

# Interplay of Tau and Amyloid Beta Pathologies in Alzheimer's Disease

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## ABSTRACT

Alzheimer's is a progressive neurodegenerative disease that is associated with cognitive decline and dementia. It is characterized by the buildup of beta-amyloid ( $A\beta$ ) plaques and neurofibrillary tau tangles in the brain. The  $A\beta$  plaques are formed through insoluble  $A\beta$  fragments clumping together in between neurons and blocking synaptic function. On the other hand, neurofibrillary tau tangles are formed through the misfolding of tau monomers which then accumulate within neurons. Although original research focused on the two components separately, recent research has attempted to view the interplay between  $A\beta$  and tau to figure out the impact and discover potential treatments for Alzheimer's. A lot about Alzheimer's is still unknown and we are still figuring out how exactly the plaques and tangles are created. Alzheimer's currently does not have a cure, but there are FDA-approved treatments that can differ depending on the stage of Alzheimer's. These medications are synthesized to either slow disease progression or alleviate the symptoms temporarily. The objectives of this paper are to look into the relationship between the beta-amyloid plaques and the tau tangles, explore their combined impact, and consider the implications of their interactions that will potentially help us treat Alzheimer's in the future.

## Introduction

Alzheimer's disease (AD) is a neurological condition that is deadly and poses a significant challenge for the affected people and our society at large. It has risen to be the sixth most common cause of death in the United States of America. It affects more than 6 million Americans annually. Dr. Alois Alzheimer made the first scientific discovery of Alzheimer's. He characterized Alzheimer's as a steady decline in memory and cognitive function. Neurofibrillary tau tangles and amyloid beta plaques in the brain are the hallmark signs of Alzheimer's disease.



**Figure 1:** Normal Brain (Left) vs. Alzheimer's Brain (Right)

Beta-amyloid ( $A\beta$ ) plaques and neurofibrillary tangles (NFTs) are the two main features of Alzheimer's disease (AD). The amyloid precursor protein (APP), which is broken down through proteolytic cleavage, creates  $A\beta$  plaques that end up impairing neuronal function in Alzheimer's disease. On the other hand, tau plays a crucial role in neurons by maintaining their structure through the stabilization of microtubules.

In AD, the abnormal hyperphosphorylation of the tau protein causes tau to separate from microtubules. This also starts the formation of neurofibrillary tangles.

Recent research suggests an interaction between A $\beta$  and tau. While A $\beta$  aggregates can induce the misfolding and aggregation of tau, tau tangles can further increase A $\beta$  accumulation and toxicity. This mutual relationship highlights how their interactions drive neurodegeneration and cognitive decline in Alzheimer's. By looking into the interplay between A $\beta$  and tau pathologies, we can explain the underlying workings of AD and discover potential therapeutic targets to treat and hopefully disrupt and halt the disease's progression.

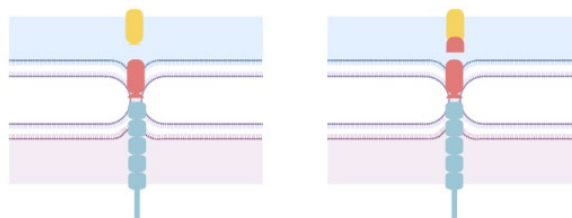
In this research paper, I aim to investigate the relationship between A $\beta$  and tau in AD.

## Role of Amyloid Beta in Alzheimer's

The amyloid hypothesis is currently the most accepted model in comprehending how Alzheimer's disease works. The theory suggests that amyloid-beta (A $\beta$ ) plays a vital role in the progression of Alzheimer's and A $\beta$  buildup creates plaques which is how the disease manifests in patients.

### Basics of Amyloid-Beta

A $\beta$  comes from the amyloid precursor protein (APP), a type 1 membrane protein with diverse biological functions, including neuronal development, signaling, and intracellular transport. APP is expressed in numerous tissues, and it has a significant localization in neuronal synapses. APP consists of a large N terminus and a short C terminus and is a member of a more prominent protein family. APP undergoes a process known as proteolysis, which is where enzymes break down peptides into smaller fragments.  $\beta$ -secretase,  $\alpha$ -secretase, and  $\gamma$ -secretase all play a role in cutting APP and this is what leads to the generation of A $\beta$  peptides.



