008). This mechanism could potentially be the result of Aß oligomers increasing glutamate levels in the synaptic cleft alongside increasing the activation of NMDARs.

Synaptic dysfunction can also in return affect Aß accumulation in AD. The production and secretion of Aß into the synaptic cleft is tightly regulated by neuronal activity, with high neuronal activity enhancing Aß production and low neuronal activity having the opposite effect. Moreover, synaptic vesicle release has been shown to be the primary mediator of changes in extracellular Aß levels that are linked to synaptic activity in vivo (Cirrito et al., 2005). Synaptic dendrites have also been shown to release pathogenic Aß species (Wei et al., 2009). This relationship between Aß accumulation and synaptic dysfunction has been hypothesized to be a potential therapeutic treatment option for AD (Mucke & Selkoe, 2012).

Astrocytes in Aß Accumulation

Astrocytes have a role in contributing to Aß accumulation in AD by having a hand in the production of Aß. Beta-secretase (BACE1) is an enzyme that cleaves APP at ß-secretase sites causing it to be a necessary prerequisite for ß-amyloid accumulation. BACE1 has also been shown to increase the rate of Aß plaque aggregation causing it to be a key risk factor in AD (Cole & Vassar, 2007). Neurons have been shown to be the main source of Aß peptide production as BACE1 is mainly expressed and localized around neurons in the brain (Cole & Vassar, 2007). However, recent studies have shown that specific types of glia, most notably astrocytes, could prove to be an alternative source of BACE1 especially under certain neuroinflammatory conditions. Cytokines regulate the host response to infection and proinflammatory cytokines are a type of cytokine that act to make a disease worse under certain neuroinflammatory conditions. Studies have shown that the treatment of the proinflammatory cytokine interferon γ (IFNγ) into mouse brains resulted in increased levels of BACE1 expression within astrocytes (Hong et al., 2003). The Janus Kinase Pathway 2 (JAK2) is a signaling pathway associated with triggering inflammatory responses and the Extracellular Signal-regulated Kinase ½ (ERK ½) signaling pathway participates in intracellular signal transduction (Hong et al., 2003). IFNγ has been shown to activate the JAK and ERK1/2 signaling pathways resulting in phosphorylated STAT1 to bind to the putative STAT1 binding sequences in the BACE1 promoter region to modulate further BACE1 expression in astrocytes as depicted in Figure 4 (Cho et al., 2007). It has been hypothesized that the release of pro-inflammatory cytokines like IFNγ by microglia can result in the induction of astrocytic BACE1 expression, effectively triggering the formation of ß-amyloid plaques (Smith et al., 2012). In fact, other proinflammatory cytokines alongside IFNγ including tumor necrosis factor α (TNFα) and interleukin β (IL1β) have been shown to increase the production of the Aß1-40 and Aß1-42 proteins in primary human astrocytes and astrocytic cell lines (Figure 5;Blasko et al., 2000). These findings indicate how astrocytes could contribute to further harmful Aß accumulation in AD.

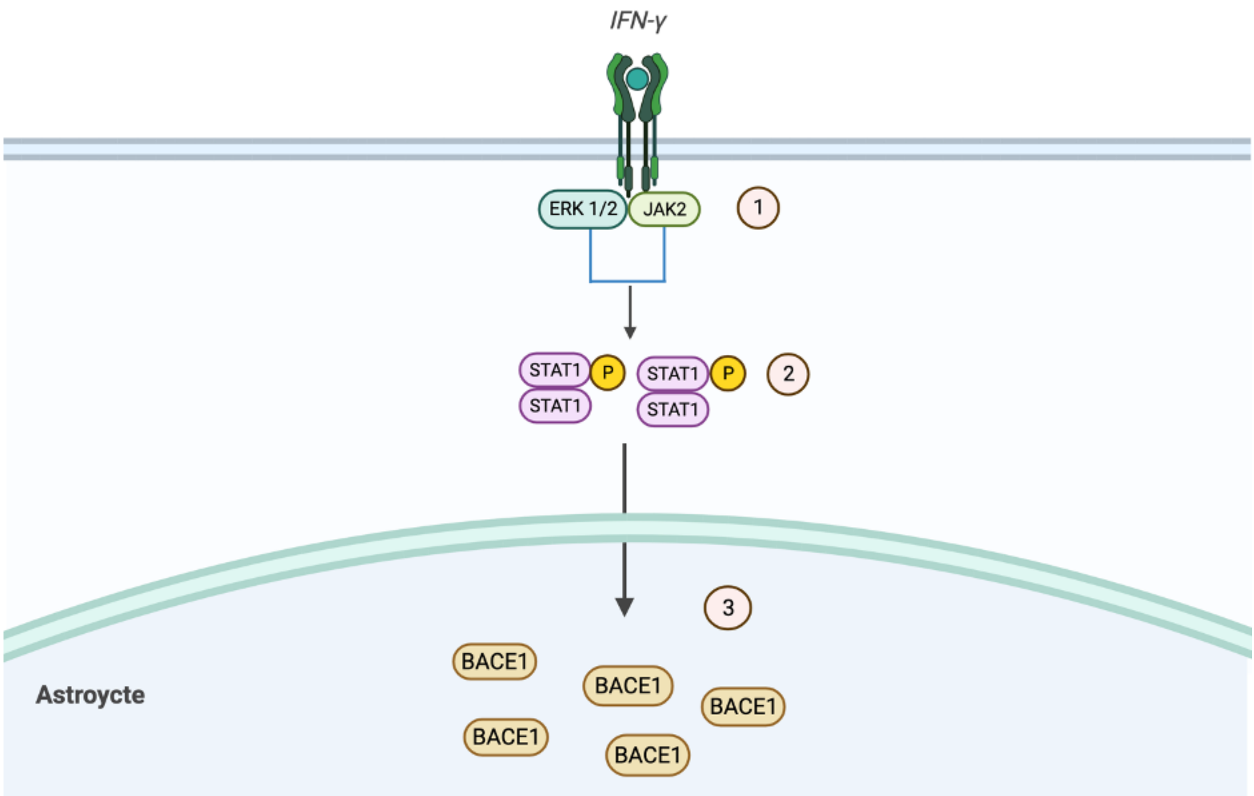

Figure 5. Depicts the process of IFNγ increasing BACE1 expression in Astrocytes. 1) IFNγ activating the JAK2 & ERK ½ signaling pathways. 2) Activation of JAK2 & ERK ½ signaling pathways trigger phosphorylated STAT1 to bind to Putative STAT1. 3) Binding triggers increased BACE1 expression in Astrocytes.

Additionally, the APOE4 genotype, the strongest risk factor for AD, under certain neuroinflammatory-driven conditions has been connected to furthering proinflammatory cytokine production, neurotoxicity, and Aß in AD. Astrocytes and microglia are the primary producers of APOE in the brain. Several in vivo studies have shown that when lipopolysaccharide (LPS), an endotoxin that stimulates immune responses, is injected into APOE4 mice, higher levels of IL1β and TNFα can be seen (Lynch et al., 2003; Zhu et al., 2012). Recently, a study showed that only APOE4 mice, not APOE3 mice, led to increased neurotoxicity in mice (Maezawa et al., 2006). Increased toxicity of APOE4 has been correlated with higher proinflammatory cytokines levels, thus contributing to astrocytes neurotoxic role in AD. Furthermore, this secretion of proinflammatory cytokines by APOE4 further contribute to Aß production and accumulation in AD.

Furthermore, it has been proposed that an increase in BACE1 expression in astrocytes may be responsible for the localized increase of amyloidogenic AP, associated with the creation of Aß peptids, fragment accumulation (Rossner et al., 2005). Studies have shown that reactive astrocytes can express APP during chronic gliosis (Martins et al., 2001) which can result in the increased accumulation of Aß peptides and BACE1 fragments (Zhao et al., 2007). It should be noted, however, that the increased astrocytic BACE1 expression only contributes to the pathogenesis of AD if the astrocytes also express the BACE1 substrate APP. Although previous research has shown that BACE1 is mainly expressed in neurons, the expression of BACE1 in astrocytes would still greatly contribute to Aß accumulation in AD, given the vast quantity of astrocytes in the brain.

Zhao et al. proposes a feed-forward mechanism where Aß induced-inflammation results in reactive astrocytes release of Aß prerequisite proteins leading to Aß accumulation (Zhao et al., 2011). In this study Zhao et al. utilized mouse primary activated astrocytes and found that proinflammatory cytokine combinations of TNFα+IFNγ stimulated an increase in BACE1, APP, and Aß in astrocytes. Thus, resulting in the formation of Aß42 oligomers and fibrils which maintained and elevated cerebral Aß levels to induce chronic inflammation. These findings suggest the involvement of a vicious and continuous cycle of Aß accumulation by activated astrocytes in AD.

