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THE ROLE OF AMYLOID BETA PLAQUES AND TAU TANGLES IN THE PROGRESSION OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a progressive, currently irreversible brain disorder that destroys memory and thinking skills and is widely recognized as the most common category of dementia, a specific group of symptoms that affect memory, problem-solving, language, and behavior that can widely interfere with both daily life and standards of living. Alzheimer's disease is a disease that is primarily caused by a buildup of both amyloid and tau proteins in the brain. These proteins form plaques and tangles that block communication between nerve cells, which leads to their death. In addition, in terms of the manner in which Alzheimer's disease functions, Alzheimer's can be categorized as a progressive disease, through which symptoms start mild and gradually worsen over time. As of the present day, there is no cure for Alzheimer's disease, but medications and management strategies can temporarily improve symptoms. Out of all the factors that can widely affect the progression of Alzheimer's disease, such as genetics, vascular health, lifestyle, and age, something that can largely contribute to the overall development of the disease is none other than amyloid beta plaques and tau tangles.

KEYWORDS: Alzheimer's, Memory, Dementia, Amyloid Beta Plaques, Tau Tangles

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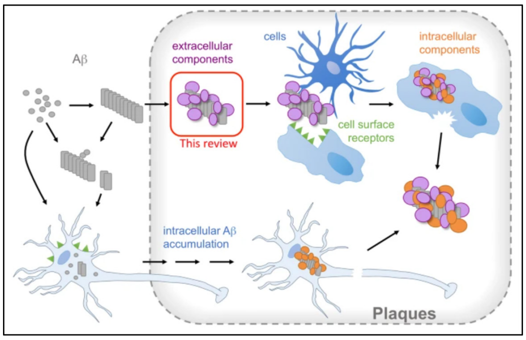
INTRODUCTION

In Alzheimer's disease, both amyloid beta plaques and tau tangles are considered key pathological markers. The accumulation of these abnormal proteins aggregating within the brain is believed to lead to the disruption of neuronal communication and function. Further leading to cell death and the progressive cognitive decline characteristic of the disease. Amyloid beta plaques primarily form outside neurons and can trigger inflammation. Meanwhile, tau tangles form inside neurons, impairing their internal transport system and causing damage to synapses.

Amyloid beta plaques are formed by the aggregation of a protein fragment called amyloid beta (Aβ). They can disrupt synaptic function by accumulating around synapses and interfering with signal transmission. They may also trigger inflammatory responses in the brain by activating microglia (immune cells). Recent research suggests that soluble forms of amyloid beta (oligomers) may be more toxic than the large plaques themselves.

Meanwhile, tau tangles are composed of abnormally phosphorylated tau protein, a protein normally involved in stabilizing microtubules within neurons. When tau becomes hyperphosphorylated, it loses its structural integrity and forms tangled fibers within the neuron. Therefore, these tangles disrupt the transport system within neurons, impairing the delivery of essential nutrients and causing neuronal damage. Furthermore, a widely accepted theory proposes that the accumulation of amyloid beta plaques initiates a cascade of events, leading to the production of abnormal tau and ultimately neuronal death. All of these are directly correlated with the implications of diseases such as dementia, or more specifically, Alzheimer's.



Source: BioMed Central (2021)

This paper aims to discern an investigation between the interplay of amyloid beta and tau tangles. This paper will examine how recent research suggests a complex interaction between amyloid beta and tau tangles, where the accumulation of one protein might contribute to the formation of the other, highlighting the need for therapies addressing both pathways and exactly how amyloid beta and tau tangles play a significant role in the progression of the disease

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by disrupting neuronal function, triggering inflammation, and ultimately leading to neuronal death.

