The Role of Tau Protein Aggregation in Alzheimer's Disease Progression

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ABSTRACT:

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease associated with memory loss and progressive decline in cognitive ability. Tau protein aggregation has emerged as an essential factor in the progression of AD. While the amyloid hypothesis suggests that the accumulation of Amyloid beta (Aβ) is what instigates the progression of AD, tau protein aggregation has been shown to have higher correlation rates with the progression of AD. The spread of tau pathology follows a predictable pattern, correlating strongly with disease progression. Unlike amyloid-β plaques, which appear early and are not exclusive to AD, tau pathology is more closely associated with neurodegeneration and clinical symptoms. This literature review examines the role of tau protein aggregation in AD progression, highlighting its mechanisms, impact on neuronal function, and therapeutic targets.

Methods

This study utilized findings from clinical research and PET imaging. A thorough literature review of peer-reviewed articles and scientific journals was conducted, with the majority of the articles being pulled from the PubMed database. The inclusion criteria for this study were that studies should have explored the molecular mechanisms of tau protein aggregation in AD, examined correlations between tau protein aggregation and AD progression, included research on PET imaging and Braak staging, and evaluated therapeutic strategies to combat tau pathology. Articles were also screened to ensure a publication date no earlier than 2000, with the exception of an explanation of Braak Staging.

Results

The results of this review indicate that hyperphosphorylation of the tau protein causes neurofibrillary tangles (NFTs), which disrupts neuronal signaling and function. The transneuronal hypothesis states that tau spreads from neuron to neuron, causing neurodegeneration and disease progression. Additionally, PET-based Braak staging is a staging system that marks the progression of tau-based NFT pathology and correlates it with the staging/progression of AD. Therapeutic strategies that target tau include kinase inhibitors and

immunotherapy vaccines. Both strategies require additional confirmation, but seem to be promising.

Discussion
Further research on this topic should include combination therapies, search for biomarkers, and imaging techniques that focus specifically on capturing visualizations of tau. Understanding the mechanisms driving tau aggregation and propagation offers valuable insights into the pathophysiology of Alzheimer's disease and highlights potential therapeutic targets aimed at halting or reversing neurodegeneration.

INTRODUCTION:
Alzheimer's Disease (AD) is the biological process that begins with the appearance of a buildup of proteins in the form of amyloid plaques and neurofibrillary tangles in the brain [1]. AD is associated with memory loss, spatial disorientation, and gradual deterioration of intellectual capacity [2]. According to the Alzheimer's Association, an estimated 6.9 million Americans aged 65 and older were living with AD in 2024, and almost two-thirds of Americans with AD are women [3] . Two major hallmarks of AD include extracellular amyloid plaques made of amyloid-β (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau [4].

In recent years, tau aggregation has garnered more attention than amyloid plaques in Alzheimer's research. There are two major hypotheses that explain Alzheimer's disease aggregation. They are Amyloid hypothesis and Tau Hypothesis. The amyloid hypothesis states that Aβ aggregation triggers the chain of events that ultimately result in AD pathology and symptoms, including tau protein aggregation and hyperphosphorylation [5]. Despite evidence for this hypothesis, tau tangles can be seen in the brains of patients with no Aβ pathology and very mild dementia, and tau pathology correlates more closely with AD severity and progression than Aβ plaque load does [6].

Furthermore, the tau protein and its aggregation in the brain have received more attention than amyloid plaques in recent years partly because autopsies of Alzheimer's patients have revealed that tau is concentrated precisely where brain atrophy is most severe [7]. In this context, another relevant hypothesis is the transneuronal spread hypothesis, in which tau proteins act as toxic agents and propagate along connected neurons [8]. The transneuronal spread hypothesis essentially conveys that Alzheimer's disease progresses due to the spread of tau protein along neuronal connections, triggering a series of damage leading to disease progression. This hypothesis sheds light on the potential processes that direct the advancement of AD as well as other tau-related illnesses. It also emphasizes the importance of understanding coordinated activity between neurons in disease recognition.

Additionally, tau PET imaging has predicted how much atrophy would develop in the brain, and in what specific regions, evidencing that tau is a contributing factor to AD [7]. The goal of this paper is to evaluate the role of tau protein aggregation in the progression of Alzheimer's disease by focusing on its mechanisms, therapeutic targets, and correlation between tau aggregation and AD progression.

METHODS:

A thorough literature review of peer-reviewed articles and scientific journals was conducted to write this paper. The search was performed in December of 2024. The inclusion criteria for this study were that studies should have explored the molecular mechanisms of tau protein aggregation in AD, examined correlations between tau protein aggregation and AD progression, included research on PET imaging and Braak staging, and evaluated therapeutic strategies to combat tau pathology. Articles were also screened to ensure a publication date no earlier than 2000, with the exception of an explanation of Braak Staging. Eligible articles were reviewed in detail in order to convey strong understanding and key information of tau biology, pathology, and aggregation mechanisms.

