Support for the Amyloid Cascade Hypothesis in Guiding Further Avenues of Treatment in Alzheimer's Disease

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Alzheimer’s disease currently affects 50 million individuals and is expected to increase to 152 million by 2050. Despite this prevalence, the neurodegenerative disease still has minimal treatments, and there are minimally FDA approved drugs that show any slowing in cognitive decline. One of these drugs, aducanumab (Aduhelm), attacks the amyloid-beta plaques that form in Alzheimer’s. This evidence coincides with the predominant theory in Alzheimer’s pathogenesis, the Amyloid Cascade Hypothesis (ACH). However, there are conflicting reports about whether evidence supporting aducanumab warranted FDA approval. Some scientists suggest that the underlying pathology of Alzheimer’s is via tau, which involves the accumulation of neurofibrillary tau tangles that progress to the disease’s diagnostic lesions. To determine if degrading amyloid plaques is the most beneficial path of treatment, a comprehensive literature review of current Alzheimer’s research and understanding of how the disease is treated was conducted. This review found that the ACH should remain the prevailing theory based on Alzheimer’s progression, with findings that indicate amyloid plaques are necessary to induce the phosphorylation crucial to the development of tau tangles. This data suggests that Alzheimer’s disease develops via an amyloid-induced tau-pathology. In addition, a multitude of other treatments has been shown to reduce these plaques along with aducanumab, which renews promise in using the ACH to develop treatments. Using the ACH as a guide and implementing the treatments listed in this paper, new drugs like aducanumab target the perpetrator of Alzheimer’s and may stop or reverse progression to more severe presentations of the disease.

Abbreviations:  ACH – Amyloid Cascade Hypothesis; Aβ – amyloid-beta; AD – Alzheimer’s Disease; NFT – neurofibrillary tangle

Keywords:  Aβ plaque; aducanumab; neurofibrillary tau tangle; neurotoxicity; pathogenesis; peptide

Introduction

Alzheimer’s disease (AD) is a chronic neurodegenerative disease that is the most common form of dementia. Symptomatic presentation of AD is categorized as the severe inhibition of personal daily activities as well as a stark decline in neurological processing (De-Paula et al. 2012). The disease is characterized by neuritic plaques and tau neurofibrillary tangles that occur after the formation of amyloid-beta (Aβ) peptides in the medial temporal lobe and neocortical structures of the brain (De-Paula et al. 2012). The treatment and prevention of AD has become a matter of dramatically increased interest, as currently there are around 50 million individuals that are affected by some form of the disease worldwide, with estimates projecting that this number will reach 152 million by 2050 (Brejyyeh et al. 2020). Deaths attributed to the disease are also increasing, with an 89% increase in deaths in the US from 2000 to 2014 (Alzheimer’s Association, 2017). There is no cure for AD, however there are some medications that clinical trials have shown to reduce the evolution of the disease, as well as to alleviate certain symptoms. There are two categories of drugs approved by
the FDA for the treatment of AD: a) therapies that may temporally alleviate the symptoms of the disease, which in itself is broken into two subcategories (NMDA antagonists and acetylcholinesterase inhibitors), and b) drugs that may slow down or halt the clinical degeneration of patients, as well as improve cognition and function (Alhazmi and Albratty, 2022). The latter of these approved treatments contains only one recently approved drug, aducanumab (Aduhelm). This drug is an anti-amyloid antibody that attaches to forms of Aβ in the brain and has been shown to lower amyloid in animal trials, with human clinical trials still ongoing (Ferrero et al. 2016). These various clinical trials have shown a decrease in Aβ plaques in the brain, with further trials and studies still being conducted to determine the efficacy of aducanumab (Rahman et al. 2023). These Aβ plaques are critical in the pathology of AD and have been studied extensively.

Aβ plaques have been suggested to be a causative factor of AD, however they have also been suggested to simply be a symptom of the disease’s pathogenesis. This has led to the term “Amyloid Cascade Hypothesis (ACH)” being coined (Verdile, 2004). The key foundation of the ACH is based on an imbalance in Aβ metabolism and the subsequent deposition and aggregation of senile plaques that cause neuronal death (Verdile, 2004). Aβ is made up of a few protein components, with the major proteolytic product of the 4kDa amyloid-β-protein being a much larger protein than the other components denoted as the amyloid precursor protein (APP) (Glenner and Wong, 1984). The proteolytic cleavage of APP via presenilins, a transmembrane protein that regulates the cleavage of other proteins (Tandon and Fraser, 2002), is now widely accepted to be the main mechanism to produce Aβ plaques (Tandon and Fraser, 2002). There are two main species of Aβ: Aβ40 and Aβ42, corresponding to the number of amino acids that make up the protein (Klafki et al. 1996). The Aβ40 form is the most common species found, accounting for approximately 90% of all Aβ that is produced normally within the brain. This species appears to be relatively unproblematic, only contributing to AD pathology in the later phases of the disease (Asami-Odaka et al. 1995). Aβ42 however, is shown to be the predominant form that is found in the amyloid plaques that are the hallmarks of AD (Lippa et al. 1998). The dysregulation of APP cleavage that occurs in the early stages of AD results in an altered metabolism of Aβ where there is an overproduction of the Aβ42 protein form (Verdile, 2004). After enough substantial Aβ42 is produced, it begins to harden and forms plaques on the synaptic terminals. These plaques on their own do not directly cause AD. However, as they begin to mature, they rearrange into β-pleated sheets that eventually progress into neuritic plaques. These neuritic plaques are the culprits of AD pathogenesis, resulting in microglial and astrocytic activation, oxidative injury, the aggregation of unbound tau and hyperphosphorylation of these tau peptides. This culminates in neuronal degradation and synaptic dysfunction (Cummings et al. 1996).

