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Amyloid Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's disease Neurons

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Abstract

Amyloid Beta (A β) and hyperphosphorylated tau are hallmark lesions of Alzheimer disease (AD). However, the loss of synapses and dysfunctions of neurotransmission are more directly tied to disease severity. The role of these lesions in the pathoetiological progression of the disease remains contested. Biochemical, cellular, molecular and pathological studies provided several lines of evidence and improved our understanding of how amyloid beta and hyperphosphorylated tau accumulation may directly harm synapses and alter neurotransmission. In-vitro evidence suggests that amyloid beta and hyperphosphorylated tau have both direct and indirect cytotoxic effects that affect neurotransmission, axonal transport, signaling cascades, organelle function, and immune response in ways that lead to synaptic loss and dysfunctions in neurotransmitter release. Observations in preclinical models and autopsy studies support these findings, suggesting that while the pathoetiology of positive lesions remains elusive, their removal may reduce disease severity and progression. The purpose of this article is to highlight the need for further investigation of the role of tau in disease progression and its interactions with A β and neurotransmitters alike.

Keywords

Amyloid; tau; synapse; neurotransmitters

Introduction

Alzheimer disease (AD) is a progressive neurodegenerative disorder marked by the accumulation of beta-amyloid (A β) plaques and hyperphosphorylated tau tangles. Although these positive lesions receive a great deal of attention, the loss of neuronal synapses is the

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best correlate of cognitive decline in patients with AD [1–7]. Deterioration of synapses begins at the level of dendritic spines [8–10]. As such, a great deal of focus has been placed on attempts to understand the mechanisms underlying the structural and functional plasticity of dendritic spines and synapses in AD [11].

Alterations of neurons, synapses, and neurotransmission are common observations in AD and are therefore hypothesized to play a major role in its progression [11–12]. From these studies come the observation that phosphorylated tau has been mislocalized to the postsynaptic compartment [11]. It is important to note, however, that synaptic and dendritic spine pathology is common amongst several neurodegenerative diseases and may represent the same pathogenic mechanisms across them all [11]. In the following review, we will focus on findings that are primarily unique to AD and will highlight significant areas of overlap with other neurodegenerative diseases that may be known.

Neurotransmitter abnormalities in Alzheimer's disease

Acetylcholine—In-depth coverage of neurotransmitter changes in AD has previously been reported [13–14]. Death of cholinergic neurons was amongst the first findings in AD pathology. Given their known physiological roles, combined with the symptomology of AD, loss of cholinergic neurons was originally postulated as the cause of the disease and was dubbed “the cholinergic hypothesis” [15]. Evidence for this hypothesis came from several sources. Neuronal loss in areas with high cholinergic neuron populations, such as the nucleus Basalis of Meynert (nBM), the hippocampus and cortical areas, is well documented and consistent [16–20]. Further cholinergic system dysfunctions include a decrease in acetylcholine (ACh) synthesis, decreased choline acetyltransferase (ChAT) activity, reduced choline uptake, [21] and altered levels of acetylcholine receptors (AChRs) [22]. Additionally, severe deficits of presynaptic cholinergic markers had been noted in the cerebral cortex of patients with early-onset AD since the late 1970's [16, 23–25]. Even in the earliest stages of AD as well as its common precursor mild cognitive impairment (MCI) decreased trophic responses in nBM neurons are consistently observed [26]. To date, cholinergic deficits are still the strongest neurochemical correlate of dementia severity in AD [1, 27–30].

However, recent studies no longer support that cholinergic depletion is solely responsible for causing AD. PET-labeled acetylcholinesterase (AChE) ligands show only mild loss of activity in patients with MCI and early stage AD [20, 31] and autopsies show no change in ChAT activity in a number of brain regions studied in these groups [20, 32] nor in the number of ChAT-positive cells in MCI patients [33]. Further support comes from the lack of efficacy of acetylcholinesterase inhibitors (AChEIs) in clinical trials [34, 35] and the finding that cholinergic depletion does not result in severe memory deficits in rats [30, 36]. Finally, basal forebrain cholinergic cell degeneration is common in many neurodegenerative disorders, including Parkinson's disease [37–39], Down-syndrome (DS), progressive supranuclear palsy, Creutzfeldt-Jakob disease [40], Korsakoff's syndrome [41–43], and traumatic brain injury [44–45]. This led Craig, Hong, and McDonald to propose that although ACh depletion is not the cause of AD, it leads to a reduction in the ability of the brain to compensate for secondary insults. In their model, this depletion would reduce the

ability of the brain to compensate for the accumulation of risk factors that occur with increasing frequency during the aging process [46]. Support for this model can be found in literature on rodents, nonhuman, and human primate models [46]. Detailed information about cholinergic dysfunctions in AD can be found elsewhere [47].

NMDA—Similar to the cholinergic deficits observed in AD, several lines of evidence suggest a role for the presynaptic N-methyl-D-aspartate receptor (NMDAR) localization in reshaping synaptic transmission by regulating presynaptic glutamate release [48]. A combination of increased presynaptic glutamate release and decreased reuptake is believed to result in an excess of extracellular glutamate, which in turn leads to a tonic activation of these receptors [49]. This view is further supported by a study by Bell et al., which showed that MCI subjects displayed a paradoxical elevation in glutamatergic presynaptic bouton density, similar to that observed in the cholinergic system, which then depletes and drops with disease progression [50]. These findings further demonstrated that dystrophic neurite generation and reduced presynaptic bouton densities detrimentally influenced neurotransmission and cognitive function in later stages of AD [50]. More information on NMDA-based synaptic dysfunction is given in a review article by Mota and colleagues [51].

GABA—Disruption of neurotransmission in AD is not limited to excitatory pathways. Several studies indicate dysfunctions in GABAergic signaling, including results from autopsy, neuroimaging, and CNS GABA marker studies [52]. Normally, GABA is released by neurons in response to glutamate excitotoxicity [53–54] and while chronic growth factor deprivation causes GABA transmission to change from an inhibitory to an excitatory stimulus [55], the significance of this transition is not entirely clear [56].