Astrocytes also contribute to Aß accumulation by affecting Aß deposition and clearance. Astrocytes have phagocytic abilities that allow them to ingest and destroy toxic materials in place of other dysfunctional microglia through their phagocytic receptors, Axl and Mertk (Konishi et al., 2020). During the early stages of AD, astrocytes have been shown to be more effective than other microglia in clearing Aß (Nielsen et al., 2010). Cultured astrocytes engulf Aß in a process conditional to the Aß binding receptors CD36 and CD47 (Jones et al., 2012) and at times are reliant on APOE that is localized to plaques-associated reactive astrocyte mechanism for the degradation of Aß (Jiang et al., 2008). Astrocytes have also been shown to take longer in degrading ingested cells compared to other microglia (Lööv et al., 2015), which can lead to Aß being stored in astrocytes for longer periods of time (Figure 6). Extracellular astrocytic deposition and degradation of Aß has been shown to be influenced by the amyloid-degrading peptidase protease neprilysin (El-Amouri et al., 2008). Intracellular astrocytic degradation of Aß, however, is influenced by lysosomal pathways as lysosome biosynthesis can improve Aß clearance and reduce Aß load (Xiao et al., 2014).

Impairments to astrocytes phagocytic abilities can lead to further Aß accumulation. Recent studies have shown that astrocytes engulf large amounts of Aβ42 protofibrils and store them for long periods of time rather than degrade them (Söllvander et al., 2016). This intracellular Aß accumulation caused severe endosomal and lysosomal deficiencies which resulted in the reduction of astrocytes degradation capacity, decreased Aß clearance, and increased Aß load (Figure 6). This accumulation of Aß within astrocytes yielded the formation of enlarged astrocytic endosomes. Thus, the inefficient degradation of Aß in astrocytes can lead to increased Aß build up, furthering the pathogenesis of AD. Aß accumulation has also been shown to trigger a neuroinflammatory response in the brain resulting in Aß controlling the activation of certain inflammatory responses which can then determine the stimulation of astrocytes' phagocytic mechanism to uptake and clear Aß from the brain (Fiala & Veerhuis, 2010). The amount of Aß accumulation that occurs determines whether these proinflammatory systems are activated or not demonstrating how Aß aggregation influences astrocytic inflammatory response.

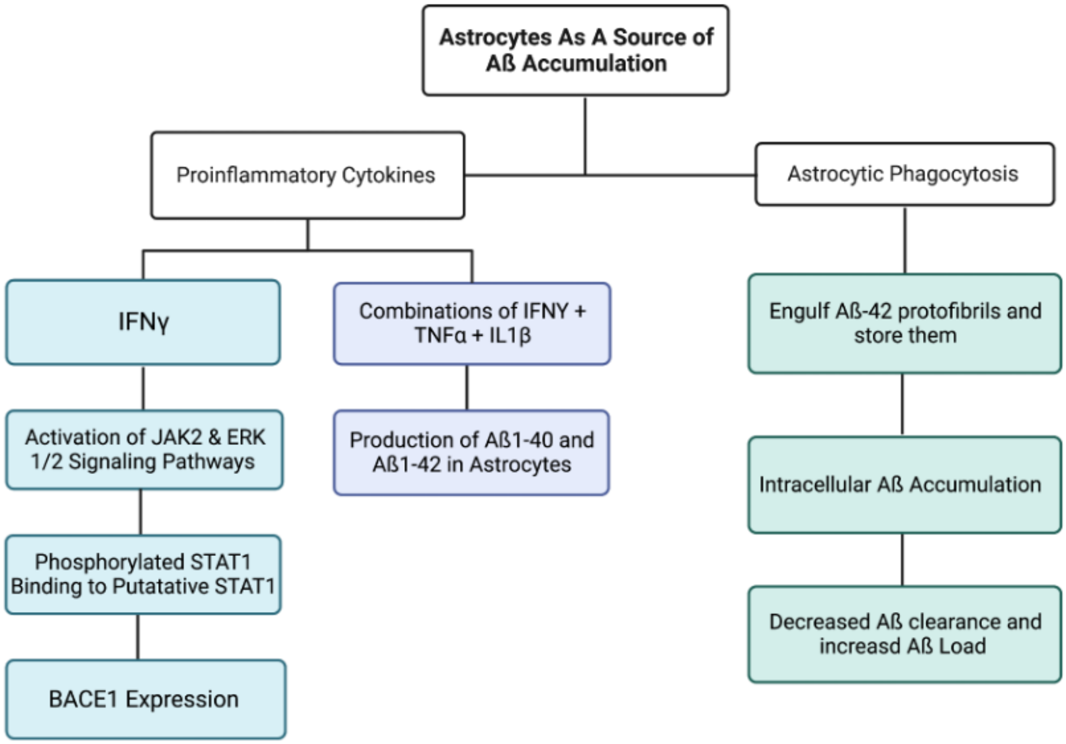

Figure 6. Chart summarizing how astrocytes can be a source of Aß accumulation through proinflammatory cytokines or astrocytic phagocytosis.

Astrocytes in Synaptic Dysfunction

Astrocytic Gliotransmission & Calcium Level Impairment

As discussed before, astrocytes have the ability to control synaptic transmission through the process of astrocytic gliotransmission. During synaptic activity, the release of neurotransmitters results in changes to intracellular calcium levels in astrocytes. Astrocytes express several G-protein-coupled receptors (GPCRs), transmembrane proteins that convert extracellular signals into intracellular responses, which react to neurotransmitters through the arousal of inositol triphosphate type 2 receptors (IP3R2), a critical component in the astrocytic-synaptic signaling pathway, to mediate calcium release in the synapse (Figure 7) (Kofuji & Araque, 2021). Astrocytes themselves use the chemical transmitter Ca2+ for intracellular communication resulting in astrocytic control of the voltage-gated Ca2+ channels (VCGG) in the cell membrane (Kim et al., 2019). In situ and in vivo studies have shown that temporary rises in intracellular Ca2+ concentration have been seen in astrocytes, causing Ca2+ to be an important part of astrocytic gliotransmitter release (Fiacco et al., 2007)(Agulhon et al., 2010) . Astrocytic gliotransmission has been proven to modulate neuronal activity and synaptic transmission in several brain regions including the basal ganglia (Martín et al., 2015) and cerebral cortex (Poskanzer & Yuste, 2016) in AD. This bidirectional exchange of information between astrocytes and neurons can be seen in the concept of the tripartite synapse that shows astrocytes as essential to presynaptic and postsynaptic processes.