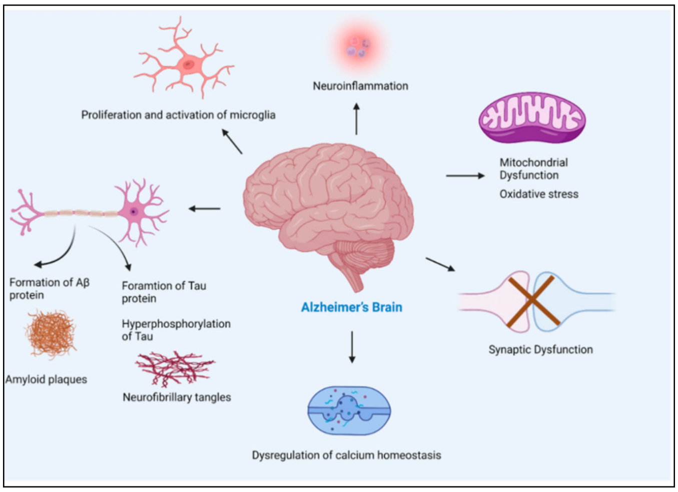
LITERATURE REVIEW

Amyloid Beta Plaques

Amyloid beta plaques are made up of beta-amyloid protein fragments that clump together. Beta-amyloid is a protein that comes from the breakdown of the amyloid precursor protein (APP), which is found in the fatty membrane around nerve cells. Beta-amyloid is chemically “sticky” and can misfold into different molecular forms. The beta-amyloid 42 form is especially toxic and more likely to form plaques. Amyloid plaques are mainly found in the brain’s grey matter, particularly in the amygdala and hippocampus. Amyloid plaques can disrupt cell function by blocking cell-to-cell signaling and triggering inflammation. They can also weaken blood vessel walls, increasing the risk of hemorrhage or rupture. They can also appear around blood vessels in the brain. Aβ is a protein that normally exists in several molecular forms, but in AD, abnormal levels of the protein clump together to form plaques. The beta-amyloid 42 form is thought to be particularly toxic. In its clustered form, Aβ can bind to receptors on nerve cells, which triggers a process that damages synapses. Synapses are the connections between nerve cells that are essential for memory, thought, and emotion processing. In addition, Aβ plaques cause cellular metabolic disorders, such as oxidative stress, ER stress, and cell cycle disturbances. These disorders further lead to neuronal apoptosis and synaptic deterioration. Plaques and tangles build up in brain regions associated with memory, learning, personality, and decision-making. This can lead to symptoms like impulsive decision-making and short-term memory problems.

In terms of the specific role of Amyloid beta plaques in relation to Alzheimer’s disease, the proteins are considered a key hallmark of Alzheimer’s disease, as their accumulation in the brain, formed from the protein fragment beta-amyloid, is strongly associated with the progression of the disease, disrupting communication between neurons and contributing to cognitive decline by damaging synapses and potentially triggering neuroinflammation; essentially, the buildup of these plaques is thought to be a major factor in the development and progression of Alzheimer’s disease. In terms of its formation, Beta-amyloid is a naturally occurring protein fragment, but in Alzheimer’s patients, it abnormally accumulates and clumps together to form plaques between neurons.

In addition, another notable aspect is the existence of a specific form of beta-amyloid, known as Aβ42, which is considered particularly toxic due to its propensity to aggregate into plaques. These plaques can disrupt the normal functioning of neurons by interfering with synaptic transmission and causing cell damage. Therefore, this leads to the prevailing theory, known as the “amyloid cascade hypothesis,” which suggests that the accumulation of amyloid beta plaques is the primary initiating event that leads to further neurodegenerative changes in Alzheimer’s disease. Aβ has been a primary target for AD drug development, but repeated clinical trial failures have cast doubt on the amyloid cascade hypothesis. However, more recent trials have shown success and have provided some degree of reassurance. A proper diet and regular exercise may also help decrease the risk of Alzheimer’s and slow disease progression. In addition, the the U.S. Food and Drug Administration (FDA) has approved several drugs to treat Alzheimer’s disease that target amyloid beta plaques, including, Lecanemab, which has been approved for early Alzheimer’s disease, Leqembi was granted accelerated approval by the FDA. As well as Donanemab, which has been approved for early Alzheimer’s disease, donanimhaber is marketed under the name Kisunla. It’s administered as a once-monthly intravenous (IV) infusion. And finally, Aducanumab which has been approved for early Alzheimer’s disease, aducanumab is an anti-amyloid antibody. These drugs treat early Alzheimer’s by reducing amyloid plaques. Studies have shown that these drugs can slow the progression of cognitive decline over extended periods of time.

