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The Role of Amyloid-Beta and Tau in the Early Pathogenesis of Alzheimer's Disease

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The abnormal accumulation of amyloid-β (Aβ) and neurofibrillary tangles (NFTs) containing phosphorylated tau proteins are the main histopathological feature of Alzheimer's disease (AD). Synaptic damage and loss are earlier events than amyloid plaques and NFTs in AD progress and best correlate with cognitive deficits in AD patients. Soluble oligomeric Aβ initiates the progression of AD and tau mediates the subsequent synaptic impairments at an early stage of AD. In this review we discuss how Aβ or/and tau causes synaptic dysfunction. Aβ oligomers gather at synapses and give rise to synaptic death in a variety of ways such as regulating receptors and receptor tyrosine kinases, unbalancing calcium homeostasis, and activating caspases and calcineurin. A large amount of hyperphosphorylated tau exists in the synapse of the AD brain. Aβ-triggered synaptic deficits are dependent on tau. Soluble, hyperphosphorylated tau is much more correlated to cognitive decline in AD patients. Tau-targeted therapies have received more attention because the treatments targeting Aβ failed in AD. Here, we also review the therapy strategies used to intervene in the very early stages of AD. Soluble hyperphosphorylated tau forms a complex with cell surface receptors, scaffold proteins, or intracellular signaling molecules to damage synaptic function. Therefore, therapeutic strategies targeting synaptic tau at the early stage of AD may ameliorating pathology in AD. This review aims to provide an update on the role of oligomeric Aβ and soluble hyperphosphorylated tau in the early pathogenesis of Alzheimer's disease and to develop a new treatment strategy based on this.

Keywords: Alzheimer Disease • Amyloid beta-Peptides • MAPT Protein, Human • Neurofibrillary Tangles

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Background

Alzheimer's disease (AD) is characterized by two hallmark pathological lesions in the brain: the extracellular amyloid plaques deposition of amyloid-β (Aβ) peptides and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau [1,2]. The internal relations between these two hallmarks and the cognitive dysfunction occurred in AD patients remain elusive [3]. Accumulation of toxic Aβ is proposed as one of the important early events in AD, but unsuccessful clinical trials based on Aβ-targeting drugs have triggered researchers to investigate new therapeutic strategies targeting alternative disease mechanisms [4]. Aβ oligomers but not amyloid plaques target the postsynaptic compartment of excitatory synapses with high affinity, changing the structure and function of synapses [5]. More and more research indicates that the pathology of tau correlates with cognitive defects in AD [6]. However, soluble forms of tau oligomers but not NFTs appear to be an important factor inducing neuronal dysfunction and cognitive impairment [7,8]. Memory deficits highly correlate with synaptic decline in the hippocampus of AD patient's brains [9-11]. Synaptic loss is the first indicator of AD progression, even in the earliest of stage, called mild cognitive impairment (MCI), and has the strongest biological correlation with cognitive deficits found in AD patients [12-14]. Mislocalization of tau to dendrites, which is an early event in AD pathogenesis prior to tau aggregation, is a neuropathological feature of AD brains [15,16]. Synaptic tau correlates with the onset of cognitive decline in AD [17,18]. This review aims to provide an update on what is currently known about the role of Aβ and tau in the early pathogenesis of Alzheimer's disease.

Oligomeric Aβ and Synaptic Dysfunction

Long-term potentiation (LTP) and long-term depression (LTD), which are forms of activity-dependent synaptic plasticity, and the formation of dendritic spines are considered to underlie learning and memory [19]. LTP increases in synaptic strength depend on activating NMDA receptors by recurring synaptic activity. In contrast, LTD reduces synaptic activity through phosphorylation of AMPA receptors [20].

Synaptic loss can be induced by oligomeric forms of Aβ [1,21,22], suggesting that Aβ is a driver of synaptic dysfunction in AD [23]. The senile plaques were considered to be the major pathogenic substance in AD, but clinical investigations did not reveal a strong association between extracellular amyloid plaque and cognitive defects [24]. During AD progress, Aβ oligomers begin to be enriched at synapses, which is earlier than the formation of amyloid plaques or accumulation of phosphorylated tau at synapses [25,26]. Extracellular Aβ accumulates around the postsynaptic compartment more abundantly than at presynaptic terminals [27].