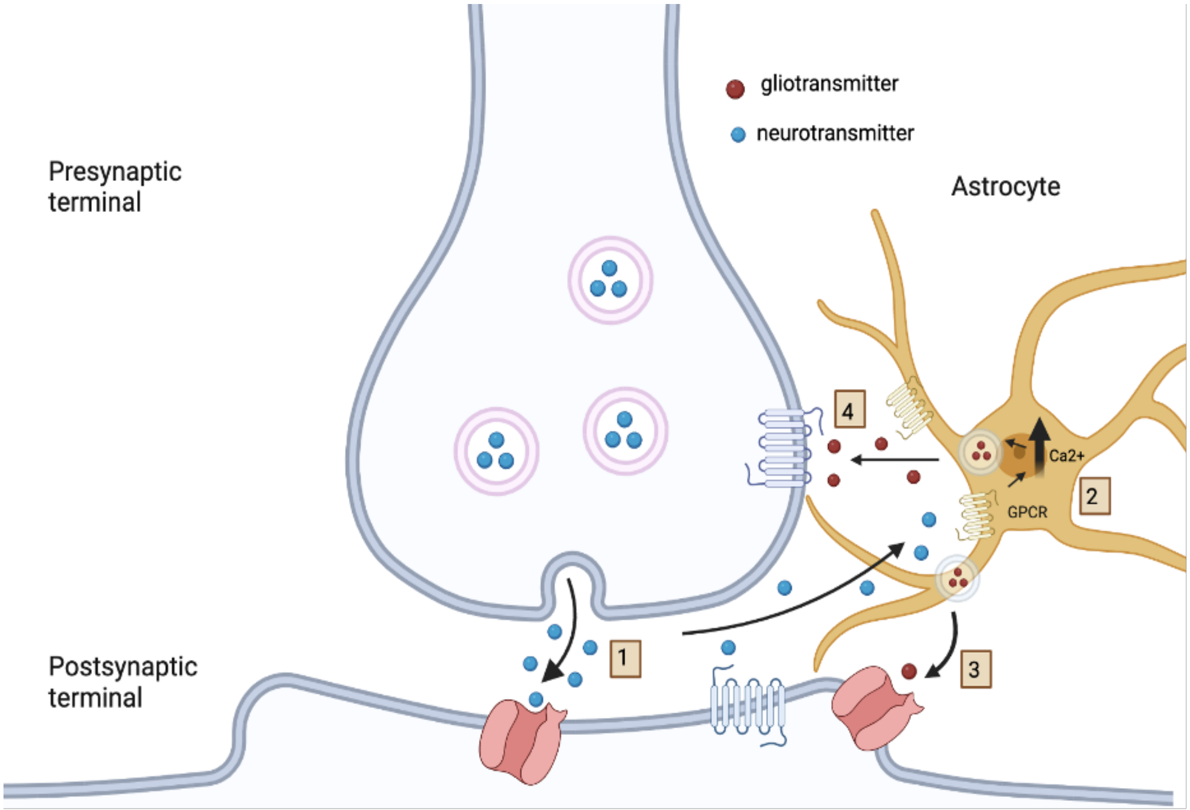

Figure 7. Representation of tripartite synapse. The tripartite synapse is made of presynaptic and postsynaptic processes with astrocytes enwrapping the synapses. (1) The release of neurotransmitters from the presynaptic terminal acts on astrocytic receptors that mediate intracellular calcium elevation with GPCRs. (2) Calcium elevation triggers the release of gliotransmitters (D-serine, GABA, Glutamate) which bind to the postsynaptic terminal receptors (3) or presynaptic receptors (4) in order to modulate synaptic transmission. (Adapted from Nanclares et al., 2021).

Gliotransmitters can be released through either a storage compartment by exocytosis or from the cytosol via plasma membrane ion channels such as purinergic P2X7 channels and volume-regulated anion channels (Hamilton & Attwell, 2010). However, Ca2+ exocytosis has been shown to be the major mechanism for the release of important gliotransmitters (D-serine, GABA and glutamate) in astrocytes as well as synaptic activity. Regulated Ca2+ exocytosis in neurons is triggered when an action potential reaches the axon terminals to provoke Ca2+ increase leading to the dependent fusion of synaptic vesicles (SVs) with the plasma membrane (Jahn & Fasshauer, 2012). Studies have revealed that astrocytes express VAMP2, a soluble NSF attachment protein receptor that modulates neurotransmitter vesicle release, raising the question of whether regulated exocytosis is the mechanism behind astrocytes' modulatory abilities in synaptic function and plasticity (Parpura et al., 1995). Experimental studies have attempted to answer this question and two key findings arose: the first being that the infusion of Ca2+ buffer solutions in astrocytes led to the disruption of regular synaptic activity (Panatier et al., 2011) and the second being that this agitation of synaptic properties in the neuronal circuit was potentially the result of VAMP2 exocytosis from astrocytes (Schiavo et al., 1992). These findings suggest that astrocytes could participate in exocytosis, implying a deeper role of astrocytes in synaptic plasticity and modulation.

Astrocytic Gliotransmitters in Synaptic Dysfunction

Glutamate & mGluR5

Glutamate is one of the main gliotransmitters released from astrocytes that allows them to play a role in presynaptic and postsynaptic functions. Astrocytes are key regulators of glutamate homeostasis through their regulation of glutamate release and reuptake (Mahmoud et al. 2019). Astrocytes express certain glutamate transporters including EAAT1 and EAAT2, which regulate glutamate uptake in the synapse, excitatory synaptic transmission, and long-term synaptic plasticity in AD (Valtcheva & Venance, 2019; Scimemi et al., 2013). Studies have shown that slow glutamate release impairs LTP and mediates the strength and direction of synaptic plasticity (Barnes et al., 2020). Astrocytic glutamate potentiates excitatory transmission in the hippocampal dentate gyrus, which is essential in memory formation, by acting on presynaptic NMDARs (Jourdain et al., 2007). In fact, one study showed that astrocytic glutamate-mediated the timing of LTD during excitatory transmission in the neocortex by activating presynaptic NMDARs (Min & Nevian, 2012). Another study showed that in the CA1 hippocampal region, astrocytic glutamate has been shown to strengthen inhibitory transmission by acting on presynaptic kainate receptors (Liu et al., 2004). Furthermore, the amino acid D-serine is a coagonist of glutamate in the activation of excitatory NMDA receptors (Peters et al., 2009). At the synaptic cleft, the calcium-dependent release of D-serine from astrocytes regulates NMDA receptor-dependent processes such as excitatory synaptic transmission and synaptic plasticity (Hennenberg et al., 2010). The withdrawal of astrocytic ensheathment of the synaptic cleft during lactation reduces levels of D-serine and leads to the induction of LTD (Panatier & Robitaille 2016). These findings thus provide a clear example of metaplasticity of synaptic transmission mediated by astrocytes through the release of the glutamate coagonist d-serine. Shrivastava et al. 2013 showed in their study that astrocytic calcium dysregulation resulted in synaptic transmission imbalances. Another study, however, had a different interpretation of mGluR5 role in synaptic transmission. Sun et al. suggested that a decrease in astrocytic mGluR5 causes a refinement of the synaptic circuitry leading to restrictions in the expression of presynaptic receptors which is needed in the tripartite modulation model (Figure 7) (Sun et al., 2013).Astrocytic glutamate has been shown to be a major participant in the synaptic plasticity, modulation, and transmission of neurons.

ATP

Adenosine triphosphate (ATP) is a neurotransmitter that mediates synaptic potential through ligand-gated cation channels (P2X receptors) and G-protein coupled receptors (P2Y receptors). ATP has been shown to be released from astrocytes as a gliotransmitter (Harada et al., 2016). Studies have revealed that astrocytes release ATP through a calcium-dependent manner via exocytosis from synaptic vesicles (Pangršič et al., 2007). Thus, increased calcium levels could trigger further ATP release in astrocytes to initiate synaptic transmission. Studies have also revealed that ATP is the primary active messenger in the extracellular communication between astrocytes (Guthrie et al., 1999). Additionally, ATP has been implicated as the excitatory medium necessary for calcium wave stimulation in astrocytes. Further research done by this group of researchers showed that ATP, mediated by P2Y1 receptors, is the predominant cause of intracellular calcium waves in hippocampal astrocytes (Bowser & Khakh, 2007). The significance of astrocytic gliotransmission of ATP in the mediation of intracellular calcium waves further implicates astrocytic involvement in synaptic transmission in AD.

ATP has also been implicated in contributing to the neuroprotective role of astrocytes in AD. One study conducted by Jung et al. showed that exogenous ATP prevented Aß42-induced reduction of synaptic molecule levels in cultured primary hippocampal neurons (Jung et al., 2012). Additionally, ATP was shown to have restored Aß-42 mediated reduction of synaptic proteins and protected Aß-42 mediated dendritic spine loss. These protective roles adopted by ATP contribute to the neuroprotective role of astroyctes in AD, as astrocytes release ATP themselves.

GABA

GABA is a type of inhibitory gliotransmitters that is released by astrocytes. Those who have AD show high GABA levels in their cerebrospinal fluid contributing to memory impairment (Farrant & Nusser, 2005). GABA is mainly released from reactive astrocytes through the GABA-permeable bestrophin 1 (Best1) channel (Lee et al., 2010) . Recent studies have shown that in the hippocampus, Best1 is highly expressed at the astrocytic microdomains near synapses (Han et al., 2013). Additionally, the GABA released from reactive astrocytes have been shown to inhibit dentanule neurate grons resulting in impairment to LTP spike probability (Jo et al., 2014). Thus, astrocytic GABA can inhibit synaptic plasticity in certain brain regions, resulting in memory impairments and further AD pathogenesis.

Astrocytes in the Relationship Between Aß Accumulation & Synaptic Dysfunction in AD

Astrocytes have been implicated in the pathogenesis of AD through their complex involvement in the relationship between Aß accumulation and synaptic dysfunction. The inflammatory mechanisms induced by Aß accumulation can result in rapid astrogliosis in AD. One study using both *in vivo* and *in vitro* approaches showed that Aß accumulation was proven to stimulate the inflammatory causing enzyme inducible nitric oxide synthase (iNOS) protein expression through the production of TNFα, a proinflammatory cytokine that contributes to neuroinflammation and extracellular signaling (Medeiros et al., 2007). TNFα and iNOS were then shown to be contributing to the rapid activation of astrocytes within Aß-treated mice. The increased production of reactive astrocytes via Aß induced proinflammatory systems could potentially contribute to the excess release of mGluR5 and GABA in astrogliosis. Furthermore, iNOS has been shown to produce NO at high concentrations. NO has been shown to be neuroportective in low concentrations and neurotoxic at higher concentrations (Steinert et al., 2010). Thus, increased iNOS production could be associated with the further pathogenesis of AD. Thus, resulting in further dysfunction of neuronal excitability and synaptic plasticity in AD.