The A class receptors (GABAARs) are crucially involved in synaptic plasticity and help to ensure that NMDARs are activated mainly during high-frequency synaptic transmission [57]. Additionally, GABAAR agonists protect neurons in culture against the neurotoxicity of A β and of various glutamate receptor agonists [58–60]. Because of this, stimulating GABAergic transmission has been attempted to treat behavioral and psychological dysfunctions in AD [52, 61], but these efforts are limited due to issues of tolerance after long-term use and side effects [52; 62]. Detailed information on GABA's role in AD was given by Paula-Lima and colleagues [63].

Serotonin—Similar to GABA, loss of serotonergic activity also appears to correlate with behavioral and psychological dysfunctions, most notably the presence of neuropsychiatric symptoms (NPS) [64], which, combined with several recent reports that suggest selective and early involvement of the dorsal raphe nucleus (DRN), in the pathogenesis of AD, led Simic et al. [64] to propose a novel pathogenic scheme of AD progression. The role of serotonin receptors in AD gained prominence when observation suggested the density of 5-HT positive neurons significantly decline in AD brains [65] and that areas of the brain concerned with learning and memory show high concentrations of these receptors [66–67]. Further support came from imaging studies [68–71] and autopsies [72–78] that showed reduced serotonin levels, receptors, reuptake sites, and metabolites in the frontal and temporal areas [79]. However, the interaction of serotonin in the nervous system is complicated because 5-HT receptors co-localize on glutamatergic, cholinergic and

GABAergic neurons, suggesting the serotonergic system may regulate a variety of other neurotransmitter systems [67]. Detailed information on alteration to serotonin in AD was given in articles by Rodriguez and colleagues [80].

Dopamine—Unlike serotonin, dopamine's involvement in AD is substantially more limited, but is still informative as it also relates to NPS. While autopsy studies show that the nigrostriatal system remains relatively intact [81], the mesolimbic system is selectively affected [82]. Neuroimaging studies confirm relative sparing of striatal dopamine metabolism and transporters. Additionally, several studies have reported that dysfunction within corticostriatal dopaminergic circuits is associated with NPS in AD. Based on the available data, greater overall behavioral disturbance is associated with lower striatal D2 receptors while higher striatal D2 receptors is associated with delusions and wandering behavior and lower dopamine transporters are associated with apathy [79].

Norepinephrine—Indeed, nearly every major neurotransmitter system is affected to some degree in AD. Perhaps the best example of a system that has been overlooked is the noradrenergic system. Although much of the histopathology of AD was documented since Alzheimer's first case in 1906, it was not until over 100 years later that the Braak and Del Tredici [83] determined that the locus coeruleus (LC), not the entorhinal hippocampal cortex, is the first area of the brain to exhibit AD pathology. This area is the primary source of norepinephrine (NE), a neurotransmitter that has been implicated in systems of learning, attention, and wakefulness [84]. Additionally, recent data from basic research in animal models of AD indicate that loss of NE incites a neurotoxic proinflammatory condition, reduces A β clearance, and negatively impacts cognition [85]. Remarkably, restoration of NE reverses these effects and slows neurodegeneration in animal models, raising the possibility that treatments which increase NE transmission may have the potential to delay or reverse AD-related pathology [85].

Amyloid Beta

Physiological roles of Amyloid Precursor Protein

Now that we have some understanding of the negative lesions of AD (i.e. synaptic loss and dysfunctions of neurotransmission), we will turn our attention to the positive lesions, A β and hyperphosphorylated tau. Understanding the physiological roles of their precursor proteins has the potential to lead us to a greater understanding of how their aberrant products may influence the pathology of AD. Full-length amyloid precursor protein (APP) has been shown to promote synaptic activity, synapse formation, and dendritic spine formation, which suggests APP has a pivotal role in learning and memory [86]. This leads to some debate as to whether the deficiency of the functional protein or accumulation of the abnormal form is more important for the progression of the disease. However, a great deal of evidence exists implicating that aberrant proteins have pathological consequences of their own, as we shall discuss below.

Amyloid-based pathology

A β is created by the abnormal cleavage of APP by β - and γ -secretases [87–89]. Suspicion of its consequences may date back as far as Alzheimer's first report [90], but strong support for the pathogenic role first arose from genetic findings in familial AD (FAD) cases, which displayed unusually high A β levels and identical clinical manifestations to the sporadic form, but had an earlier onset [89, 91]. A significant portion of these cases carried either APP or presenilin (PS) mutations, suggesting that dysregulation of their normal functions may lead to A β formation [89, 91]. These mutations were in turn the basis for several important transgenic mouse models that have been used to study AD and to evaluate potential therapeutic interventions [92–94]. These findings led to the formulation of the “amyloid hypothesis” [95], which proposed that beta amyloid accumulation is responsible for AD-related pathology, including the initiation of neurofibrillary tangles (NFTs), and eventual neuronal death [96]. However, more recent findings suggest soluble A β oligomers disrupt glutamatergic synaptic function, which in turn leads to the characteristic cognitive deficits [97–103]. More information on A β pathology is available elsewhere [104–105].

A β -induced memory impairment

Compelling evidence of A β being a causative factor in AD comes from studies in which synthetic A β microinjection into the brains of animal models led to impaired working memory in a manner consistent with the memory deficits seen in AD patients [106–108]. A series of studies utilizing synthetic, natural, and human AD-derived A β have indicated that soluble A β oligomers are both necessary and sufficient to disrupt normal learning and memory function [109–111]. At the two extremes of aggregation, monomers and fibrils appear to act in vivo both as sources and sinks of certain metastable conformations that disrupt synaptic plasticity [112].

Synaptic damage due to beta amyloid accumulations at the synaptic cleft

However, one difficulty with the original amyloid hypothesis is that the temporal patterns of amyloid deposits do not correlate well with the cognitive deficits in affected patients [113]. Furthermore, synaptic plasticity is impaired before A β deposits are detected in mouse models of AD [98, 114]. This may be explained by the existence of intraneuronal accumulations of A β that have been reported in transgenic mouse models of AD as well as in humans with AD and DS [115–116]. These accumulations correlate with the onset of synaptic and behavioral abnormalities in transgenic models [117–120] and marked intraneuronal accumulation was associated with early ultrastructural pathology, especially within distal processes and synaptic compartments [121].