Accumulated research results indicate that Aβ causes synaptic death, LTD and LTP via modulating excitatory receptors and receptor tyrosine kinases, unbalancing calcium homeostasis, and activating caspases and calcineurin. Aβ binds to AMPA receptors and causes their internalization, leading to increased LTD. Aβ binds to 7α-nicotinic acetylcholine receptors, leading to an internalization of NMDA receptors and LTD [28]. Oligomeric Aβ stimulates NMDA receptors to upregulate calcium and redox reactions, leading to synaptic dysfunction and neuronal loss [29]. Calcineurin, activated by Aβ elevated calcium, dephosphorylates actin filaments to cause dendritic spine loss. Calcineurin activation can also reduce NMDA receptor expression on the surface and lead to greater AMPA receptor internalization. Soluble Aβ dephosphorylates AMPA receptors and increases receptor internalization. Oligomeric Aβ also binds with tyrosine kinases to modulate NMDA receptor trafficking and reduce LTP [30].

Oligomeric Aβ can impair LTP while increasing LTD in a concentration-dependent manner. Low levels of oligomeric Aβ facilitate LTP, but high levels of Aβ impair it [29] by affecting calcium channel activity and glutamate receptor-dependent signaling pathways [31].

The increased NMDA activity stimulated by oligomeric Aβ can lead to increased tau accumulation. Increased phosphorylated tau associates with, and further amplifies, the dendritic spine loss [32]. Age-dependent accumulations of Aβ and tau and their interactions at synapses largely impair synaptic activity via altering LTP and LTD levels [30].

Tau and Synaptic Deficits

Tau normally exists in synapses of both healthy and AD brains, while there is a greater level of hyperphosphorylated tau present in the AD synapse [33]. Soluble, hyperphosphorylated tau is much more closely related to synaptic dysfunction and cognitive decline in AD patients compared to Aβ and aggregated tangles of tau [34]. In vivo experiments showed the role of tau in synaptic plasticity. Reduction or depletion of tau blocked the induction of LTD but not LTP. Replacement of endogenous tau with human tau restored LTD. These data support the essential role of tau in a NMDAR-dependent LTD in the hippocampus [35]. Tau's role in LTD depends on its phosphorylation at serine 396, which internalizes the AMPA receptor [36]. Reducing the phosphorylation of tau by inhibiting tau kinases rescues tau-dependent LTP deficits and alleviates synaptic loss in tau transgenic mice [37,38]. Aβ may need tau to impair LTP, since tau-null mice showed no impairment in LTP when Aβ was applied [29]. Synaptic deficits induced by Aβ were closely related with tau, since reducing endogenous tau levels in Aβ-forming AD mouse models prevented dysfunctions [39-42]. In contrast,

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overexpression of human tau in amyloidosis mouse models increased synaptic loss and memory impairment [40,43].

Transgenic mice with human P301S or P301L mutant tau had impaired LTP in the hippocampus [18,44]. Mice expressing human V337M mutant tau had reduced excitatory synaptic transmission, associated with decreased synaptic glutamate receptors levels in both the ventral striatum and the insular cortex [45]. In cortical neurons, expression of human P301L mutant tau resulted in mushroom spine loss [46].

Mitochondria and Synaptic Degeneration

Mitochondria serves as energy supplier for synaptic functions such as synaptic transmission, synaptic outgrowth, and synaptic vesicle formation [47,48]. Aβ or phosphorylated tau triggers damage and transportation of mitochondria to synaptic terminals, which may provide low levels of ATP to synapses, leading to synaptic degeneration [30]. Mitochondrial dysfunction occurs early in AD progression [49]. Synapse loss is an early event of AD, which is attributed to soluble Aβ, phosphorylated tau, and increased free radicals generated by mitochondria at synapses [30]. More abnormal mitochondria are found in synapses of AD brains compared to healthy brains [50].