Furthermore, TNFα has been proven to contribute to other Aß induced astrocytic impairments through Aß3(pE)-42, the amino-terminally truncated, oligomeric, pyroglutamated form of Aß (Saidos et al., 1995). Aß3(pE)-42 accumulates during the early stages of AD, implying that the peptide is a seeding species and plays an important role in the formation of Aß aggregates (Saido et al., 1995). One study investigated how the Aß oligomeric species Aß3(pE)-42 and Aß1-42 contributed to early synaptic dysfunction through glial cells like astrocytes (Grochowska et al., 2017). Aß3(pE)-42 is more tightly associated with astroglia as it is taken up by astrocytes to induce the glial release of TNFα resulting in Aß3(pE)-42 causing stronger astroglial proliferation in organotypic hippocampal slices than Aß1-42. This finding is logical as microglial activation and astroglial proliferation in AD is prominently triggered by Aß3(pE)-42 which could be connected to early synaptic dysfunction in AD. Additionally, the treatment of primary hippocampal culture with a conditioned medium from astrocytes induced significant synapse loss only in the case of Aß3(pE)-42. The data from the study remained consistent in this regard as it suggested that synaptic dysfunction caused by Aß3(pE)-42 required glial uptake and the release of astrocytic TNFα. The results from this indicate how Aß oligomers can trigger synaptic dysfunction during the early stages of AD via astrocytic pathological signaling pathways.

Soluble Aß peptides affect Ca2+ activity in astrocytes to further mediate synaptic dysfunction. One study investigated the astrocytic calcium activity in mouse CA1 hippocampus *stratum radiatum* and found that soluble Aß oligomers caused fast and extensive calcium hyperactivity within astrocytes resulting in early synaptic dysregulation and depression (Bosson et al., 2017). The astrocytic Ca2+ hyperactivity was in part induced by the transient receptor potential A1 (TRPA1) channels which were proven to exert strong influences on local synaptic function and were linked to the glutamatergic synapse hyperactivity in CA1 neurons. These findings suggest that astrocytes are targeted by soluble Aß oligomers resulting in early synaptic dysregulation in AD.

The Aß25-35 peptide, a neurotoxic Aß fragment found in AD, caused Ca2+ levels alteration alongside glutamate release (Pham et al., 2021). Aß25-35 induced Ca2+ reduction within Aß-preconditioned astrocytes as a result of the plasma membrane Ca2+ ATPase (PMCA). Aß25-35 also causes ATP release through the CX hemichannels, which dysregulates synaptic transmission. The Aß oligomers triggering the release of glutamate from astrocytes has been implied to be mediated by the Best-1 channels through Ca2+ activation (Han et al., 2013). Best-1 is involved in excessive GABA release in certain AD mouse models resulting in the inhibition of LTP (Jo et al., 2014). These studies implicate a connection between astrocytic glutamate and GABA release inducing LTP suppression and LTD induction.

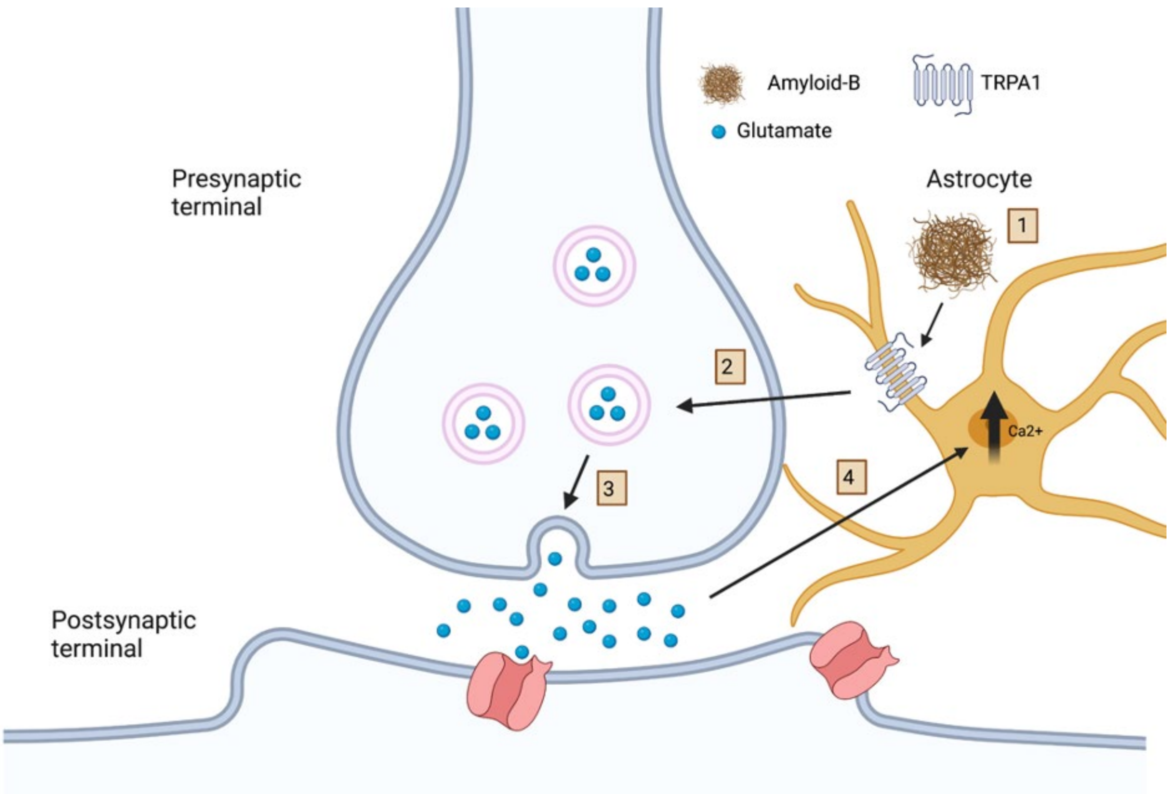

Figure 8. Depicts the process Ca2+ being mediated by synaptic glutamate via Aß. 1) Aß activates TRPA1 chaneel. 2) TRPA1 transmits signals that causes synaptic vesicles to become hyperactive. 3) Hyperactivity in synapse results in increased glutamate release in the synaptic cleft 4) Increase in excess glutamate in synaptic cleft results in increased Ca2+ in Astrocytes.

Soluble Aß oligomers have been shown to decrease the activation of glutamate transporters, therefore impairing synaptic plasticity (Huang et al., 2018). Utilizing field excitatory postsynaptic potentials (fEPSP) recordings were made of the synaptic activity in the CA1 region of mouse hippocampal slices. The study found that soluble Aß oligomers inhibited LTP and facilitated LTD through the interruption of the glutamate transporter function. Aß oligomers also decreased the expression of astrocytic glutamate transporters EAAT1 and EAAT2 in cultured astrocytes in order to shift the direction of synaptic plasticity to favor LTD. These results support the idea that Aß increased extracellular glutamate concentration by inhibiting astrocytes uptake, therefore increasing the time glutamate spends in the synaptic gap (Scimemi et al., 2013).

Interactions between Aß oligomers, the astrocytic gliotransmitters ATP, and the glutamate receptor mGluR5 contribute further to neuronal degeneration in AD. mGluR5 in astrocytes are a target for Aß oligomers to bind to and are associated with AD pathology. One group of researchers investigated the connections between Aß oligomers, mGluR5, ATP, and excitatory synapses and found that a co-accumulation of Aß oligomers and mGluR5 occur at excitatory synapses (Shrivastava et al., 2013). They further investigated how the association between the mGluR5 and ATP affected Aß oligomers interactions with astrocytes. The results of their study showed that Aß oligomers bind and cluster to astrocytes plasma membrane, mGluR5 activation and Ca2+ dependent astrocytic ATP-release occur in the presence of Aß oligomers, and an ATP-dependent slow-down of astrocyte and neuronal mGluR5 diffusion rate. Furthermore, the ATP expressed in astroglia can likely contribute to glutamate release by astrocytes causing the slow-down of neuronal mGluR5 which could possibly have an effect on synaptic transmission and Ca2+ excitability in AD. These findings imply that the rate and function of astrocyte gliotransmission is changed by Aß oligomers, thus causing changes in synaptic communication and transmission.