**Figure 2:** Amyloid Precursor Protein Cuts:  $\beta$ -secretase cuts in the amyloidogenic pathway (left) vs  $\alpha$ -secretase cuts in the non-amyloidogenic pathway (right)

There are three different locations where APP can be cut. The N-terminal of the A $\beta$  domain using the  $\beta$ -secretase, the C-terminal of the A $\beta$  domain using the  $\gamma$ -secretase, as well as within the A $\beta$  domain using  $\alpha$ -secretase. While  $\beta$ -secretase cuts happen within endosomes through the amyloidogenic pathway,  $\alpha$ -secretase cuts occur within the plasma membrane through non-amyloidogenic pathways. This difference in cuts creates increased A $\beta$  levels with APP that is cut using  $\beta$ -secretase. Additionally, with the  $\beta$ -secretase cut, insoluble A $\beta$  fragments are created compared to the soluble A $\beta$  fragments made using the  $\alpha$ -secretase. The insoluble A $\beta$  fragments form plaques that block receptors and this creates an interference in neuronal communication as well as a stimulation of immune responses and inflammation.

The hallmark feature of AD is the accumulation of A $\beta$  peptides in specific brain regions, notably the hippocampus, and neocortex. These aggregated A $\beta$  peptides form extracellular amyloid plaques which are characterized by dense cores of fibrillar A $\beta$ . Additionally, they are surrounded by dystrophic neurites and activated microglia. The

presence of amyloid plaques is believed to initiate a cascade of events contributing to neurotoxicity, neuronal dysfunction, and cognitive impairment.

### Spread of A $\beta$ Plaques

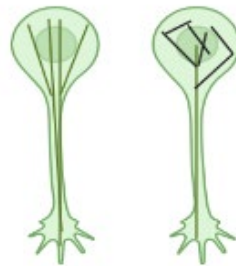
Recent research has provided further insights into the specific interplay between high baseline neuronal activity and amyloid beta (A $\beta$ ) plaques in Alzheimer's disease, shedding light on the underlying mechanisms involved. Studies used transgenic mouse models that expressed human amyloid precursor protein (APP) to demonstrate that the injection of A $\beta$  extracts can not only begin the formation of plaques but can also help A $\beta$  spread to axonal connected regions, including the entorhinal cortex and the dentate gyrus of the hippocampus. This propagation of A $\beta$  pathology along neuronal pathways highlights the importance of synaptic connections in the progression of Alzheimer's disease.

### Calcium Signaling

In addition to synaptic alterations, the presence of A $\beta$  has been implicated in the dysregulation of calcium signaling within neurons. Soluble A $\beta$  oligomers can elevate intracellular calcium levels. Unbalanced calcium levels disrupt the delicate balance that is required for proper neuronal functioning. Excessive calcium can trigger other events, including synaptic dysfunction, impaired neurotransmitter release, and activation of detrimental cellular processes.

### Loss of Dendritic Spines

Scientists have investigated the effects of A $\beta$  fragments during the early stages of Alzheimer's on neuron health. These fragments have been shown to start neuronal degeneration because they create synaptic damage which, in turn, causes the loss of dendritic spines. Dendritic spines are important for synaptic communication and plasticity. The disruption of this synaptic structure contributes to the cognitive impairments that are seen in the disease.



**Figure 3:** Normal Dendritic Spine (Left) vs. Alzheimer's Impaired Dendritic Spine (Right)

### Neuronal Health and A $\beta$

Studies have also identified that A $\beta$  can affect the function of cellular components vital for neuronal health. A $\beta$ -induced disturbances have been observed in microtubules. Microtubules are essential for maintaining the proper transport of cellular materials along neuronal processes. Disruptions to microtubule stability can compromise axonal transport and impair the delivery of vital nutrients and signaling molecules to synapses. Mitochondria, the powerhouses of cells, are also affected by A $\beta$ . Research has shown that A $\beta$  can lead to mitochondrial dysfunction, which, in turn, causes impaired energy production and increased production of reactive oxygen species. Such mitochondrial impairments contribute to cellular oxidative stress, worsen neuronal damage, and promote neurodegeneration.