Synaptic Proteins and Synaptic Function

Extensive studies on synaptic proteins in a large number of healthy controls and AD patients reveal that postsynaptic and presynaptic proteins are important for synaptic function and may be related to cognitive impairments in AD [51]. Synaptophysin, a presynaptic protein, was decreased by around 25% in MCI patients, which can occur before Aβ plaque formation. Loss of synaptophysin correlates with cognitive decline and is also a marker for disease progression in AD patients [11]. The postsynaptic density-95 (PSD-95) protein is the most abundant scaffold proteins inside the postsynaptic density (PSD), a densely packed multi-protein structure for synaptic formation and function at the distal tip of dendritic spine heads [52-54]. PSD-95 is crucial for trafficking and anchoring of synaptic glutamate receptors [55-58]. It is predicted that tau, Fyn, PSD-95, and NMDARs form a protein complex at the synapse [59]. Loss of PSD-95 results in decrease of synapses containing glutamate receptors and impairments in AMPAR and NMDAR transmissions [60]. It has been reported that the expression of PSD-95 is aberrant in several human disorders, including AD [61-65]. Researchers identified postmortem synapse and synaptic marker loss from AD patients in a meta-analysis [66].

Other Factors Related to Aβ and Tau in AD

Infection

The "inflammation hypothesis" [67], "cholinergic hypothesis" [68], and "amyloid cascade hypothesis" [69] are three important hypotheses on the etiopathogenesis of AD. Several microbes, such as human herpesviruses, spirochetes, *Chlamydia pneumoniae*, and *Borrelia burgdorferi*, have been proposed as triggers of AD [70]. Infections may induce the generation of Aβ in the brain [71]. The antiviral property of Aβ could protect the brain from infection [72].

Oxidative Stress

Oxidative stress (OS) plays a critical role in AD pathogenesis [73,74]. Oxidative stress promotes both tau hyperphosphorylation and Aβ deposition and then the loss of synapses and neurons [75].

Prions of Aβ and Tau

Prions are defined as host-encoded proteins that adopt alternative conformations and are self-propagating [76]. Both Aβ and tau are found to have prion features in AD [77]. Tau prions has been shown to spread throughout the brain along known neuroanatomical pathways over the course of AD [78].

The Gut Microbiota

Activated proinflammatory cytokines by the altering of gut microbiota increase intestinal permeability and lead to insulin resistance that is associated with AD [79]. Aβ oligomers translocating from the gut to the brain contribute to the onset of AD and neuroinflammation [80]. *Eubacterium rectale*, *Porphyromonas gingivalis*, and *Lactobacillus rhamnosus* are important in the origination of AD [81-85].

Astroglia

Astrocytes are key components of the neurovascular unit (NVU) [86]. In pathological situations, astrocytes turn into reactive astrocytes undergoing a series of morphological and functional alterations. Reactive astrocytes are typically found in the region with high Aβ or tau pathology in postmortem AD brains [87-89]. Reactive astrocytes release cytokines, inflammatory factors, and reactive oxygen species (ROS), thus contributing to neuroinflammatory changes in AD [90].

TREM2

Genome-wide association studies (GWAS) identified the gene triggering receptor expressed on myeloid cells 2 (TREM2) that

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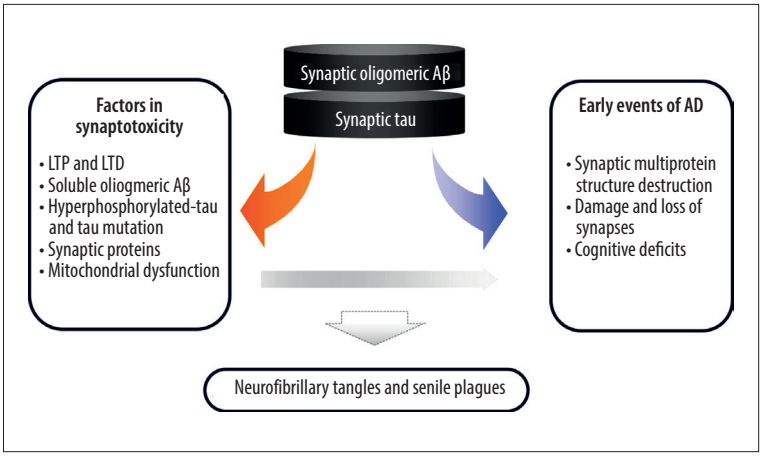