Studies have shown that the connexin 43 (Cx43) hemichannel mediates the Aß peptide induction of ATP from astrocytes (Kajiwara et al., 2018). Furthermore, Cx43 is upregulated in AD mouse models and AD human brains (Nagy et al., 1996). Additionally, Aß peptides have been shown to enhance ATP release in astrocytic cultures and hippocampal slices in AD (Haughey & Mattson, 2003). Exposure of astrocytes to Aß1-42 increased the amplitude of calcium waves mediated by increased ATP release. ATP release from astrocytes may further the pathogenesis of AD. ATP activation of calcium-permeable channels including P2X7 receptors or the activation of NMDAR receptors could reduce the survival of neurons in AD (Orellana et al., 2011). Dysregulated release of gliotransmitters like glutamate and ATP from reactive astrocytes in AD can induce neurotoxicity leading to memory impairments.

Conclusion

In AD, astrocytes play an essential role in the relationship between Aß accumulation and synaptic dysfunction. Astrocytes undergo reactive astrogliosis in AD as a response to various AD-associated pathological conditions including neuroinflammation and soluble Aß oligomers. Astrocytes contribute to Aß accumulation in AD in two main ways: one, they express the Aß precursor proteins BACE1 and APP and two, they decrease Aß deposition within astrocytes by engulfing Aß42 protofibrils but not degrading them. The feed-forward mechanism hypothesis proposes that proinflammatory cytokines including TNFα and IFNγ induce APP and BACE1 expression in astrocytes to create Aß42 oligomers, resulting in a vicious cycle of Aß production. Astrocytes release gliotransmitters including glutamate, ATP, and GABA as well as the glutamate receptor mGluR5 through gliotransmission causing astrocytes to regulate calcium levels, LTP induction, and synaptic plasticity. Astrocytic gliotransmission has been shown to increase intracellular astrocytic calcium levels, causing astrocytes to mediate synaptic transmission as seen in the tripartite synapse model (Figure 1). It can be concluded that Aß accumulation triggers dysfunctions in astrocyte gliotransmission, thus inducing synaptic transmission impairments and synaptic dysfunction in AD. The accumulation of soluble Aß oligomers has been shown to trigger higher rates of reactive astrogliosis, decrease activation of glutamate transporters, and slow mGluR5 and ATP activation in astrocytes all of which induce synaptic degeneration in AD. Additionally, the release of astrocytic TNFα via Aß3(pE)-42 and increases in calcium levels in astrocytes via Aß accumulation result in further synaptic loss in AD.

There have been various therapeutic treatments targeting astrocytes' ability to impair Aß aggregation and synaptic dysfunction in AD. Studies that use the AD mouse model APPswePS1dE9 (increased APP levels) and specifically target reactive astrocytes to reduce astrogliosis show improved cognitive abilities (Smit et al., 2021). These findings indicate that targeting reactive astrocytes should be included when creating novel therapies for AD. Additionally, studies that downregulated Aß-induced inflammasome in astrocytes and in 5xFAD mice resulted in the increasing of astrocytes phagocytosis of Aß in vivo (McManus et al., 2017) and in vitro (Couturier et al., 2016), thus decreasing Aß accumulation. This provides another potential therapeutic route for

AD that targets astrocytes phagocytic abilities. Although astrocytes have shown to have a strong connection in the link between Aß accumulation and synaptic dysfunction in AD, there are still various unknowns about mechanisms and pathways that connect them. Further research is needed to determine how exactly astrocytic Aß accumulation and astrocytic gliotransmission result in synaptic dysfunction and loss in AD. Further exploring the role of astrocytes in the relationship between Aß accumulation and synaptic dysfunction would allow for better understanding in astrocytes contribution to AD pathogenesis.

Acknowledgments

I would like to thank my summer program mentor Arij Daou for the valuable insight provided to me on this topic.

References

Acosta, C., Anderson, H. D., & Anderson, C. M. (2017). Astrocyte dysfunction in Alzheimer disease. *Journal of Neuroscience Research*, *95*(12), 2430–2447. https://doi.org/10.1002/jnr.24075

Agulhon, C., Fiacco, T. A., & McCarthy, K. D. (2010). Hippocampal short- and long-term plasticity are not modulated by astrocyte ca 2+ signaling. *Science*, *327*(5970), 1250–1254. https://doi.org/10.1126/science.1184821

Alifragis, P., & Marsh, J. (2018). Synaptic dysfunction in Alzheimer's disease: The effects of amyloid beta on synaptic vesicle dynamics as a novel target for therapeutic intervention. *Neural Regeneration Research*, *13*(4), 616. https://doi.org/10.4103/1673-5374.230276

Barnes, J. R., Mukherjee, B., Rogers, B. C., Nafar, F., Gosse, M., & Parsons, M. P. (2020). The relationship between glutamate dynamics and activity-dependent synaptic plasticity. *The Journal of Neuroscience*, *40*(14), 2793–2807. https://doi.org/10.1523/jneurosci.1655-19.2020

Blasko, I., Veerhuis, R., Stampfer-Kountchev, M., Saurwein-Teissl, M., Eikelenboom, P., & Grubeck-Loebenstein, B. (2000). Costimulatory effects of interferon-γ and interleukin-1β or tumor necrosis factor α on the synthesis of AB1-40 and AB1-42 by human astrocytes. *Neurobiology of Disease*, *7*(6), 682–689. https://doi.org/10.1006/nbdi.2000.0321

Bosson, A., Paumier, A., Boisseau, S., Jacquier-Sarlin, M., Buisson, A., & Albrieux, M. (2017). TRPA1 channels promote astrocytic ca2+ hyperactivity and synaptic dysfunction mediated by oligomeric forms of amyloid-β peptide. *Molecular Neurodegeneration*, *12*(1). https://doi.org/10.1186/s13024-017-0194-8

Bowser, D. N., & Khakh, B. S. (2007). Vesicular ATP is the predominant cause of intercellular calcium waves in astrocytes. *Journal of General Physiology*, *129*(6), 485–491. https://doi.org/10.1085/jgp.200709780

Chen, G.-fang, Xu, T.-hai, Yan, Y., Zhou, Y.-ren, Jiang, Y., Melcher, K., & Xu, H. E. (2017). Amyloid beta: Structure, biology and structure-based therapeutic development. *Acta Pharmacologica Sinica*, *38*(9), 1205–1235. https://doi.org/10.1038/aps.2017.28

Chen, Y., Fu, A. K. Y., & Ip, N. Y. (2019). Synaptic dysfunction in Alzheimer's disease: Mechanisms and therapeutic strategies. *Pharmacology & Therapeutics*, *195*, 186–198. https://doi.org/10.1016/j.pharmthera.2018.11.006

Cho, H. J., Kim, S.-K., Jin, S. M., Hwang, E.-M., Kim, Y. S., Huh, K., & Mook-Jung, I. (2007). IFN-γ-induced BACE1 expression is mediated by activation of JAK2 and ERK1/2 signaling pathways and direct binding of STAT1 to BACE1 promoter in astrocytes. *Glia*, *55*(3), 253–262. https://doi.org/10.1002/glia.20451

Chun, H., & Lee, C. J. (2018). Reactive astrocytes in Alzheimer's disease: A double-edged sword. *Neuroscience Research*, *126*, 44–52. https://doi.org/10.1016/j.neures.2017.11.012