The precise mechanisms underlying the toxic effects of A $\beta$  in Alzheimer's are not fully understood, though several hypotheses have been proposed. One theory, based on dendritic spine research, suggests that soluble forms of A $\beta$  interfere with synaptic function which, in turn, disrupts neuronal communication. Another hypothesis implicates A $\beta$  in neuroinflammation, where activated microglial cells release pro-inflammatory cytokines which, when administered to humans produce fever and tissue destruction, but in the brain can lead to neuronal damage or cell death. Furthermore, A $\beta$  has been found to disrupt various cellular processes including mitochondrial function, oxidative stress, and calcium homeostasis, as mentioned above, all of which contribute to neuronal dysfunction and eventual cell death.

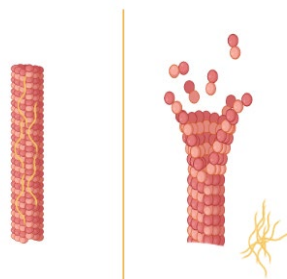
Understanding the intricate mechanisms around A $\beta$  generation, aggregation, and toxicity is crucial for developing effective therapeutic strategies to target AD. Various approaches, such as immunotherapies aimed at clearing A $\beta$  from the brain, inhibition of A $\beta$  production through secretase inhibitors, and modulation of A $\beta$  aggregation and clearance pathways, have shown promise in preclinical studies. However, translating these approaches into effective treatments for AD patients remains a challenge.

## Role of Tau in Alzheimer's

Tau is a microtubule-associated protein. It plays a pivotal role in Alzheimer's disease (AD). Tau serves as an essential component in axonal stabilization, neuronal development, and polarity. Its function is to stabilize axonal microtubules, and it provides quick transit pathways for vesicles. Tau is encoded by the microtubule-associated protein tau (MAPT) gene on chromosome 17. Mutations in the MAPT gene have been linked to frontotemporal dementia, a neurodegenerative disorder characterized by the accumulation of tau pathology. These mutations increase the formation of tau tangles and decrease the stability of microtubules, intensifying the neurodegenerative process.

### Formation of Tau Tangles

The process of tau aggregation starts with the misfolding of tau monomers. These monomers eventually form tau dimers. Subsequently, the addition of polyanions leads to the transition of tau into beta structures, in hexapeptide motifs. This structural transformation allows the assembly of paired helical filaments (PHFs) which are the core component of neurofibrillary tangles (NFTs). Researchers have identified PHF inhibitors to stop the aggregation. Additionally, other chemicals such as Congo red and thioflavin, have been discovered to be effective when observing and studying tau aggregation. A technique known as atomic force microscopy has been used to observe tau. In this technique, soft polymer brushes around the core of tau fibers. Atomic force microscopy has allowed us to identify both the fatty basic rigid body of tau and the acidic outer core.



**Figure 4:** Normal Microtubule with Tau Support (Left) vs. Destabilized Microtubule with Tau Tangles (Right)

Tau undergoes various isoforms which are transcribed into nuclear RNA. It has specific regions like exons 2, 3, and 10. This can further be classified depending on the amount of carboxy-terminal repeat domain groups the tau

has. For example, exon 10 is sometimes known as tau 4R when it has four of these domain groups. A sign of the longest tau isoform in the central nervous system would be where there is a high number of leftovers which can be phosphorylated, but a low number of other proteins.

Tau is an unstructured protein that is primarily hydrophilic and highly soluble. The hexapeptide region of the tau protein is the only region where the protein is hydrophobic, making it partly responsible for aggregation. Because of its highly soluble character, unless assisted by something, tau does not aggregate by itself. Enzymes and kinases can modify tau which initiates the formation of tangles. In AD, tau undergoes abnormal modifications and accumulates in the form of neurofibrillary tangles (NFTs), which are aggregates in between the cells that disrupt normal cellular functions. As Alzheimer's progresses, these tangles increase, while the microtubules decrease creating chaos.