RESULTS:

The tau protein is a microtubule-associated protein, predominantly expressed in the neurons and closely associated with the proper functioning of the cytoskeletal network in terms of microtubule assembly. Tau protein is encoded by the MAPT (Microtubule associated protein tau) gene on human chromosome 17 and has four regions: the N-terminal, the proline-rich, the repeat, and the C-terminal [9]. Tau does not have a well-defined structure and is highly soluble and hydrophilic [9]. Tau has six isoforms in the adult human brain and they vary in size and amino acid composition [10]. Typically, its function is to stabilize neuronal microtubules under normal physiological conditions [10].

During AD, tau becomes abnormally hyperphosphorylated, which ultimately causes the microtubules to disassemble, and the free tau molecules aggregate into paired helical filaments [2]. The filaments tangle together and then disrupt the transport system of neurons and lead to neuronal apoptosis (neuron death) [11]. A tauopathy is a neurodegenerative disorder that is caused by abnormal tau protein aggregates in cells [12]. Alzheimer's is therefore classified as a tauopathy. MAPT can undergo a number of post-translational modifications including phosphorylation [13].

When tau is hyperphosphorylated, it dissociates from microtubules and aggregates into paired helical filaments (PHFs) and NFTs [14]. The tau hypothesis indicates that tau tangle pathology precedes Aβ plaque formation and that tau phosphorylation and aggregation is the primary cause of neurodegeneration in AD [15]. Tau can receive various post-translational modifications. These include phosphorylation, methylation, acetylation, etc [16]. This is supported by Haj-Yahya and

Lashuel, who state that there is an abundance of evidence that suggests post-translational modifications regulate the function(s) of tau, including its subcellular localization, clearance, aggregation, toxicity, and pathological spreading [17].

This is a significant property of tau because tau then has the potential to have less of an affinity to microtubules, which will then result in the destabilization of the neuronal cytoskeleton [18]. Tau aggregates and forms neurofibrillary tangles (NFTs) inside neurons when an extreme amount of phosphates is added to the protein [19]. This is an abnormal process known as hyperphosphorylation. The hyperposphorylation of tau can also be caused by impaired brain glucose and metabolism [20].

Normal Tau has regions that are positively charged and microtubules have negatively charged surfaces [21]. This opposite charge attraction is crucial to bind tau to microtubule, helping stabilize the structure [21]. Phosphorylation adds phosphate groups to specific amino acids on tau. The phosphate groups are negatively charged and hence hyperphosphorylation drastically increases the negative charge on tau, thereby reducing the electrostatic attraction between tau and microtubules [20]. As a result tau detaches from microtubules which leads to impaired neuronal structure [20]. The free tau is now prone to misfolding and aggregation.

Tau monomer is the normal Tau that binds microtubules via positive charges [22]. Due to hyperphosphorylation, Tau loses affinity for microtubules and misfolds [22]. Two misfolded tau molecules associate to form a dimer [22]. This is a critical point where aggregation begins [23]. Dimers are the basis for large aggregates. Dimers combine with additional tau monomers to form small, soluble oligomers that are highly toxic [23]. These oligomers disrupt synaptic function and possibly spread to other nearby neurons [23]. Oligomers organize to protofibrils which then twist into paired helical filaments(PHFs) [24]. PHFs are insoluble and less toxic than soluble oligomers. PHFs aggregate to form Neurofibrillary tangles (NFTs) [24]. NFTs interfere with cell function, ultimately causing neuronal death.

Tau propagation is a prion-like process. Misfolded tau acts as a seed initiating aggregation and promotes formation of dimers, PHFs and NFTs [25]. Intracellular tau aggregates interfere with neuronal structure and transport [25]. Tau is released into extracellular space via passive leakage from dying cells and active secreation [25]. Neighbouring neurons internalize tau. Internalized seeds convert native tau into misfolded forms and the newly misfolded forms continue the cycle thus spreading pathology from neuron to neuron in anatomical neural pathways [25].

Braak Stage describes the progressive spread of tau pathology in the human brain offering clinical relevance [26]. This matches prion-like propagation along neural networks. Understanding tau propagation helps us predict disease progression based on spread patterns and develop therapies. Heiko Braak and his team developed a staging system that categorizes the

spread of neurofibrillary tangles (NFTs) in the brain. It is used to track the progression of AD based on the topographical distribution of tau pathology [27].