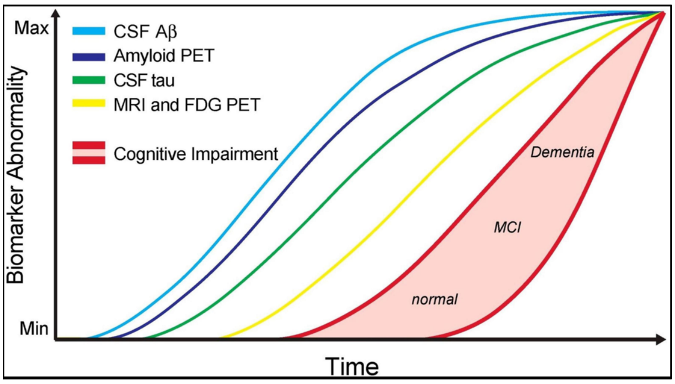


Source: MDPI (2022)

Tau Tangles

Tau tangles are thread-like structures that form inside neurons when tau proteins clump together. Tau is a protein that normally stabilizes microtubules, which help neurons maintain their shape and transport nutrients and molecules. In Alzheimer’s, abnormal chemical changes cause tau to detach from microtubules and form tangles. They are a hallmark of Alzheimer’s disease and other neurodegenerative diseases. Tau is a protein found in the axons of nerve cells that helps form microtubules. In healthy neurons, tau binds to and stabilizes microtubules, which help transport nutrients and molecules within the cell. When tau tangles form, the microtubules can no longer transport nutrients and other essential substances in the nerve cells, which eventually leads to cell death. Tau proteins are found inside the axons of neurons, where they stabilize microtubules that help transport nutrients and molecules. Within Alzheimer’s disease, chemical changes cause tau to detach from microtubules and clump together to form tangles. These tangles can spread from cell to cell and are toxic to neurons, causing them to die. Therefore, the accumulation of tau tangles damages the microtubules that support neurons, which disrupts communication between neurons. This disruption is what causes the thinking difficulties that are a symptom of dementia. Tau tangles start in the brainstem and spread to the entorhinal cortex and hippocampus, which are key regions for memory.

The amount of tau in the brain is linked to the stage and severity of the disease. Tracking tau levels can help predict and indicate cognitive decline. In addition, the presence of tau tangles is positively correlated with signs of Alzheimer's, meaning more tangles usually mean more symptoms. Therefore, the levels of a specific form of tau in the cerebrospinal fluid can track the amount of tau tangles in the brain and the degree of cognitive decline. Tau-based drugs may be beneficial for people in the later stages of the disease when tau tangles play a crucial role. Due to the fact, that experimental drugs have been developed that can reduce the toxic changes in tau proteins. In addition, brain imaging can also be beneficial as it can reliably predict the location of future brain atrophy in Alzheimer's patients based on the spread of tau tangles.

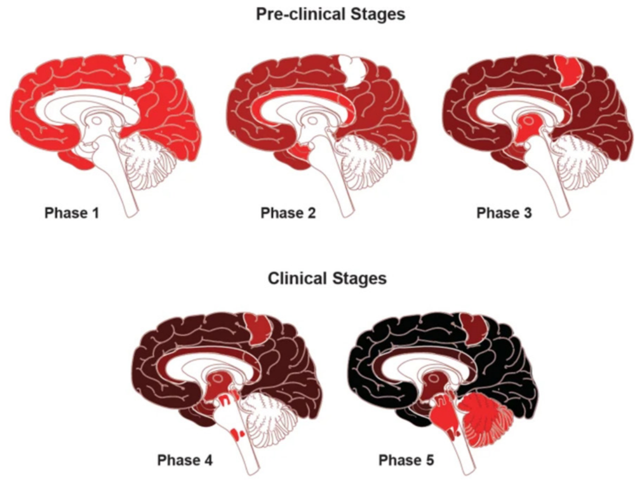


Source: Frontiers Media (2022)

Medications and Therapies

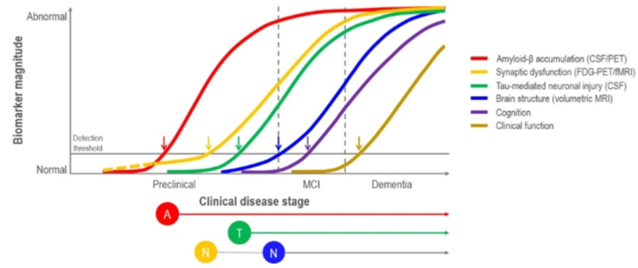
Some medications and therapies that target amyloid beta plaques and tau tangles in Alzheimer's disease include Lecanemab and donanemab, ANAVEX®2-73 (Blarcamesine), AV 1959D, Gantenerumab and solanezumab, and Crenezumab. Lecanemab and Donanimhaber FDA-approved immunotherapy drugs are given as IV infusions every two weeks and four weeks, respectively. They reduce amyloid plaques in the brain and may modestly slow memory decline. ANAVEX®2-73 (Blarcamesine) is a drug that targets sigma-1 and M1 muscarinic receptors and has been shown to reduce amyloid and tau pathologies in mice. A Phase 2B/3 study showed that blarcamesine significantly reduced cognitive decline in patients with early Alzheimer's. AV 1959D is a DNA-based vaccine that triggers an immune response against beta-amyloid. Gantenerumab and solanezumab are anti-amyloid antibodies that reduce certain biomarkers of Alzheimer's, such as brain cell damage and tau levels. Finally, Crenezumab is an anti-amyloid antibody that does not prevent or slow cognitive impairment in people with autosomal dominant Alzheimer's disease (ADAD).