The spreading of neurofibrillary tau tangles in Alzheimer's can be categorized using the Braak stages. With this model, in steps 1 and 2, the tangles are clinically silent. However, as the disease progresses and it reaches steps 3 and 4, the tangles cause mild cognitive impairment. Finally, in the last two steps: 5 and 6, the tau tangles cause severe pathology.

## Effects of Tau Tangles

The pathological consequences of tau dysfunction are widespread. Normally, tau helps to stabilize the inside structure of neurons. Tau supports the insides of microtubules. Microtubules are responsible for a wide variety of functions, and the formation of tangles results in the destruction of microtubules which causes the impairment of transport of essential cellular components, such as vesicles and mitochondria, along the axons. This can lead to the disruption of the distribution of cellular components and compromise the synaptic network creating traffic jams and subsequent cell damage. Additionally, tau aggregates can cause damage to the nuclear pore complex. This ends up causing a crucial communication deficiency between the nucleus and the rest of the cell. These disturbances in cellular processes contribute to the progressive neurodegeneration observed in AD.

## Tau Aggregation and Impact on Cellular Function

Recent research has focused on developing therapeutic strategies to target tau pathology in AD. Studies utilizing transgenic animal models and genetic manipulations have demonstrated the potential of both pro-aggregation and anti-aggregation approaches. Pro-aggregation experiments involved enhancing tau aggregation in transgenic mice and worms which resulted in disease progression. On the other hand, anti-aggregation interventions prevented further aggregation and the animals observed maintained cellular health.

Additionally, studies using transgenic mouse models, such as rTg4510 mice, have shown that the accumulation of soluble oligomers of tau leads to memory loss, and this effect is reversible when tau transgene expression is suppressed. Lowering soluble tau levels has also improved deficits in mitochondrial distribution. These findings suggest that tau impairs neuronal function through other methods rather than just through their aggregation. These findings challenge the traditional view that tau pathology primarily exerts its detrimental effects through the accumulation of tau into neurofibrillary tangles. Instead, the destabilization of microtubules appears to play a significant role in impairing neuronal function.

In conclusion, tau, as a microtubule-associated protein, plays a significant role in AD pathology. This contributes to the formation of neurofibrillary tangles and subsequent neurodegeneration. Understanding the complex interplay between tau and other cellular components involved in AD pathology is crucial for developing effective therapeutic interventions. Explicating the structural characteristics of tau, its interactions with microtubules, and the factors influencing its aggregation can pave the way for developing novel treatments. Researchers aim to halt or slow down the neurodegenerative process by targeting tau pathology, providing potential therapeutic implications for addressing the cognitive decline in AD.

## Correlation between Beta-Amyloid and Tau in Alzheimer's

Amyloid beta and tau protein are the two main hallmarks of Alzheimer's. A $\beta$  forms plaques in between the neurons while tau forms neurofibrillary tangles (NFTs) within and between the neurons. Tau pathology and neurodegeneration are thought to be triggered by A $\beta$  accumulation. As A $\beta$  plaques and toxic oligomeric forms of A $\beta$  aggregate, it starts the hyperphosphorylation of tau. Additionally, tau can quicken A $\beta$  accumulation. As research has shown, the presence of neurofibrillary tangles leads to increased A $\beta$  plaques as well as A $\beta$  deposition. Both oligomeric forms of A $\beta$  and soluble tau have been found to contribute to synaptic dysfunction, neuron loss, and impaired cognitive function. This has been shown through both in vitro and in vivo studies. However, tau has been shown to aggregate before A $\beta$  as there is a stronger cognitive impairment associated with tau.

Biomarkers such as cerebrospinal fluid levels and imaging techniques can be used to monitor Alzheimer's progression in both research and clinical settings. Because of this, there are therapeutic strategies that target both A $\beta$  and tau. These strategies aim to target both A $\beta$  and tau at the same time in order to halt disease progression.