The progression of AD can be broken down into seven stages [28]. This development is closely aligned with Braak staging, a semiquantitative measure of the severity of NFT pathology [28]. This staging system has six stages (Stage I to Stage VI), each marking the progression of tau-based NFT pathology from least to greatest within the medial temporal lobe memory circuit in AD [28]. Stage 1 typically occurs before symptoms appear, while stages 2 and 3 are associated with memory loss [29]. Postmortem work has established that the earliest cortical tau pathology and neuronal loss in AD occurs in the entorhinal cortex (located in the medial temporal lobe), likely contributing to memory impairment [29].

Stage 4 includes other cognitive impairments, such as difficulty with language, organization, and calculations [29]. Stages 5 and 6 is where symptoms intensify greatly, and patients can experience strong emotional changes and significant decreases in independence [29]. Stage 7 culminates in a lack of physical control, where the destruction of brain cells eventually reduces mobility and increases vulnerability to infections [29].

Table 1.

Braak Stage	Brain Region Affected	Clinical correlation
I-II	Entorhinal cortex, transentorhinal region	Early cognitive impairment
III-IV	Hippocampus, limbic system	Mild cognitive impairment including memory deficits
V-VI	Association areas of neocortex	Severe cognitive impairment including language and executive functions

The correlation between Tau aggregation and Alzheimer's disease progression can be supported by evidence from the spatial spread of tau pathology and biomarkers like tau PET imaging, cerebrospinal fluid (CSF) tau levels, and phosphorylated tau in plasma [29].

According to a study published in 2021 by Chen et al, significant cognitive decline was first observed in stage 1 of a topographic PET staging system when tau levels only increased in transentorhinal regions [30]. Furthermore, rates of cognitive decline and clinical progression

accelerated from stage 2 to stage 3 and stage 4, and highly accumulated tau in temporal regions independently led to cognitive deterioration [30].

This idea has been supported in other works as well, including an article published by Macedo et al in 2024, which aimed to investigate the association between PET-based Braak stages and functional impairment and assess whether PET-based Braak staging predicts a longitudinal decline in the performance of activities of daily living [31]. The results of this study suggest that functional impairment increases with the severity of tau accumulation. These findings also indicate that PET-based Braak staging is a good predictor of functional impairment in the AD continuum, and also provide evidence for the clinical significance of the PET-based Braak staging framework. Both studies by Chen et al and Macedo et al reinforce the idea that tau accumulation/pathology serves as an important biomarker for cognitive decline, and increases as the disease progresses.

A study by the Science Translational Medicine Journal, discussed a studying consisting of 32 patients in the early stages of AD who were tested to identify whether β-amyloid and tau-PET could predict brain atrophy measured using longitudinal magnetic resonance imaging acquired at the time of PET [32]. Quantitative analysis showed that the intensity of tau-PET, but not β-amyloid–PET, signal predicted the rate of subsequent atrophy [32]. The data supported disease models in which tau pathology is a major driver of local neurodegeneration and highlighted the relevance of tau-PET as a precision medicine tool to help predict individual patient's progression [32].

Similarly, a research study conducted with 20 patients with AD to investigate the topographical distribution of tau pathology and its effect on patients with Alzheimer's disease concluded that the accumulation of pathologic tau is more closely related to functional and structural deterioration in the AD spectrum than β-amyloid [33]. These quantitative findings from reputable studies outline the strong correlation between tau aggregation and Alzheimer's disease progression.

DISCUSSION:

The findings from this literature review indicate support for the idea that tau protein aggregation is a strong contributor to the progression of AD. The aforementioned prion-like propagation of the tau protein further suggests that tau aggregation is an active contributor to AD and other neurodegenerative diseases due to its predictable progression through particular regions of the brain that is consistent with Braak staging. While there is currently no cure for AD, recent advances in the understanding of tau protein aggregation and its role in AD progression, have led to therapeutic methods that aim to diminish its effects on AD progression. [34]

There have also been several strides in the establishment of tau protein's importance as a biomarker and therapeutic target. Specifically, vaccines such as ACI-35 and AADvac-1 serve as hopeful methods of slowing AD progression [34]. ACI-35 is a liposome-based vaccine that contains 16 copies of a synthetic tau fragment phosphorylated at S396 and S404, and is currently used in Phase 1 clinical trials for the treatment of AD in the USA, while AADvac-1 is an axon peptide 108 conjugated to KLH that is formed of a synthetic peptide that originates from amino acids 294–305 of the tau sequence that is used in Phase 2 clinical trials for the treatment of AD in the USA [34]. Both are vaccines that aim to adjust the immune system.

Furthermore, gene editing & epigenetic modulation methodologies aim at reducing tau pathology and neurodegeneration by disrupting or modifying genes involved in tau aggregation, an example of this is CRISPR-Cas9. Overall, the progression of AD is driven by the accumulation of tau protein, and continued research into the protein's role in AD can eventually lead to improved outcomes for AD patients.

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