Fig. 1: Traditional neuropathological phases of amyloid-β deposition in Alzheimer's disease dementia.



Source: Nature (2021)

Fig. 2: Hypothetical biomarker evidence-driven model of AD pathophysiology.



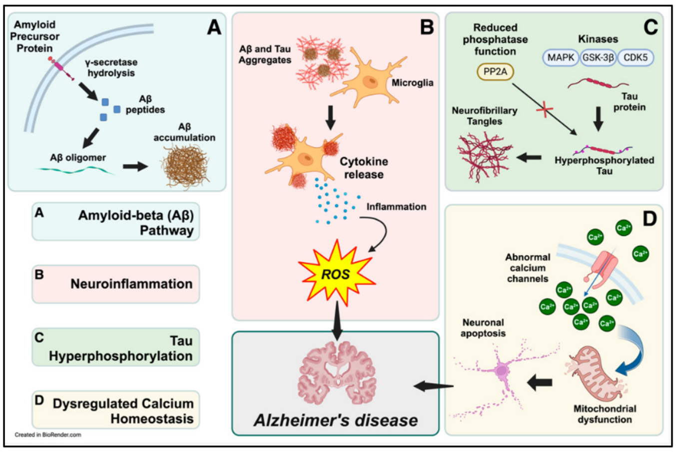
Source: Nature (2021)

METHODOLOGY

This study followed a secondary qualitative methodology. Thus, all sources for this review were obtained from both reliable and scientific databases, including Google Scholar, Nature, and the National Institute on Aging. Additionally, numerous research articles, medical journals, and examinations were consulted. All research has been derived from sources published within the last 3 years in order to capture the most relevant, efficient, and recent research findings and medical breakthroughs. This assisted in successfully presenting accurate and thorough research conclusions that align with the present day.

ANALYSIS & DISCUSSION

While amyloid beta plaques are often considered the initial trigger in Alzheimer's disease, research indicates a complex interaction between amyloid beta and tau, with each protein potentially exacerbating the toxicity of the other. In addition, recent studies suggest that soluble forms of both amyloid beta and tau, rather than the aggregated plaques and tangles themselves, might be more damaging to neurons. Therefore, their accumulation in the brain is believed to play a central role in the progression of the disease by disrupting neuronal function, causing synaptic loss, and ultimately leading to cognitive decline; the "amyloid cascade hypothesis" suggests that amyloid beta plaque formation initiates a chain of events that results in tau tangle development and subsequent neurodegeneration. For instance, the "amyloid cascade hypothesis" proposes that Aβ plaque deposition is the initial trigger in Alzheimer's, leading to further pathological changes including tau phosphorylation and neuronal damage. While the exact toxic species of Aβ is debated, soluble oligomers of Aβ are considered particularly harmful, disrupting synaptic function and causing neuronal dysfunction.



Source: MDPI (2024)

Likewise, in Alzheimer's disease, tau becomes hyperphosphorylated, leading to its misfolding and aggregation into intracellular neurofibrillary tangles (NFTs). Studies suggest that Aβ accumulation can trigger tau phosphorylation and tangle formation, further contributing to neuronal damage. The most prominent mechanisms of neurotoxicity consist of synaptic dysfunction, mitochondrial dysfunction, and neuroinflammation. Regarding synaptic dysfunction, both Aβ and tau, especially in their soluble oligomeric forms, can disrupt synaptic plasticity and impair neuronal communication, impacting memory and cognitive functions. Within mitochondrial dysfunction, accumulating evidence indicates that Aβ and tau can impair mitochondrial function, leading to increased oxidative stress and further neuronal damage.