Chung, W.-S., Allen, N. J., & Eroglu, C. (2015). Astrocytes control synapse formation, function, and elimination. *Cold Spring Harbor Perspectives in Biology*, *7*(9). https://doi.org/10.1101/cshperspect.a020370
Cirrito, J. R., Yamada, K. A., Finn, M. B., Sloviter, R. S., Bales, K. R., May, P. C., Schoepp, D. D., Paul, S. M., Mennerick, S., & Holtzman, D. M. (2005). Synaptic activity regulates interstitial fluid amyloid-β levels in vivo. *Neuron*, *48*(6), 913–922. https://doi.org/10.1016/j.neuron.2005.10.028
Cole, S. L., & Vassar, R. (2007). The Alzheimer's disease beta-secretase enzyme, BACE1. *Molecular Neurodegeneration*, *2*(1), 22. https://doi.org/10.1186/1750-1326-2-22
Couturier, J., Stancu, I.-C., Schakman, O., Pierrot, N., Huaux, F., Kienlen-Campard, P., Dewachter, I., & Octave, J.-N. (2016). Activation of phagocytic activity in astrocytes by reduced expression of the inflammasome component ASC and its implication in a mouse model of Alzheimer disease. *Journal of Neuroinflammation*, *13*(1). https://doi.org/10.1186/s12974-016-0477-y
Das, S., Li, Z., Noori, A., Hyman, B. T., & Serrano-Pozo, A. (2020). Meta-analysis of mouse transcriptomic studies supports a context-dependent astrocyte reaction in acute CNS injury versus neurodegeneration. *Journal of Neuroinflammation*, *17*(1). https://doi.org/10.1186/s12974-020-01898-y
De Mena, L., Smith, M. A., Martin, J., Dunton, K. L., Ceballos-Diaz, C., Jansen-West, K. R., Cruz, P. E., Dillon, K. D., Rincon-Limas, D. E., Golde, T. E., Moore, B. D., & Levites, Y. (2020). ASS40 displays amyloidogenic properties in the non-transgenic mouse brain but does not exacerbate ASS42 toxicity in drosophila. *Alzheimer's Research & Therapy*, *12*(1). https://doi.org/10.1186/s13195-020-00698-z
Dorostkar, M. M., Zou, C., Blazquez-Llorca, L., & Herms, J. (2015). Analyzing dendritic spine pathology in Alzheimer’s disease: Problems and opportunities. *Acta Neuropathologica*, *130*(1), 1-19. https://doi.org/10.1007/s00401-015-1449-5
El-Amouri, S. S., Zhu, H., Yu, J., Marr, R., Verma, I. M., & Kindy, M. S. (2008). NEPRILYSIN: An enzyme candidate to slow the progression of Alzheimer's disease. *The American Journal of Pathology*, *172*(5), 1342–1354. https://doi.org/10.2353/ajpath.2008.070620
Farrant, M., & Nusser, Z. (2005). Variations on an inhibitory theme: Phasic and tonic activation of Gabaa receptors. *Nature Reviews Neuroscience*, *6*(3), 215–229. https://doi.org/10.1038/nrn1625
Fiacco, T. A., Agulhon, C., Taves, S. R., Petravicz, J., Casper, K. B., Dong, X., Chen, J., & McCarthy, K. D. (2007). Selective stimulation of astrocyte calcium in situ does not affect neuronal excitatory synaptic activity. *Neuron*, *54*(4), 611–626. https://doi.org/10.1016/j.neuron.2007.04.032
Fiala, M., & Veerhuis, R. (2010). Biomarkers of inflammation and amyloid-β phagocytosis in patients at risk of Alzheimer disease. *Experimental Gerontology*, *45*(1), 57–63. https://doi.org/10.1016/j.exger.2009.08.003
Grochowska, K. M., Yuanxiang, P. A., Bär, J., Raman, R., Brugal, G., Sahu, G., Schweizer, M., Bikbaev, A., Schilling, S., Demuth, H. U., & Kreutz, M. R. (2017). Posttranslational modification impact on the mechanism by which amyloid-β induces synaptic dysfunction. *EMBO Reports*, *18*(6), 962–981. https://doi.org/10.15252/embr.201643519
Guthrie, P. B., Knappenberger, J., Segal, M., Bennett, M. V., Charles, A. C., & Kater, S. B. (1999). ATP released from astrocytes mediates glial calcium waves. *The Journal of Neuroscience*, *19*(2), 520–528. https://doi.org/10.1523/jneurosci.19-02-00520.1999
Hamilton, N. B., & Attwell, D. (2010). Do astrocytes really exocytose neurotransmitters? *Nature Reviews Neuroscience*, *11*(4), 227–238. https://doi.org/10.1038/nrn2803
Han, K.-S., Woo, J., Park, H., Yoon, B.-J., Choi, S., & Lee, C. J. (2013). Channel-mediated astrocytic glutamate release via bestrophin-1 targets synaptic nmdars. *Molecular Brain*, *6*(1). https://doi.org/10.1186/1756-6606-6-4
Harada, K., Kamiya, T., & Tsuboi, T. (2016). Gliotransmitter release from astrocytes: Functional, developmental, and pathological implications in the brain. *Frontiers in Neuroscience*, *9*. https://doi.org/10.3389/fnins.2015.00499

Haughey, N. J., & Mattson, M. P. (2003). Alzheimer's amyloid β-peptide enhances ATP/gap junction-mediated calcium-wave propagation in astrocytes. *NeuroMolecular Medicine*, *3*(3), 173–180. https://doi.org/10.1385/nmm:3:3:173

Henneberger, C., Papouin, T., Oliet, S. H., & Rusakov, D. A. (2010). Long-term potentiation depends on release of D-serine from astrocytes. *Nature*, *463*(7278), 232–236. https://doi.org/10.1038/nature08673

Holcomb, L. A., Gordon, M. N., Jantzen, P., Hsiao, K., Duff, K., & Morgan, D. (1999). Behavioral Changes in Transgenic Mice Expressing Both Amyloid Precursor Protein and Presenilin-1 Mutations: Lack of Association with Amyloid Deposits. *Behavior Genetics*, *29*(3), 177–185. https://doi.org/10.1023/a:1021691918517

Hong, H. S., Hwang, E. M., Sim, H. J., Cho, H.-J., Boo, J. H., Oh, S. S., Kim, S. U., & Mook-Jung, I. (2003). Interferon γ stimulates β-secretase expression and sappβ production in astrocytes. *Biochemical and Biophysical Research Communications*, *307*(4), 922–927. https://doi.org/10.1016/s0006-291x(03)01270-1

Huang, S., Tong, H., Lei, M., Zhou, M., Guo, W., Li, G., Tang, X., Li, Z., Mo, M., Zhang, X., Chen, X., Cen, L., Wei, L., Xiao, Y., Li, K., Huang, Q., Yang, X., Liu, W., Zhang, L., … Xu, P. (2018). Astrocytic glutamatergic transporters are involved in AB-induced synaptic dysfunction. *Brain Research*, *1678*, 129–137. https://doi.org/10.1016/j.brainres.2017.10.011

Jahn, R., & Fasshauer, D. (2012). Molecular machines governing exocytosis of synaptic vesicles. *Nature*, *490*(7419), 201–207. https://doi.org/10.1038/nature11320

Jiang, Q., Lee, C. Y. D., Mandrekar, S., Wilkinson, B., Cramer, P., Zelcer, N., Mann, K., Lamb, B., Willson, T. M., Collins, J. L., Richardson, J. C., Smith, J. D., Comery, T. A., Riddell, D., Holtzman, D. M., Tontonoz, P., & Landreth, G. E. (2008). ApoE promotes the proteolytic degradation of AB. *Neuron*, *58*(5), 681–693. https://doi.org/10.1016/j.neuron.2008.04.010

Jo, S., Yarishkin, O., Hwang, Y. J., Chun, Y. E., Park, M., Woo, D. H., Bae, J. Y., Kim, T., Lee, J., Chun, H., Park, H. J., Lee, D. Y., Hong, J., Kim, H. Y., Oh, S.-J., Park, S. J., Lee, H., Yoon, B.-E., Kim, Y. S., … Lee, C. J. (2014). GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. *Nature Medicine*, *20*(8), 886–896. https://doi.org/10.1038/nm.3639

Jones, R. S., Minogue, A. M., Connor, T. J., & Lynch, M. A. (2012). Amyloid-β-induced astrocytic phagocytosis is mediated by CD36, CD47 and rage. *Journal of Neuroimmune Pharmacology*, *8*(1), 301–311. https://doi.org/10.1007/s11481-012-9427-3

Jourdain, P., Bergersen, L. H., Bhaukaurally, K., Bezzi, P., Santello, M., Domercq, M., Matute, C., Tonello, F., Gundersen, V., & Volterra, A. (2007). Glutamate exocytosis from astrocytes controls synaptic strength. *Nature Neuroscience*, *10*(3), 331–339. https://doi.org/10.1038/nn1849

Jung, E. S., An, K., Hong, H. S., Kim, J. H., & Mook-Jung, I. (2012). Astrocyte-originated ATP protects Aβ(1-42)-induced impairment of synaptic plasticity. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *32*(9), 3081–3087. https://doi.org/10.1523/JNEUROSCI.6357-11.2012

Kajiwara, Y., Wang, E., Wang, M., Sin, W. C., Brennand, K. J., Schadt, E., Naus, C. C., Buxbaum, J., & Zhang, B. (2018). Gja1 (Connexin43) is a key regulator of Alzheimer's disease pathogenesis. *Acta Neuropathologica Communications*, *6*(1). https://doi.org/10.1186/s40478-018-0642-x

Kamenetz, F., Tomita, T., Hsieh, H., Seabrook, G., Borchelt, D., Iwatsubo, T., Sisodia, S., & Malinow, R. (2003). App Processing and synaptic function. *Neuron*, *37*(6), 925–937. https://doi.org/10.1016/s0896-6273(03)00124-7