Indeed, soluble oligomers of A β have a direct synaptotoxic effect at nanomolar concentrations [122]. In a mouse model of AD, the vicinity of amyloid plaques was characterized by highly dysmorphic neurites and spine turnover [123–124] causing a net loss of spines. Continuous overproduction of A β at dendrites or axons acts locally to reduce the number and plasticity of synapses [125–126]. In hippocampal culture, soluble A β produced abnormalities in spine composition, shape, and abundance that strongly support the hypothesis that soluble A β initiates toxic mechanisms in AD brains that account for synaptic damage [127]. Continued exposure to A β caused abnormal spine morphology and a

significant decrease in spine density [127]. In a direct investigation of the acute effects of extracellular and intracellular A β 42 peptides on synaptic transmission, Moreno et al. [128] noticed inhibition of synaptic transmission by nanomolar concentrations of intracellular oligomeric A β 42, but not extracellular oligomeric A β 42 or oligomeric A β 40. Thus, local dendritic and axonal abnormalities associated with amyloid deposits lead to loss of synapses and the destruction of dendrites and axons in AD [124, 129]. Parihar and Brewer [130] have provided detailed on the synaptotoxic effects of A β in AD.

Additionally, while numerous reports indicate that A β causes impaired synaptic plasticity, there are paradoxical lines of evidence from both *in vitro* and *in vivo* studies that have shown that increased synaptic activity may induce A β secretion [102, 131–132]. This suggests that although excessive production of A β is synaptotoxic, lower concentrations may serve as a physiological molecule that regulates normal synaptic plasticity and memory [105]. In the following sections we will discuss how A β may mediate synaptic damage. A summary schematic is provided in figure 1.

Signaling Partners of A β

Although there is no consensus on the precise molecular pathways involved for A β oligomer-induced synaptic deficits a number of intracellular signaling pathways have been implicated [104]. Attempts to identify signaling partners, both those that directly bind to A β and those affected by its presence, offer great insights into how A β -induced synaptotoxicity may occur. We therefore turn our attention to some of the most promising candidates of such interactions described herein.

Cellular prion protein (PrPC)

We start with Cellular prion protein (PrPC) because the loss of synaptic markers in APP/ Presenilin 1 (PS1) mice is fully dependent on it [133] and treatment of aged APP/PS1 mice with anti-PrPC antibodies allows a recovery of depleted synaptic density in the dentate gyrus [134]. *In vitro* studies have described dendritic spine loss after acute A β oligomer exposure and imaging of spines continuously over 6h shows that A β oligomer treatment of dissociated hippocampal neurons induces a 10–15% loss of spines. On the other hand, PRioN Protein knockout (*Prnp*^{−/−}) cultures are fully protected [135]. Further support that PrPC mediates A β oligomer effects on spine composition, morphology and density comes from the observation that PrPC colocalizes to synapses and is present in the postsynaptic density [135–136] similar to A β [127, 137–138]. See [139] for more information on PrPC's role in AD.

Amyloid Precursor Protein (APP)

Next, we consider APP because a direct interaction between A β fibrils and the ectodomain of APP has been demonstrated using a variety of experimental conditions [140–142]. In contrast with fibrillar A β , monomeric A β peptide does not bind APP [140–142], suggesting that conversion of monomeric A β into toxic amyloid fibrils is required for binding to APP. The potential pathologic relevance of these observations is suggested by reports showing accumulation of APP at the proximity of fibrillar neuritic A β plaques in AD brains [143]. It is also likely that toxic A β assemblies other than fibrils could also bind APP including

dimers, oligomers, or protofibrils. Bignante and colleagues [144] have provided detailed information on APP's normal functioning in humans.

Mammalian target of rapamycin (mTOR)

Mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine protein kinase that plays an essential role in the control of mRNA translation and cell growth [145–147]. While it may be best known for its association with cancer biology, numerous reports have firmly established a pivotal role of mTOR in central nervous system function, including its effects on the consolidation of long-term memory [148–157]. Decreased mTOR signaling has been reported in the brains of an APP-PS1 AD transgenic mouse model [158], which is consistent with subsequent findings that rapamycin, a specific inhibitor of mTORC1, exacerbates neurotoxicity of A β [159]. More information on mTOR's role in AD was given in a review article by Ma and Klann [105].

Receptor for Advanced Glycation End products (RAGE)

Mounting evidence suggests that the damage caused by A β includes immune-mediated responses, which may lead to additional neuronal injury [160]. This will be discussed in greater detail in section 2.1.6 “A β -induced immune responses”. Receptor for advanced glycation end products (RAGE), is an immunoglobulin-like cell surface receptor that is important for A β -mediated cellular perturbation relevant to the pathogenesis of AD [160]. The interaction of RAGE with A β in neurons, microglia, and vascular cells accelerates and amplifies deleterious effects on neuronal and synaptic function *in vitro* [160–163] and in animal models [164–168] including cognitive deficits [165]. Blockade of RAGE significantly attenuates neuronal and synaptic injury [164–166].

Fyn

In addition to immune-response reactions, A β may interfere with the function of synaptic receptors by synergizing with Fyn, which induces aberrant increases in neuronal activity, triggering inhibitory mechanisms that limit network overexcitation but that may also diminish the capacity for synaptic plasticity [104]. Fyn increases NMDA receptor-mediated currents, modulates release of calcium from intracellular stores, and enhances synaptic transmission [169–172]. Overexpression of Fyn and A β in FYN/hAPP–J9 double-transgenic mice results in severe neuronal and cognitive impairments similar to those otherwise seen only in hAPP mice with much higher levels of A β production (hAPP-J20 mice) [173–176]. Conversely, ablation of Fyn prevents several aspects of A β -induced neurotoxicity [97, 174].