Figure 1. Feedback mechanisms of synaptic Aβ and tau in the progress of Alzheimer's disease. Soluble oligomeric Aβ is the primary cause of synaptic dysfunction, whereas synaptic tau is the mediator in the progress. They locate in the synapse and work with receptors, synaptic proteins, and mitochondria to cause synaptic dysfunction, and ultimately lead to cognitive deficits. During the pathogenesis of AD, this is the early event, which occurs long before the formation of neurofibrillary tangles and senile plaques.

are associated with a high risk of AD [91]. TREM2, a microglia surface receptor, is especially highly expressed in microglial cells [92,93]. The R47H and D87N TREM2 mutation confer significant risk of AD in humans [91,94]. Soluble TREM2 levels are related to levels of total tau and phospho-tau in cerebrospinal fluid (CSF), but not to Aβ1-42 levels in AD brains [95-98].

Synapse-Based Therapy in Alzheimer's Disease

Synaptic deficiency is an early sign of AD pathogenesis and is closely correlated with the cognitive decline in AD. Oligomeric Aβ or soluble hyperphosphorylated tau interacts with cell surface receptors, scaffold proteins, or intracellular signaling molecules to destroy synaptic structure and function. Therefore, therapeutic strategies targeting synaptopathy at the early stage of AD may ameliorate pathology in AD [99]. To date, no effective intervention alleviating Aβ load has been developed, although oligomeric Aβ is the main factor involved in the synaptotoxicity in AD. It is more important to find Aβ species-specific interventions [100]. For example, Aβ*56 identified in the brains and CSF of people with normal cognitive function triggers a specific intracellular response to hyperphosphorylated tau through CaMKIIα but not GSK-3β or Cdk5. Aβ*56 or its downstream signaling cascades may be promising targets for early-stage AD interventions [101]. Moreover, because APP processing is regulated by neuronal activity, enhancing synaptic function, which prevents synaptic dysfunction and reduces Aβ production, could have a dual beneficial effect in reversing AD progression [3]. Since tau is more closely associated with cognitive decline than Aβ in the AD brain, great efforts have been made to explore tau-focused therapeutic interventions [102], and approaches focusing on pathological tau removal have been developed. Antibody-mediated [103-106] or anti-sense oligonucleotide (ASO)-mediated tau reduction [107] successfully reduced synaptic dysfunction and cognitive deficits in AD animal models. Drugs which aim at new molecular targets related to dendritic and postsynaptic tau need more exploration. Since the synaptotoxicity of Aβ is mediated by receptor complexes, multiple strategies have been developed to target these cell surface proteins and their downstream signaling pathways. Extracellular regulation of the activity of these receptors makes them more accessible targets for AD treatment.

Conclusions

Synaptic defects closely associated with cognitive decline are considered the early events in AD pathogenesis. Based on a large number of studies, soluble Aβ oligomers appear to be the primary cause of synaptic dysfunction, and synaptic tau seems to be the indispensable mediator in the process (**Figure 1**). Aβ oligomers affect LTP, LTD, and synaptic death by acting on receptors, unbalancing calcium homeostasis, and activating caspases and calcineurin. Soluble hyperphosphorylated tau impairs synaptic function by interacting with scaffold proteins, cell surface receptors, or intracellular signaling molecules. Aβ or phosphorylated tau also triggers synaptic degeneration via damaging and transportation of mitochondria.

However, further investigations are still needed to answer key questions: 1) Why have therapeutic strategies targeting Aβ all failed if Aβ oligomers are the initiator of AD's early pathology? 2) Why is synaptic tau required in the synaptotoxicity attributed to Aβ? In the future, a combination therapy targeting synaptic tau and Aβ together may be a potential therapeutic approach for AD patients at the very early stage.

Declaration of Figure Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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