Studies have shown that abnormally phosphorylated tau can isolate normal tau and high molecular weight microtubule-associated proteins (HMW-MAPs), leading to the disassembly of microtubules. The association between tau and abnormally phosphorylated tau in AD does not result in the formation of filaments or tangles but instead, it disrupts microtubule assembly. APOE4, a genetic risk factor for AD, has been found to potentiate the effects of A $\beta$  on tau phosphorylation and the formation of tau tangles. The co-occurrence of APOE4 and A $\beta$  further increases the deposition of tau tangles, suggesting a synergistic effect between APOE4, A $\beta$ , and tau pathology.

### Relationship Between Beta-Amyloid and Tau

Transgenic mice have been important in studying the relationship between A $\beta$  and tau and exploring potential interventions. To investigate the role of tau in A $\beta$ -related cognitive deficits, researchers have conducted experiments using mouse models that express mutant APP (amyloid precursor protein) and tau knockout lines. By removing the misfolded tau in these mice, they found that the A $\beta$ -induced cognitive effects were prevented, and the occurrence of seizures was reduced. This highlights the role of tau in creating the cognitive issues associated with Alzheimer's as well as its significance in mediating the effects of A $\beta$  on synaptic function.

In human studies, soluble A $\beta$  oligomers derived from the brains of individuals with Alzheimer's disease have been shown to create neuron degeneration and hyperphosphorylation of tau. Interestingly, some individuals exhibit plaques and tangles in their brains but do not manifest dementia symptoms. This discrepancy suggests that tau pathology may differ between normal individuals and those with dementia.

### Alzheimer's Phosphorylated Tau vs. Microtubule-Associated Proteins

A study was conducted to explore the interaction between AD phosphorylated tau (AD P-tau) and microtubule-associated proteins (MAPs) using various methods. Rat brain cytosol was prepared from chilled brain tissue, and the Kopke method was employed to isolate AD P-tau and tau. Additionally, MAP1 and MAP2 were isolated from rat brain tissue to obtain high molecular weight MAPs. The binding of AD P-tau to MAPs was investigated through techniques such as vortexing, bath sonication, and radioimmunoassay. The analysis of the results involved multiple approaches, including protein determination, immunoblots, dephosphorylation, and electron microscopy. Notably, the study revealed that the coaggregation of HMW-MAPs and AD P-tau did not lead to the formation of tangles. Furthermore, it was observed that normal tau displayed a greater affinity for AD P-tau (45.7% bound protein) compared to MAPs (MAP1: 24%, MAP2: 30.7% bound protein). The direct association of AD P-tau with HMW-MAPs provided valuable insights into their interaction.

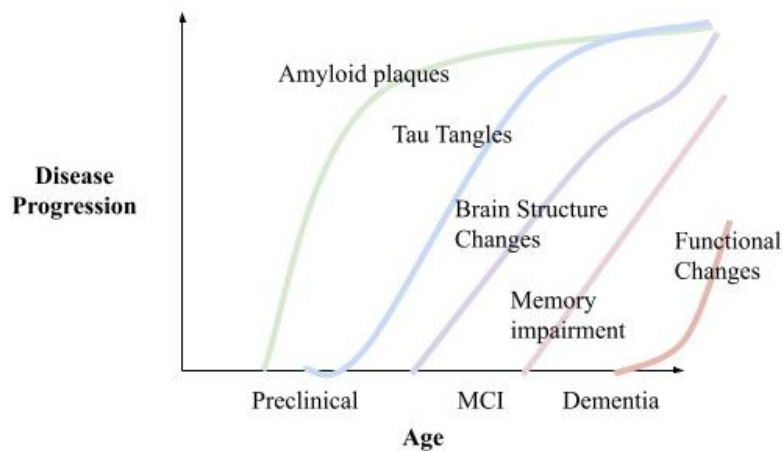
Moreover, APOE4 has been shown to modulate the association between A $\beta$  and tau, impacting the progression of both pathologies. Screening for the APOE4 allele is of importance in AD research and clinical settings, as its presence can influence the deposition of A $\beta$ , tau pathology, and cognitive decline.