Glycogen synthase kinase-3 β (GSK3 β)

Dysregulation of Glycogen synthase kinase-3 (GSK3 β) activity has been observed in both sporadic and FAD and increasing evidence suggests that the relationship between GSK3 β and A β is bidirectional [105]. For example, high GSK3 β activity may interfere with normal APP processing via modulation of the function of secretases, leading to A β accumulation [177–179]. Suppression of GSK3 β activity by either pharmacological inhibitors or genetic manipulations results in abolishment of A β production and reducing plaque pathology in the brains of AD transgenic mice [178, 180]. Conversely, A β can activate GSK3 β through

dephosphorylation, which is linked to downregulation of the PI3K/Akt signaling pathway [181–186]. GSK3 β also has been proposed to play an important role in synaptic plasticity [184, 186] and evidence is accumulating to suggest the therapeutic potential of GSK3 β inhibition for AD-related synaptic dysfunction based on rescue of long term potentiation (LTP) in the hippocampus of an AD transgenic mouse by two structurally distinct GSK3 β antagonists [187] and pretreatment of rat brain slices with a specific GSK3 β inhibitor [181].

A β effects on Long-term potentiation and depression (LTP/LTD)

A plethora of studies have examined the effects of A β on LTP *in vitro* and *in vivo*. In most cases, LTP can be blocked by either direct exogenous A β application (at a concentration of 100 nM or above for synthetic A β), or in AD transgenic mouse models in which an abnormally high level of A β is present [188]. Of note, multiple lines of evidence suggest that there is an early, pre-plaque phase when learning and memory deficits are not detected in AD transgenic mice, but LTP is already impaired [117, 187, 189]. These observations are in line with the hypothesis that soluble A β oligomers are synaptotoxic [190, 191].

Compared to LTP, few studies have been conducted to examine the effects of A β on long-term depression (LTD) [192–194]. It was reported that LTD *in vivo* induced by low-frequency stimulation (LFS) can be facilitated by injection of different forms of synthetic A β [195, 196]. Additional studies on LTD *in vitro* have confirmed that LFS-induced LTD is enhanced by A β from various sources, including synthetic, cell culture, and human AD brains extracts [111, 197]. It should also be noted that LTD induced by stronger LFS protocol is not altered by A β [198–199].

Significant parallels were found between A β -induced synaptic changes and LTD suggesting that A β affects synaptic function and dendritic spine morphology through LTD-related signaling mechanisms [200]. Overexpression of A β resulted in decreased spine density and postsynaptic AMPA receptor number. Notably, expression of a mutant form of AMPA receptor that resists LTD-driven endocytosis blocked the morphological effects and synaptic depression induced by A β therefore implicating the endocytosis of AMPA receptors as a major mechanism through which A β causes synaptic dysfunction [200]. A β 's effects on LTP/LTD may therefore occur through interaction with calcium channel activity [201–202] or glutamate receptor dependent signaling pathways [125, 197, and 200].

A β effects on organelle function

Mitochondria—The properties of mitochondrial membranes are essential to their ability to transport metabolites and maintain the necessary conditions for oxidative phosphorylation. Mitochondrial dysfunction is a common finding in AD postmortem brains [203–208] and A β treated cell [209–218], suggesting a role for loss of energy production and generation of radical oxygen species (ROS) in the progression of the disease. Voltage-dependent anion channel proteins (VDACs) are ubiquitously located in the mitochondrial outer membrane and are thought to be the primary means for metabolite diffusion between the mitochondria and the cytosol [219–222]. A β interacts with VDAC1, blocking the mitochondrial permeability transition pore complex (MTP) pores, which stops transport of mitochondrial

proteins from the nucleus leading to defective oxidative phosphorylation, which may in turn induce an increase in free radical production [223].

Additionally, A β has been suspected of affecting NMDAR activity by binding to intracellular mitochondrial cyclophilin D (CypD) or mitochondrial A β alcohol dehydrogenase (ABAD), as well as other targets [130]. Synaptic terminals from aged rats were shown to be more sensitive to A β toxicity, evidencing an age-related decline in mitochondrial activity in both resting and depolarized conditions. In addition, ultrastructural changes including increased mitochondrial size and a significant reduction of synaptic vesicle contents were also observed in presynaptic nerve endings from rat hippocampi exposed to A β at different ages [224].

It is likely that in pathological situations, unusually high levels of ROS are produced constantly, overwhelming the ability of the endogenous antioxidants, which then results in impairments in synaptic function. For example, AD mutant mice with decreased mitochondrial superoxide dismutase (SOD-2) expression exhibit elevated levels of brain A β and accelerated cognitive dysfunction [225–226]. Conversely, it has been shown that overexpression of SOD-2 in two different AD mouse models is capable of reducing brain A β deposition and preventing memory deficits [227–228].

More recently, it was demonstrated using both pharmacological and genetic approaches that AD-associated synaptic plasticity impairments can be prevented and reversed by targeting ROS derived from mitochondrial, but not NADPH oxidase [229]. An interesting implication that arises from these studies is that ROS play different roles in synaptic plasticity, depending either on their subcellular localization or on the age of the animals being studied [105, 230–232].

Alternatively, A β has been shown to interact with dynamin-related protein 1 (Drp1), which leads to increased mitochondrial fission and decreased fusion that ultimately results in increased mitochondrial fragmentation [233]. Mitochondrial fragmentation may lead to accelerated ROS production and we can therefore see that A β has multiple effects on mitochondria that may occur simultaneously, leading to synaptic damage and neuronal loss.

The Endoplasmic Reticulum and Golgi—Likewise, microarray analyses demonstrated that exposure of SN56.B5.G4 cells to oligomeric β -amyloid (1–42) affected the expression level of a number of genes that were not influenced by non-specific oxidative stress, suggesting that A β displays a particular toxicity for cholinergic neurons [234]. Many of the gene products affected were present in the endoplasmic reticulum (ER), Golgi apparatus or were otherwise involved in protein modification and degradation (chaperones, ATF6) indicating a possible role for ER-mediated stress in A β -mediated toxicity [234].

Lysosome—Finally, new insight into the broad dysfunction of the lysosomal system in AD was obtained following the identification of cathepsins in A β plaques. These findings combined with our understanding of APP cleavage to bring proteases to the forefront of investigation in neurodegenerative diseases [235].