Kervern, M., Angeli, A., Nicole, O., Léveillé, F., Parent, B., Villette, V., Buisson, A., & Dutar, P. (2012). Selective impairment of some forms of synaptic plasticity by oligomeric amyloid-β peptide in the mouse hippocampus: Implication of extrasynaptic NMDA receptors. *Journal of Alzheimer's Disease*, *32*(1), 183–196. https://doi.org/10.3233/jad-2012-120394

Kim, Y., Park, J., & Choi, Y. K. (2019). The role of astrocytes in the central nervous system focused on BK channel and heme oxygenase metabolites: A Review. *Antioxidants*, *8*(5), 121. https://doi.org/10.3390/antiox8050121

Koffie, R. M., Meyer-Luehmann, M., Hashimoto, T., Adams, K. W., Mielke, M. L., Garcia-Alloza, M., Micheva, K. D., Smith, S. J., Kim, M. L., Lee, V. M., Hyman, B. T., & Spires-Jones, T. L. (2009). Oligomeric amyloid β associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. *Proceedings of the National Academy of Sciences*, *106*(10), 4012–4017. https://doi.org/10.1073/pnas.0811698106

Kofuji, P., & Araque, A. (2021). G-protein-coupled receptors in astrocyte–neuron communication. *Neuroscience*, *456*, 71–84. https://doi.org/10.1016/j.neuroscience.2020.03.025

Konishi, H., Okamoto, T., Hara, Y., Komine, O., Tamada, H., Maeda, M., Osako, F., Kobayashi, M., Nishiyama, A., Kataoka, Y., Takai, T., Udagawa, N., Jung, S., Ozato, K., Tamura, T., Tsuda, M., Yamanaka, K., Ogi, T., Sato, K., & Kiyama, H. (2020). Astrocytic phagocytosis is a compensatory mechanism for microglial dysfunction. *The EMBO Journal*, *39*(22). https://doi.org/10.15252/embj.2020104464

Kullmann, D. M., & Lamsa, K. P. (2007). Long-term synaptic plasticity in hippocampal interneurons. *Nature Reviews Neuroscience*, *8*(9), 687–699. https://doi.org/10.1038/nrn2207

Lee, S., Yoon, B.-E., Berglund, K., Oh, S.-J., Park, H., Shin, H.-S., Augustine, G. J., & Lee, C. J. (2010). Channel-mediated tonic GABA release from glia. *Science*, *330*(6005), 790–796. https://doi.org/10.1126/science.1184334

Li, S., & Selkoe, D. J. (2020). A mechanistic hypothesis for the impairment of synaptic plasticity by soluble AB oligomers from alzheimer's brain. *Journal of Neurochemistry*, *154*(6), 583–597. https://doi.org/10.1111/jnc.15007

Li, S., Hong, S., Shepardson, N. E., Walsh, D. M., Shankar, G. M., & Selkoe, D. (2009). Soluble oligomers of amyloid β protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. *Neuron*, *62*(6), 788–801. https://doi.org/10.1016/j.neuron.2009.05.012

Liang, J., Kulasiri, D., & Samarasinghe, S. (2017). Computational investigation of amyloid-β-induced location- and subunit-specific disturbances of NMDAR at hippocampal dendritic spine in Alzheimer's disease. *PLOS ONE*, *12*(8). https://doi.org/10.1371/journal.pone.0182743

Liu, L., Wong, T. P., Pozza, M. F., Lingenhoehl, K., Wang, Y., Sheng, M., Auberson, Y. P., & Wang, Y. T. (2004). Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. *Science*, *304*(5673), 1021–1024. https://doi.org/10.1126/science.1096615

Liu, Q.-song, Xu, Q., Arcuino, G., Kang, J., & Nedergaard, M. (2004). Astrocyte-mediated activation of neuronal kainate receptors. *Proceedings of the National Academy of Sciences*, *101*(9), 3172–3177. https://doi.org/10.1073/pnas.0306731101

Lööv, C., Mitchell, C. H., Simonsson, M., & Erlandsson, A. (2015). Slow degradation in phagocytic astrocytes can be enhanced by lysosomal acidification. *Glia*, *63*(11), 1997–2009. https://doi.org/10.1002/glia.22873

Mahmoud, S., Gharagozloo, M., Simard, C., & Gris, D. (2019). Astrocytes maintain glutamate homeostasis in the CNS by controlling the balance between glutamate uptake and release. *Cells*, *8*(2), 184. https://doi.org/10.3390/cells8020184

Martins, R. N., Taddei, K., Kendall, C., Evin, G., Bates, K. A., & Harvey, A. R. (2001). Altered expression of apolipoprotein E, amyloid precursor protein and presenilin-1 is associated with chronic reactive gliosis in rat cortical tissue. *Neuroscience*, *106*(3), 557–569. https://doi.org/10.1016/s0306-4522(01)00289-5

Martín, R., Bajo-Grañeras, R., Moratalla, R., Perea, G., & Araque, A. (2015). Circuit-specific signaling in astrocyte-neuron networks in basal ganglia pathways. *Science*, *349*(6249), 730–734. https://doi.org/10.1126/science.aaa7945

Masters, C. L., Bateman, R., Blennow, K., Rowe, C. C., Sperling, R. A., & Cummings, J. L. (2015). Alzheimer's disease. *Nature Reviews Disease Primers*, *1*(1). https://doi.org/10.1038/nrdp.2015.56

Matos, M., Augusto, E., Oliveira, C. R., & Agostinho, P. (2008). Amyloid-beta peptide decreases glutamate uptake in cultured astrocytes: Involvement of oxidative stress and mitogen-activated protein kinase cascades. *Neuroscience*, *156*(4), 898–910. https://doi.org/10.1016/j.neuroscience.2008.08.022

McManus, R. M., Finucane, O. M., Wilk, M. M., Mills, K. H., & Lynch, M. A. (2017). FTY720 attenuates infection-induced enhancement of AB accumulation in APP/PS1 mice by modulating astrocytic activation. *Journal of Neuroimmune Pharmacology*, *12*(4), 670–681. https://doi.org/10.1007/s11481-017-9753-6

Medeiros, R., Prediger, R. D., Passos, G. F., Pandolfo, P., Duarte, F. S., Franco, J. L., Dafre, A. L., Di Giunta, G., Figueiredo, C. P., Takahashi, R. N., Campos, M. M., & Calixto, J. B. (2007). Connecting TNF- signaling pathways to inos expression in a mouse model of Alzheimer's disease: Relevance for the behavioral and synaptic deficits induced by amyloid protein. *Journal of Neuroscience*, *27*(20), 5394–5404. https://doi.org/10.1523/jneurosci.5047-06.2007

Min, R., & Nevian, T. (2012). Astrocyte signaling controls spike timing–dependent depression at neocortical synapses. *Nature Neuroscience*, *15*(5), 746–753. https://doi.org/10.1038/nn.3075

Morris, G. P., Clark, I. A., & Vissel, B. (2014). Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. *Acta Neuropathologica Communications*, *2*(1). https://doi.org/10.1186/s40478-014-0135-5

Mucke, L., & Selkoe, D. J. (2012). Neurotoxicity of amyloid -protein: Synaptic and network dysfunction. *Cold Spring Harbor Perspectives in Medicine*, *2*(7). https://doi.org/10.1101/cshperspect.a006338

Mucke, L., & Selkoe, D. J. (2012). Neurotoxicity of amyloid -protein: Synaptic and network dysfunction. *Cold Spring Harbor Perspectives in Medicine*, *2*(7). https://doi.org/10.1101/cshperspect.a006338

Nagy, J. I., Li, W., Hertzberg, E. L., & Marotta, C. A. (1996). Elevated connexin43 immunoreactivity at sites of amyloid plaques in alzheimer's disease. *Brain Research*, *717*(1-2), 173–178. https://doi.org/10.1016/0006-8993(95)01526-4

Nanclares, C., Baraibar, A. M., Araque, A., & Kofuji, P. (2021). Dysregulation of astrocyte–neuronal communication in alzheimer’s disease. *International Journal of Molecular Sciences*, *22*(15), 7887. https://doi.org/10.3390/ijms22157887

Nielsen, H. M., Mulder, S. D., Beliën, J. A., Musters, R. J., Eikelenboom, P., & Veerhuis, R. (2010). Astrocytic AB1-42 uptake is determined by AB-aggregation state and the presence of amyloid-associated proteins. *Glia*, *58*(10), 1235–1246. https://doi.org/10.1002/glia.21004