Finally, within neuroinflammation, the presence of Aβ plaques and tau tangles can activate microglia (immune cells in the brain), promoting neuroinflammatory responses that contribute to neuronal loss. On the other spectrum, it is important to note that a wide array of factors can potentially contribute to the progression of Alzheimer's disease, such as genetics, vascular conditions, metabolic diseases, brain atrophy, neuropsychological factors, immunological factors, social stress, lifestyle factors, and other medical conditions.

Other potential factors that can contribute to Alzheimer's include cerebrovascular diseases, dyslipidemia, marital status, stress, inadequate sleep, and loneliness or social isolation. For example, vascular conditions can damage blood vessels, which can reduce blood flow and oxygen to the brain. This can lead to inflammation and other pathological changes in the brain. Vascular conditions contribute to the progression of Alzheimer's disease by damaging blood vessels in the brain, which reduces blood flow and oxygen supply to neurons, leading to neuronal damage and cognitive decline; this can happen through mechanisms like impaired blood-brain barrier function, increased amyloid-beta accumulation, and chronic cerebral hypoperfusion, ultimately accelerating the disease process. Overall, key points regarding vascular contributions to Alzheimer's include reduced blood flow, blood-brain barrier disruption, inflammation, and cerebral hypoperfusion. In addition, the "Vascular Hypothesis" of Alzheimer's is a theory that proposes that vascular problems are not just a contributing factor but may be a primary driver of Alzheimer's disease pathology, with vascular damage leading to the cascade of events that result in cognitive decline. Conditions like high blood pressure, atherosclerosis, and diabetes can narrow or damage blood vessels in the brain, leading to decreased blood flow and oxygen delivery to neurons, causing them to malfunction and die.

Meanwhile, damaged blood vessels can disrupt the blood-brain barrier, allowing harmful substances to enter the brain while preventing essential nutrients from reaching neurons. Along with that, reduced blood flow and damaged blood vessels can trigger inflammatory responses in the brain, further exacerbating neuronal damage. Finally, chronic lack of blood supply to the brain due to vascular issues (cerebral hypoperfusion) is considered a major contributor to cognitive decline in Alzheimer's disease.

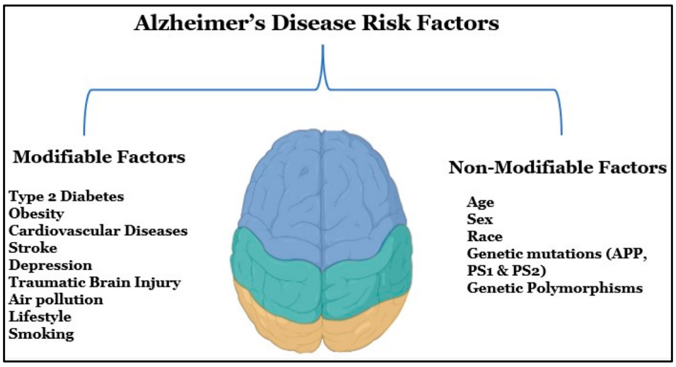
Social stress can also contribute to the progression of Alzheimer's disease by activating the body's stress response system, leading to increased levels of cortisol which can damage brain cells, particularly in the hippocampus (critical for memory), and promote the formation of amyloid plaques, a hallmark of Alzheimer's, thus accelerating the disease's progression; additionally, chronic social stress can trigger inflammation in the brain, further contributing to neuronal damage. Social stress can have significant effects on Alzheimer's disease through hormonal effects, neuroinflammation, social isolation, and an impact on the hippocampus. When experiencing social stress, the body releases cortisol, a stress hormone that can impair cognitive function and disrupt the brain's natural repair mechanisms, potentially accelerating the decline in Alzheimer's patients. Therefore, social stress can trigger an inflammatory response in the brain, leading to further damage to neurons and contributing to cognitive decline. Furthermore, this causes the hippocampus, a brain region crucial for memory, to be particularly vulnerable to the effects of stress hormones like cortisol, which can lead to memory impairment. Hence, research indicates that social isolation, a form of chronic stress, is strongly linked to an increased risk of developing Alzheimer's disease.