A β -induced immune responses

Under ideal circumstances, organelle dysfunctions like those discussed above may elicit immune responses that prevent damaged neurons from having deleterious effects on others. However, immune responses may overreact and exacerbate local cellular damage. Microglia play a critical role in A β -mediated neuronal dysfunction and death in the pathogenesis of AD [236–242] and many inflammatory mediators detected in AD brains are of microglial origin [236, 242–247]. Increased microglial activation, microglial association with senile plaques, and elevated levels of proinflammatory mediators (i.e. cytokines, chemokines and free radicals) have all been observed in the AD brain and AD mouse models and evidence indicates that these processes contribute to neuronal damage [236, 248–249]. Observations of brains from AD patients and AD mouse models show that activated microglia and astrocytes accumulate to the greatest extent in the proximity of amyloid plaques [236]. Furthermore, studies carried out with an *in vitro* cell culture model show that direct administration of A β to multiple cell types can induce cellular stress, and this effect is probably increased in the presence of activated microglia [236, 240]. Information A β -mediated responses was given by Yan and colleagues [250].

A β effects on synaptic vesicle transport

Although we have now seen how A β may damage neurons through several direct and indirect process, arguably its most fundamental effect is the disruption of neurotransmission. Endogenous A β peptides appear to have a crucial role in activity dependent regulation of synaptic vesicle release [251]. Deleterious effects of A β oligomers were shown to be present on multiple steps of synaptic vesicle trafficking [252] and acute treatment of cultured rat hippocampal neurons with A β oligomers decreased vesicle endocytosis and regeneration, which led to weakened synaptic transmission [252]. Furthermore, these effects were prevented by an antibody against A β [252]. Electron microscopy (EM) studies demonstrate that oligomeric A β is localized within the synaptic compartment [121] or that it is bound to the extracellular surface of the spine suggesting that oligomeric A β may interact directly at the synapse to cause dysfunction and spine collapse [253].

Presynaptic proteins such as SNAP-25, synaptophysin, and synaptotagmin were reduced in brains of patients with AD [254] and in the hippocampus of Tg2576 mice one month after injection of A β into the third ventricle [255]. Russell et al. [256] demonstrated a time-dependent interaction of A β with synaptophysin in presynaptic terminals of hippocampal neurons and electrophysiology recordings in hippocampal brain slices confirmed that A β affects baseline neurotransmission. Additionally, A β oligomers can alter dynamin-1, a neuron-specific GTPase that pinches off synaptic vesicles, allowing them to re-enter the synaptic vesicle pool [257–258]. For more information on how A β affects synaptic vesicle trafficking, see [51].

A β -induced Neurotransmitter Modulation

In addition to synaptic changes, A β is suspected of altering the actions of several major neurotransmitter systems. A summary of A β 's proposed effects is depicted in figure 2.

Acetylcholine—Physiological levels of A β (within the picomolar range) can activate presynaptic nicotinic acetylcholine receptors (nAChR) and evoke changes in Ca²⁺ levels in rat hippocampus and neocortex while toxic levels (within the nanomolar range) inhibit both the presynaptic nAChR and presynaptic Ca²⁺ levels [259]. Binding of A β to nAChR can modulate presynaptic glutamate-mediated synaptic transmission or glutamate release, which suggests A β 42 activates a signal transduction mechanism that results in synaptic transmission and memory consolidation via nAChR [260].

However, it is unknown if these effects are due to a direct physical interaction of A β peptide and nAChRs [130]. Immunohistochemical (IHC) studies on human sporadic AD brains show that A β 42 and nAChR are both present in neuritic plaques and co-localize in individual cortical neurons [261], but A β may regulate nAChR function through binding of membrane lipids [262]. A β 42 acting through nAChRs, can elicit ERK/MAPK activation in hippocampal cultures [263–264] via Ca²⁺ influx [265–266]. ERK may then phosphorylate CREB and Elk-1 [267], which help initiate transcription of memory associated genes that contain their respective regulatory elements [268]. Therefore, A β may lead to an overactivation of nAChRs and excessive Ca²⁺ influx that impairs the signaling cascades of memory formation [16, 25]. For more information on ACh and A β , see [130 and 269].

Glutamate—There is an abundant literature on the interactions of glutamatergic neurons and A β [51, 63, 104, 130, 270–272]. In brief, A β promotes glutamatergic excitotoxicity and disrupts glutamatergic synapses and plasticity providing an explanation for the cognitive deficits seen in AD [190]. Although A β greatly reduces levels of AMPA and NMDA receptors at the neuronal plasma membrane through endocytosis [127, 138, 272], it is unclear how this loss is induced [273].

AMPA—A β oligomers are believed to interact with complexes containing the glutamate alpha-2 (GluA2) subunit of AMPA receptors (AMPA) based on co-immunoprecipitation and photoactivated amino acid cross-linking studies [274] as well as the observation that pharmacological inhibition and removal of surface AMPARs reduce A β binding to neurons [274–276]. Similarly, a mouse model of AD showed that the synaptic removal of AMPAR plays a key role in the A β -induced synaptic dysfunction [277]. D'Amelio et al., [277] demonstrated an increase of A β -dependent synaptotoxicity leading to a synaptic activation of mitochondrial-dependent protease, caspase-3, which activates calcineurin. Calcineurin then dephosphorylates GluR1 subunit of AMPARs triggering their removal from post-synaptic sites. This reduction of AMPAR mediated currents leads to an increase of LTD, which correlates with dendritic spine degeneration and memory loss [271].