## Methods

**Literature Review:** In order to compile all the information needed to investigate the beta-amyloid and tau interplay, a literature review was conducted where databases such as *PubMed* were scoured using keywords. Data was taken and analyzed from recent studies to uncover new patterns and insights.

**Data Analysis:** From the given studies, data was extracted and analyzed. This helped to provide a clearer general picture and the data formed the basis for understanding the interplay between A $\beta$  and tau.

## Results



**Graph 1:** Alzheimer's Progression with Age and Associate Effects

Through the research done, we see that there is a direct relationship between beta-amyloid plaques and tau tangles during Alzheimer's disease progression. From the graph above, we can see that after an exponential increase in the A $\beta$  plaques, the tau tangles begin to spread rapidly. As both key hallmarks increase throughout the disease, the patient enters the mild cognitive impairment stage (MCI) which is where the disease is normally diagnosed. Soon, the number of amyloid plaques and tau tangles plateau out as the brain structure changes and the memory begins to be impaired. Here, Alzheimer's patients may forget tiny bits of information from earlier that day such as where they kept their car keys or what they had for breakfast. Finally, they enter the last stage, which is dementia, and here, the patients are heavily mentally and physically impaired. Most of the time, people in these stages are placed in an Alzheimer's care home where they receive 24/7 care.

## Discussion

Although the past few decades of research have yielded valuable information about Alzheimer's, we still have some ways to go before we fully understand and can treat and cure neurodegenerative disorders. As we answer more questions, new unanswered questions pop up. Because both A $\beta$  plaques and tau tangles lead to synaptic loss, and since

synapses assist in the spread of Alzheimer's, there are a lot of questions about the exact mechanisms that contribute to the loss of synapses. A better understanding of how exactly the loss of synapses affects physical responses is important to better control Alzheimer's in patients. Additionally, the exact areas that the plaques and tangles spread to and the path they follow are not fully known. So, further research into how the synapses are affected in earlier stages of Alzheimer's and how they develop throughout the progression of Alzheimer's is needed to allow for interventions that target synaptic dysfunction and can pave the way for new treatment approaches.

Also, not all forms of A $\beta$  and tau are toxic. Hence, the question arises of separating the toxic and nontoxic forms of the pathologies in Alzheimer's. Answering this question will help more accurately target toxic structures. Especially since we do not know for sure if the toxic amyloid beta aggregates are soluble, more research needs to be done in that area. If they are soluble, then the current therapies may be harmful rather than beneficial to the Alzheimer's patient.

## Conclusions

In summary, the relationship between A $\beta$  and tau in Alzheimer's is complex and multifaceted. Both pathologies contribute to the neurodegenerative process and the impairment of cognitive function. Understanding the interplay between A $\beta$  and tau is crucial for developing effective therapeutic strategies that target both pathologies. Biomarkers related to A $\beta$ , and tau provide valuable insights into disease progression and response to treatment. Additionally, genetic factors like APOE4 play a modulatory role in the development and progression of A $\beta$  and tau pathology. Further research is necessary to unravel the intricate mechanisms underlying the relationship between A $\beta$  and tau that will help us identify novel therapeutic targets for Alzheimer's disease.

Overall, although amyloid beta and tau do seem to interact a bit, they don't interact as much as I thought in my initial hypothesis. They mostly develop their pathologies separately, but they can quicken or slow down the process of the other. They also affect each other through indirect methods. A $\beta$  plaques create cellular dysfunction which contributes to neurofibrillary tangles while the destabilization of microtubules with the tau tangles contributes to the creation of A $\beta$  plaques.

I hope continued study of these pathologies both separately and together will lead us to better diagnosis strategies and enable an earlier intervention in Alzheimer's allowing for a higher chance of the disease being cured. In addition, it is clear to me that effective therapies can be discovered when focusing on beta-amyloid and tau rather than targeting just one hallmark. Other neurodegenerative diseases such as Parkinson's and frontotemporal dementia have similar interactions between different factors and the research done between tau and A $\beta$  can also work as a blueprint for treating them.

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