Orellana, J. A., Froger, N., Ezan, P., Jiang, J. X., Bennett, M. V., Naus, C. C., Giaume, C., & Sáez, J. C. (2011). ATP and glutamate released via astroglial connexin 43 hemichannels mediate neuronal death through activation of Pannexin 1 hemichannels. *Journal of Neurochemistry*, *118*(5), 826–840. https://doi.org/10.1111/j.1471-4159.2011.07210.x

Panatier, A., & Robitaille, R. (2016). Astrocytic mGluR5 and the tripartite synapse. *Neuroscience*, *323*, 29–34. https://doi.org/10.1016/j.neuroscience.2015.03.063

Panatier, A., Vallée, J., Haber, M., Murai, K. K., Lacaille, J.-C., & Robitaille, R. (2011). Astrocytes are endogenous regulators of basal transmission at central synapses. *Cell*, *146*(5), 785–798. https://doi.org/10.1016/j.cell.2011.07.022

Pangršič, T., Potokar, M., Stenovec, M., Kreft, M., Fabbretti, E., Nistri, A., Pryazhnikov, E., Khiroug, L., Giniatullin, R., & Zorec, R. (2007). Exocytotic release of ATP from cultured astrocytes. *Journal of Biological Chemistry*, *282*(39), 28749–28758. https://doi.org/10.1074/jbc.m700290200

Parpura , V., Fang , Y., Basarsky , T., Jahn , R., & Haydon , P. G. (1995). Expression of synaptobrevin II, Cellubrevin and syntaxin but not snap-25 in cultured astrocytes. *FEBS Letters*, *377*(3), 489–492. https://doi.org/10.1016/0014-5793(95)01401-2

Pham, C., Hérault, K., Oheim, M., Maldera, S., Vialou, V., Cauli, B., & Li, D. (2021). Astrocytes respond to a neurotoxic AB fragment with state-dependent ca2+ alteration and multiphasic transmitter release. *Acta Neuropathologica Communications*, *9*(1). https://doi.org/10.1186/s40478-021-01146-1
Poskanzer, K. E., & Yuste, R. (2016). Astrocytes regulate cortical state switching in vivo. *Proceedings of the National Academy of Sciences*, *113*(19). https://doi.org/10.1073/pnas.1520759113
Puzzo, D., Privitera, L., Leznik, E., Fa, M., Staniszewski, A., Palmeri, A., & Arancio, O. (2008). Picomolar amyloid- positively modulates synaptic plasticity and memory in Hippocampus. *Journal of Neuroscience*, *28*(53), 14537–14545. https://doi.org/10.1523/jneurosci.2692-08.2008
Role of microglia and astrocytes in Alzheimer's disease. (2004). *The Role of Glia in Neurotoxicity*, 319–332. https://doi.org/10.1201/9781420039740-23
Rossner, S., Lange-Dohna, C., Zeitschel, U., & Perez-Polo, J. R. (2005). Alzheimer's disease beta-secretase BACE1 is not a neuron-specific enzyme. *Journal of Neurochemistry*, *92*(2), 226–234. https://doi.org/10.1111/j.1471-4159.2004.02857.x
Saido, T. C., Iwatsubo, T., Mann, D. M. A., Shimada, H., Ihara, Y., & Kawashima, S. (1995). Dominant and differential deposition of distinct β-amyloid peptide species, ABN3(PE), in senile plaques. *Neuron*, *14*(2), 457–466. https://doi.org/10.1016/0896-6273(95)90301-1
Schiavo, G. G., Benfenati, F., Poulain, B., Rossetto, O., de Laureto, P. P., DasGupta, B. R., & Montecucco, C. (1992). Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of Synaptobrevin. *Nature*, *359*(6398), 832–835. https://doi.org/10.1038/359832a0
Scimemi, A., Meabon, J. S., Woltjer, R. L., Sullivan, J. M., Diamond, J. S., & Cook, D. G. (2013). Amyloid-1-42 slows clearance of synaptically released glutamate by mislocalizing astrocytic GLT-1. *Journal of Neuroscience*, *33*(12), 5312–5318. https://doi.org/10.1523/jneurosci.5274-12.2013
Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 Years. *EMBO Molecular Medicine*, *8*(6), 595–608. https://doi.org/10.15252/emmm.201606210
Shrivastava, A. N., Kowalewski, J. M., Renner, M., Bousset, L., Koulakoff, A., Melki, R., Giaume, C., & Triller, A. (2013). B-amyloid and ATP-induced diffusional trapping of astrocyte and neuronal metabotropic glutamate type-5 receptors. *Glia*, *61*(10), 1673–1686. https://doi.org/10.1002/glia.22548
Smit, T., Deshayes, N. A., Borchelt, D. R., Kamphuis, W., Middeldorp, J., & Hol, E. M. (2021). Reactive astrocytes as treatment targets in Alzheimer's disease—systematic review of studies using the appswe ps1de9 mouse model. *Glia*, *69*(8), 1852–1881. https://doi.org/10.1002/glia.23981
Smith, J. A., Das, A., Ray, S. K., & Banik, N. L. (2012). Role of pro-inflammatory cytokines released from microglia in Neurodegenerative Diseases. *Brain Research Bulletin*, *87*(1), 10–20. https://doi.org/10.1016/j.brainresbull.2011.10.004
Sondag, C. M., Dhawan, G., & Combs, C. K. (2009). Beta amyloid oligomers and fibrils stimulate differential activation of primary microglia. *Journal of Neuroinflammation*, *6*(1). https://doi.org/10.1186/1742-2094-6-1
Steinert, J. R., Chernova, T., & Forsythe, I. D. (2010). Nitric oxide signaling in brain function, dysfunction, and dementia. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, *16*(4), 435–452. https://doi.org/10.1177/1073858410366481
Sturcher-Pierrat , C., & Staufenbiel, M. (2006). Pathogenic mechanisms of alzheimer's disease analyzed in the app23 transgenic mouse model. *Annals of the New York Academy of Sciences*, *920*(1), 134–139. https://doi.org/10.1111/j.1749-6632.2000.tb06915.x
Sun, W., McConnell, E., Pare, J.-F., Xu, Q., Chen, M., Peng, W., Lovatt, D., Han, X., Smith, Y., & Nedergaard, M. (2013). Glutamate-dependent neuroglial calcium signaling differs between young and adult brains. *Science*, *339*(6116), 197–200. https://doi.org/10.1126/science.1226740
Söllvander, S., Nikitidou, E., Brolin, R., Söderberg, L., Sehlin, D., Lannfelt, L., & Erlandsson, A. (2016). Accumulation of amyloid-β by astrocytes results in enlarged endosomes and microvesicle-induced apoptosis of neurons. *Molecular Neurodegeneration*, *11*(1). https://doi.org/10.1186/s13024-016-0098-z

Südhof, T. C. (2018). Towards an understanding of synapse formation. *Neuron*, *100*(2), 276–293. https://doi.org/10.1016/j.neuron.2018.09.040
Valtcheva, S., & Venance, L. (2019). Control of long-term plasticity by glutamate transporters. *Frontiers in Synaptic Neuroscience*, *11*. https://doi.org/10.3389/fnsyn.2019.00010
Wei, W., Nguyen, L. N., Kessels, H. W., Hagiwara, H., Sisodia, S., & Malinow, R. (2009). Amyloid beta from axons and dendrites reduces local spine number and plasticity. *Nature Neuroscience*, *13*(2), 190–196. https://doi.org/10.1038/nn.2476
Xiao, Q., Yan, P., Ma, X., Liu, H., Perez, R., Zhu, A., Gonzales, E., Burchett, J. M., Schuler, D. R., Cirrito, J. R., Diwan, A., & Lee, J.-M. (2014). Enhancing astrocytic lysosome biogenesis facilitates a clearance and attenuates amyloid plaque pathogenesis. *Journal of Neuroscience*, *34*(29), 9607–9620. https://doi.org/10.1523/jneurosci.3788-13.2014
Zhao, J., Fu, Y., Yasvoina, M., Shao, P., Hitt, B., O'Connor, T., Logan, S., Maus, E., Citron, M., Berry, R., Binder, L., & Vassar, R. (2007). -site amyloid precursor protein cleaving enzyme 1 levels become elevated in neurons around amyloid plaques: Implications for Alzheimer's disease pathogenesis. *Journal of Neuroscience*, *27*(14), 3639–3649. https://doi.org/10.1523/jneurosci.4396-06.2007
Zhao, J., O'Connor, T., & Vassar, R. (2011). The contribution of activated astrocytes to AB production: Implications for alzheimer's disease pathogenesis. *Journal of Neuroinflammation*, *8*(1). https://doi.org/10.1186/1742-2094-8-150