NMDA—The binding of A β oligomers to synapses may involve the assembly of a multi-protein receptor complex created by interaction with NMDAR [278]. Once bound to synaptic membranes, A β instigates synaptic failure by down-regulating plasticity-related receptors, which leads to abnormal trafficking or degradation [63]. Although A β selectively enhances NMDAR-mediated currents and synaptic transmission at physiological levels [258, 279] at higher concentrations it promotes endocytosis of NMDARs in cortical neurons and produces a rapid and persistent depression of NMDA-evoked currents via activation of nAChRs [138, 280–281]. Activation of NMDARs and mGluRs, in turn, promotes the

amyloidogenic processing of APP, increasing A β levels in vitro [282–283]. Thus A β instigates a positive feedback cycle, in which A β induces glutamate receptor overactivation, leading to the generation of more A β [63]. A β can also promote cytotoxicity through increased Ca²⁺ influx and elevated levels of potentially toxic ROS in an NMDAR dependent manner [258, 284]. Collectively, these findings suggest that NMDARs are specifically required for pathogenic A β binding to dendrites and that binding induces the endocytosis of NMDAR and other plasticity-related membrane receptors, culminating in synapse failure and elimination [63].

Norepinephrine—In contrast, very little work has examined the effects of A β on NE. We were only able to find one such study [285]. In it, they examined the effects of A β 1–40 on the release of [3H] NE from rat brain cortical slices and synaptosomes, respectively. The results show that 3nM A β 1–40 decreased electrically stimulated [3H]NE release approximately 50%, and increased [Ca²⁺]_i by 78%. Complete prevention of both effects was observed when the free radical scavenger 1mM N-tert-butyl- α -phenylnitrone (PBN) was present or used as pretreatment. This led them to conclude that A β 1–40 allows a PBN-sensitive free radical to deleteriously effect both evoked [3H]NE release and [Ca²⁺]_i regulation in rat cortical slices and synaptosomes [285].

GABA—Also like NE, little work has been done on A β 's interaction with GABA. This is likely because soluble A β oligomers do not bind to GABAergic neurons [127, 286] and, as previously mentioned, the significance of the transition of GABAergic neurons from inhibitory to excitatory in AD is not yet understood. GABA is often known as the major inhibitory neurotransmitter in the brain and A β has been observed to inhibit whole-cell and single-channel nicotinic currents from rat GABAergic interneurons by directly blocking the postsynaptic α 7-nAChR channels [241]. For more information of GABA's interaction with A β , see [104 and 271].

Tau

Physiological role of Tau proteins

Tau proteins play an important role in the assembly of tubulin monomers into microtubules and in stabilizing microtubules to other cytoskeletal elements in neurons [287]. Microtubule formation is a dynamic process of assembly and disassembly that is crucial for axonal transport. Disruption of this process by abnormal phosphorylation of tau may therefore lead to synaptic transmission dysfunction and neuronal death.

Tau-based pathology

Observations from molecular analyses suggest that the aggregation of tau filaments inside of neurons may be caused by abnormal phosphorylation. This, combined with the observation that a direct correlation between the progressive involvement of the neocortical areas and the increasing severity of dementia, suggests that pathological tau proteins may be a reliable marker of the neurodegenerative process [287]. The conformation and hydrophobicity of tau oligomers play a critical role in the initiation and spread of tau pathology in the naïve host in a manner reminiscent of sporadic AD. These oligomers were shown to be potent inhibitors

of LTP in hippocampal brain slices and to disrupt memory in wild type mice [288]. Furthermore, intracerebral injection of brain extracts containing tau aggregates in transgenic animals can induce tau pathology and tau oligomers directly extracted from the cerebral cortex of an AD brain can propagate abnormal tau conformation of endogenous murine tau after prolonged incubation [288]. These findings highlight how abnormal phosphorylation of tau can lead to impairment of neuronal functioning and spread in a prion-like fashion.

Synaptic damage due to phosphorylated tau accumulations—Transgenic mouse models of AD have implicated tau as a major mediator of A β toxicity at the postsynaptic compartment and dendritic spines [11]. Crossing of APP transgenic mice with tau transgenic mice, promoted NFT pathology [289–291] and immunization of APP/Psn/tau triple transgenic (3xTg-AD) mice with antibodies against A β reduced the levels of hyperphosphorylated tau [292]. Consistent with previous work in cultured neurons [293], removing endogenous tau can prevent A β -induced behavioral deficits in an AD mouse model expressing human APP and block excitotoxin-induced neuronal dysfunction in both transgenic and nontransgenic mice [294]. Synaptic physiological data also indicate that tau reduction corrects several abnormalities in multiple hippocampal subregions of hAPPJ20 mice [295]. Together, these studies support the notion that tau phosphorylation abnormalities contribute to disease pathogenesis [100] via promoting the accumulation of the toxic A β peptides [11].

It may seem confusing as to how tau, a normally presynaptic protein, could end up influencing A β in the postsynaptic compartment, but a study by [296] indicated that phosphorylated tau could accumulate in dendritic spines where it may affect the synaptic trafficking and/or anchoring of glutamate receptors, which in turn affects postsynaptic function; thus revealing a critical role for tau phosphorylation in causing mislocalization of tau and subsequent synaptic impairment, thereby establishing dendritic spines as pathogenic targets of tau action. Conversely, A β could enhance the production of hyperphosphorylated tau by activating a number of kinases, including cyclin-dependent kinase-5 (CDK5) [297–298], Fyn kinase [174, 299], GSK3 β [300], and MARK [301–303]. Ittner et al. [304] showed that the interaction of tau with Fyn leads to the targeting of Fyn to dendritic spines, where Fyn can phosphorylate NMDA receptor subunit 2 (GluR2), resulting in stabilization of the interaction between GluR2 and post synaptic density-95 (PSD-95), which leads to enhanced excitotoxicity. PSD-95 also interacts with tau, further supporting a dendritic role of tau outside of its axonal function [304]. Importantly, the toxic effects of APP/A β were attenuated by interfering with GluR2/PSD-95 interaction with a cell-permeable peptide [304], supporting that dendritic tau-mediated Fyn recruitment and GluR2/PSD-95 interaction confer A β toxicity at the postsynapse. Thus, a “tau hypothesis” has been postulated which states: A β triggers the phosphorylation of tau, causing tau to dissociate from the microtubules and accumulate at the dendritic compartments. Phosphorylated tau then interacts with Fyn, localizing Fyn to dendritic spines. Fyn then sensitizes the NMDA receptors, which renders neurons more vulnerable to the toxicity of A β in the postsynaptic compartment (see figure 3) [305].