Moreover, lifestyle factors can also contribute to the progression of Alzheimer's disease by increasing the risk of other conditions that are associated with Alzheimer's. These conditions include heart disease: high blood pressure, high cholesterol, and obesity can all increase the risk of heart disease, which is also associated with Alzheimer's, diabetes: type 2 diabetes is a risk factor for Alzheimer's, and diets that reduce the risk of type 2 diabetes may also help prevent Alzheimer's, and stroke: high blood pressure and other vascular conditions can increase the risk of stroke, which is also associated with Alzheimer's.

Other lifestyle factors that may contribute to Alzheimer's include Smoking as Smoking increases the risk of Alzheimer's and other conditions associated with Alzheimer's and alcohol consumption since excessive drinking can often lead to high blood pressure or brain injuries, both of which increase the risk of Alzheimer's.

Other contributing factors include physical inactivity since a lack of physical activity in later life increases the risk of Alzheimer's, as well as a poor diet, due to an unhealthy diet, high in saturated fat, sugar, and salt, can increase the risk of Alzheimer's. Finally, traumatic brain injuries because a blow or jolt to the head can increase the risk of Alzheimer's. Research also suggests that lifestyle changes, such as diet and physical activity, may help reduce the risk of Alzheimer's. Therefore, although amyloid beta plaques and tau tangles are prominent features of Alzheimer's disease, other factors like genetic predisposition, inflammation, and vascular issues likely contribute to the disease progression. Hence, it can be concluded that no, amyloid beta plaques and tau tangles are not the only factors that can contribute to the progression of Alzheimer's disease; research indicates that a complex interplay of factors, including vascular issues, inflammation, genetic predisposition, and environmental influences, likely play a significant role alongside these protein abnormalities.

While emerging evidence suggests that Alzheimer's-related brain changes may result from a complex interplay among abnormal tau and beta-amyloid proteins, other modifiable risk factors such as sleep, smoking habits, hypertension, or diabetes can further increase the risk and overall progression of the disease.



Source: MDPI (2022)

CONCLUSION

Amyloid beta plaques and tau tangles are considered key pathological markers for Alzheimer's disease, where the accumulation of amyloid beta outside neurons triggers a cascade of events that leads to the abnormal phosphorylation and aggregation of tau protein inside neurons, ultimately causing neuronal damage and contributing significantly to cognitive decline associated with the disease. Amyloid beta plaques are deposits formed by the aggregation of amyloid beta protein outside neurons, which is thought to initiate the disease process by triggering inflammation and disrupting synaptic function. In regards to tau tangles, when tau protein, which normally helps stabilize microtubules within neurons, becomes abnormally phosphorylated, it can clump together forming neurofibrillary tangles inside the neurons, disrupting intracellular transport and leading to neuronal death. The "Amyloid cascade hypothesis" is a widely accepted theory that suggests that the accumulation of amyloid beta is the primary event in Alzheimer's disease, which then triggers the subsequent abnormal phosphorylation and aggregation of tau protein.

While the aggregated plaques and tangles are visible markers, research indicates that the most toxic forms of these proteins may be soluble oligomers which can directly interfere with neuronal function. Both amyloid beta and tau can disrupt the connections between neurons (synapses), impairing communication and leading to cognitive decline. In addition, the presence of amyloid beta plaques can activate immune cells in the brain, leading to chronic inflammation that further damages neurons. Abnormal amyloid beta and tau can disrupt mitochondrial function, which is crucial for energy production within neurons. The combined effects of synaptic loss, inflammation, and impaired cellular processes eventually lead to neuronal death, contributing to brain atrophy observed in Alzheimer's disease. While the presence of amyloid beta plaques is associated with Alzheimer's, some individuals with significant plaque deposition do not show cognitive impairment, suggesting that other factors may also play a role.

Current research is actively investigating ways to target both amyloid beta and tau protein pathology for the treatment of Alzheimer's disease, however, more work and studies are necessary in order to truly grasp a better understanding of the effectiveness. Many factors contribute to the progression of Alzheimer's disease, including genetics, vascular conditions, metabolic diseases, brain atrophy, mitochondrial dysfunction, inflammation, neurofibrillary tangles, and beta-amyloid plaques. These proteins are just one component of a wide array of factors and potential triggers for the progression of Alzheimer's disease, and this paper aimed to streamline and identify, the specific effects and outcomes resulting from the influence of these proteins. Amyloid beta plaques and tau tangles are certainly not the only constituents that could increase the progression of Alzheimer's disease, and there is a wealth of other factors that must be taken into account, and that future research should aim to progress our knowledge and understanding of.

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