Effects of phosphorylated tau on mitochondria—Similar to A β , phosphorylated tau has been shown to interact with VDAC1 in AD postmortem brains and in 3xTg-AD mice [223]. This interaction may interrupt axonal transport to the mitochondria resulting in synaptic damage [306]. Likewise, phosphorylated tau also interacts with Drp1 [307], as did A β , highlighting the dual site of interaction for these lesions within the mitochondria and further supporting the notion that phosphorylated tau-mediated disruption of axonal transport to the mitochondria may lead to synaptic damage.

Factors affecting tau accumulation

In addition to the factors we have already discussed, SRPK2, and S6K1 have been implicated as phosphorylating tau leading to its toxic accumulation [308–309]. Factors specifically involved in the “tau hypothesis” mentioned above include PAR-1/MARK and its activator, LKB1 [11] as well as ALOX5 [310], and PS1 [311]. Conversely, magnesium has been suggested to reduce tau accumulations, which is believed to occur via increased inhibitory phosphorylation of GSK-3 β [312].

mTOR—mTOR’s interactions with A β were previously discussed, but upregulation of mTOR has also been reported in tangle-bearing neurons of postmortem AD brains [313]. This finding is in agreement with a recent report showing that mTOR signaling is enhanced in the 3xTg-AD mouse model [314]. However, studies using other mouse models have not found the same results [187; 315] suggesting that mTOR’s response to excess A β is driven by PS or tau mutations. Observations on mTOR’s role in AD remain unclear as studies often contain several differences in methodology including the mouse model used, the age of the mice, and the experimental conditions making it difficult to draw interpretations across experiments [187, 314, and 315]. However, mTOR’s involvement connects A β and tau to work on the insulin-PI3K-Akt pathway in AD, as this pathway is a well-established upstream regulator of mTOR [182; 183; 316–319]. More information on phosphorylated tau’s interactions with mTOR was given in a review article by Ma and Klann [105].

Neurotransmitter abnormalities due to phosphorylated tau accumulations at the synaptic cleft

Far fewer investigations appear to have examined the role of tau on neurotransmitter dysfunction than A β . The only substantial literature appears to deal with tau’s potential interaction with the cholinergic system.

Acetylcholine—Patients with MCI and AD have been shown to have tau pathology in cholinergic basal forebrain neurons [30, 320–323]. Single cell gene expression profiling of human cholinergic basal forebrain neurons revealed a shift in the ratio of three-tandem repeat to four-tandem repeat tau within the nBM and CA1 hippocampal neurons that is exclusive to the progression of AD compared to normal aging [324]. Furthermore, observations of pretangles and tangles in the basal forebrain prior to entorhinal/perirhinal cortex pathology suggest that abnormalities in cortical cholinergic neurons and tau formations within the basal forebrain cholinergic system occur early in life and increase in frequency in old age and AD [30, 325–326]. Additional findings from a tau transgenic

mouse model, are consistent with observations in humans and suggest tau pathology may participate in cholinergic degeneration [327].

Conversely, nAChR activation results in a significant increase in tau phosphorylation, whereas muscarinic acetylcholine receptor (mAChR) activation may prevent this [328–329]; for reviews see [269, 330]. Nicotine was also found to induce tau phosphorylation at sites that were also hyperphosphorylated in AD [331]. Support for a nicotine-induced phosphorylation of tau model also comes from a study in which five months of nicotine administration to one-month-old 3xTg-AD mice did not change soluble A β levels but increased phosphorylation and aggregation of tau. This appears to be mediated by p38-MAP kinase [331]. Detailed information on phosphorylated tau's interaction with Ach was given in a review article by Schlieb and Arendt [47].

The nicotine-induced phosphorylation of tau model is assumed to work through the $\alpha 7$ AChR [329]. Upon activation by either nicotine or A β , $\alpha 7$ AChR has been shown to mediate high Ca $^{2+}$ permeability, which leads to dramatic increases in intracellular Ca $^{2+}$ levels [265]. This rise in intracellular Ca $^{2+}$ activates Ca $^{2+}$ -dependent kinases, which may phosphorylate tau [328–329]. Therefore, accumulation of intraneuronal A β may occur prior to plaque and neurofibrillar tangle formation and initiate tau pathology through the $\alpha 7$ AChR. This view is supported by evidence that a selective decrease in A β -42 markedly delays the progression of tau pathology [332]. Conversely, $\alpha 7$ nicotinic agonists predictably increase phosphorylation of tau protein [328], yet simultaneously attenuate A β -mediated toxicity [333]. Hence, *in vitro* and *in vivo* evidence suggests that $\alpha 7$ AChR may operate as a link between A β and tau pathology (figure 3) [334].

Amyloid Beta and hyperphosphorylated tau-independent mechanisms of synaptic damage

Although the intent of this review is to discuss amyloid and tau-mediated synaptic and neurotransmitter dysfunctions, it is important to acknowledge several other major factors that are associated with these dysfunctions as well. Some factors, like PS1, are known for their interactions with A β and tau, but have independent synaptotoxic mechanisms as well. Similar alterations in ACh and NMDA receptor-mediated components of synaptic plasticity are evident in 3xTgAD mice with PS1, amyloid precursor protein and tau mutations, suggesting that the adverse effects of mutant PS1 on synaptic plasticity can occur in the absence or presence of amyloid and tau pathologies [335]. Likewise, A β -independent mechanisms of apolipoprotein E4 (APOE4) include differential effects of apoE on cerebral energy metabolism, neuroinflammation, neurovascular function, neurogenesis, and synaptic plasticity. ApoE is believed to effect synaptic plasticity via low-density lipoprotein receptor-related protein 1 (LRP1), syndecan, and LRP8/ApoER2 [336].

Other factors, such as nitric oxide (NO) and estrogen may reduce synaptic damage. At the early stages of the disease in AD mouse models, evidence of abnormal synaptic function presents as increased LTD revealed only when homeostasis is challenged; suggesting compensatory mechanisms are recruited to maintain a functionally normal hippocampal circuit. Chakraborty et al. [337] concluded that recruitment of NO, which acts presynaptically to boost vesicle release and glutamatergic transmission, serves a compensatory role to boost synaptic transmission and plasticity during early-stage AD.

However, NO's dual role in neuroprotection and neurodegeneration may convert to maladaptive functions as the disease progresses [313]. Additionally, estrogen replacement in postmenopausal women appears to decrease the risk of developing AD [338] as estrogens promote axonal and dendritic plasticity in the limbic neurons of male and female brains [339–343]. In female mice, ovariectomy severely impairs the reactive hippocampal synaptogenesis that follows entorhinal damage, but this effect was reversed by estrogen replacement [344]. Postmenopausal estrogen deficiency may thus suppress the potential for neuroplasticity [345].

Conclusion

Throughout this review, we focused on how A β and phosphorylated tau could influence the accumulation of one another, impair synaptic integrity, and alter neurotransmission. From this we have seen that the potential interplay between these two lesions can be at times synergistic, antagonistic, and almost always complicated. Following our review of the literature a few points are readily noticeable. First, there is considerably more literature on A β 's involvement than tau's. We identified 169 articles specific to A β versus 26 for tau and only 16 explicitly looked at both. However, whether that is because A β is truly more responsible for a wider variety of issue or if this is simply because it has received more scrutiny given its historical precedent is not entirely clear. We say this because although it is reasonable for works before the early 2000s to have focused primarily on A β of the aforementioned articles on A β only 20 of them are from before 2000. Therefore the vast majority of work that we have discussed herein comes from after that time, yet shows little attention to tau; often making it unclear if observations noted for A β are absent from similar manipulations of tau or more likely that they simply have not been investigated. Given the relatively recent reassertion of tau's importance from Braak and Del Tredici [83] observation that its accumulation in the LC is the first positive lesion of AD and Brier et al.'s [346] conclusion from PET imaging that tau may be a more informative predictor of a person's cognitive decline and potential response to treatment than A β , investigations on the significance of tau, both at the cellular and clinical level, are imperative in order to achieve a fuller understanding of AD.

Likewise, while investigations of cholinergic and glutamatergic systems have provided great insights and offer potential targets for novel therapies [56] more work needs to be done on the GABAergic and noradrenergic systems. Understanding how the GABAergic system is affected is important for two reasons. First, because it is the major inhibitory system in healthy individuals, but we know that it can shift to an excitatory system in the presence of AD; the full consequences of which are unknown [56]. Second, as novel therapeutics that rely on restoring excitatory systems undergo clinical trials these drugs may face hurdles from side effects that are induced by a lack of inhibitory feedback from GABA thereby rendering otherwise successful treatments as impractical; similar to the current problem of using GABAergic agonists to treat NPS as previously discussed [52]. NE, on the other hand, has received surprisingly little attention given that the destruction of its largest source of cells, the LC, is known to be the first to show AD pathology [83] and its physiological function is believed to be involved in both memory and attention [84]; two of the hallmark aspects of AD pathology.

For these reasons, it is our recommendation that investigations of the interaction between tau and NE receive a renewed sense of priority. Although neither the formation of phosphorylated tau nor loss of NE has been observed to result in the most severe of pathologies related to AD, their unique position as the earliest events in disease progression provides reason to investigate these processes with greater scrutiny as an understanding of how these early events occur may lead to greater insights into how the disease may be delayed, prevented, or even cured.

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Figure 1.

Amyloid beta's many sites of neuronal damage. 1) Soluble intracellular oligomers of A β are cytotoxic [122,128]. 2) Interaction with PrPC leads to dendritic spine damage [139] (top right). A β fibril binds to APP during formation of extracellular plaques [144] (middle left). A β inappropriately activates GSK3 β [105] (middle right). A β synergizes with Fyn to disrupt synaptic receptors [104] (bottom left). mTOR may inhibit A β [105] (bottom right). 3) Mounting evidence suggests A β -mediated destruction of spines and synapses leads to LTP impairment and LTD enhancement [105]. 4) Mitochondrial distress may lead to production of ROS that may accelerate A β formation. A β may then affect NMDAR activity by binding to intracellular mitochondrial CypD or mitochondrial ABAD [130] (Top). A β -mediated cytotoxicity may be particularly damaging to the endoplasmic reticulum, affecting its production and modification of crucial proteins [234] (middle). Identification of cathepsins in A β plaques suggest protease dysfunctions from lysosomes may play a critical role in advancement of pathology [235] (bottom). 5) RAGE may play a prominent role in the increased microglial activation and proinflammatory markers commonly associated with senile plaques [160]. 6) A β interacts with synaptophysin in presynaptic terminals of the hippocampus [256] to impair neurotransmission (top). A β also interferes with dynamin-1 allowing synaptic vesicles to reenter the synaptic pool [257,258] (bottom).

Figure 2.

Summary of amyloid beta's interaction with neurotransmitters at neuronal synapses. 1) A β may lead to an overactivation of nAChRs and excessive Ca²⁺ influx that impairs the signaling cascades of memory formation [16, 25]. 2) A β oligomers are believed to interact with the GluA2 subunit of AMPAR [274] leading to increased LTD (top). A β promotes endocytosis of NMDARs in cortical neurons and produces a rapid and persistent depression of NMDA-evoked currents via activation of nAChRs [138, 280, 281] (bottom). 3) A β 1–40 allows a PBN-sensitive free radical to deleteriously effect evoked NE release [285]. A β inhibits nicotinic currents from GABAergic interneurons by directly blocking the postsynaptic α 7-nAChR channels [263].

Figure 3.

Tau at the synapse. 1) Phosphorylated tau accumulates in dendritic spines where it may affect the synaptic trafficking and anchoring of GluR [296]. 2) Dendritic tau-mediated Fyn recruitment and GluR2/PSD-95 interaction confer $\text{A}\beta$ toxicity at the postsynapse. 3) Upon activation by $\text{A}\beta$, $\alpha 7$ AChR mediates a rise in intracellular Ca^{2+} , which may activate kinases that phosphorylate tau [328, 329]. Thus, $\text{A}\beta$ and hyperphosphorylated tau may promote each other's role in the pathogenesis of Alzheimer's disease.