Due to a history of slow advancements in clinical trials, there are some scientists (Arnsten et al. 2020) who suggest that Aβ plaques may not be the primary causative factor when it comes to the development and progression of AD. Of the other proposed hypotheses that dispute the amyloid cascade interpretation, the most prominent is the accumulation of neurofibrillary tangles (NFTs) that are comprised of the protein tau (Ballatore et al. 2007). Microtubule associated protein (MAP) tau is a protein with a primary function to stabilize microtubules in the axons of neurons. At normal physiological conditions, tau is at a constant dynamic equilibrium, in which it contributes to major structural and regulatory cellular functions to the neuronal network (Ballatore et al. 2007). However, when this equilibrium is disturbed in any way, there is the possibility of an abnormal increase in the levels of unbound tau protein. With this increase, the tau then begins to misfold and it can start to aggregate and fibrillate (Kuret et al. 2005). This change can be triggered by a multitude of causes, such as increasing rates of phosphorylation and dephosphorylation, and is likely what contributes to AD pathogenesis. The misfolding of the unbound tau leads to small nonfibrillar tau deposits. These ‘pretangles’ then structurally rearrange into paired helical filaments, which further self-assemble into the
diagnostic lesions of AD, NFTs (Galván et al. 2001).

While Aβ and tau fibrils are linked together as causative factors for the progression of AD, the oligomers that end up triggering the amyloid cascade in the synapses of neurons are what most of the neuronal neurotoxicity associated with AD is attributed to (Golde, 2006). This is supported by the current treatments available for AD, with the only approved drug for the prevention or inhibition of the disease mechanistically attacking the plaques formed in neurons, leading to a possible reduction in the disease’s presentation. Another factor that supports the ACH is the sequencing that occurs as AD develops. Evidence obtained through in vitro and in vivo models have both shown support that tau pathology is strongly, if not entirely, induced by the formation of Aβ plaques (Stancu et al. 2014). If this is truly how AD progresses within human physiology, then the most effective treatment would be to attack the plaques themselves and prevent the NFTs from forming at all. With this information, the primary course of action for finding a cure of AD or effective treatment would be to examine the formation of the Aβ plaques and observe the possible ways in which therapeutic drugs or treatment may reduce the production or clear the plaques altogether (Atri, 2019). There are a multitude of factors that have been attributed to the reduction of Aβ plaques in neurons that will be further explored in this paper, including hormone production (Gouras et al. 2000; Xu et al. 1998), selective butyrylcholinesterase inhibition (Greig et al. 2005), and light triggered modulation (Lee et al. 2019). This review argues that the ACH should remain the primary guiding framework for future AD treatments, and that further research and development of treatments and therapies focusing on Aβ plaques could be invaluable in regard to the management of patients with AD.

Description

The role of Aβ in the development of AD

To discuss the reduction of Aβ that characterized in the pathology of AD, it is important to understand Aβ structure and the role that it plays in the disease. The overproduction of the toxic Aβ42 peptide can lead to the formation of plaques, and eventually the degradation of neurons. However, it is not just the hardened plaques that contribute to this pathology. Using transgenic mice models in which APP is expressed has allowed for the examination of how Aβ plaques are expressed and the effects that they exhibit (Holcomb et al. 1998). Most of these models failed to have any amyloid deposits formed, even though they expressed AD-like neurological deficits, synaptic loss, and inflammatory responses. What was observed was an increase in the production of the plaque producing Aβ42 form, as well as cognitive deficits (Holcomb et al. 1998). With Aβ42 being prominent in human AD patients as well (Gouras et al. 2000), these observations suggest that the Aβ plaques could possibly be a secondary event to the production of the Aβ42 (Verdile, 2004), with symptoms of AD presenting before plaques even form. One possible explanation for why the Aβ42 form has such a high degree of neurotoxicity (Lambert et al. 1998), aside from the eventual contribution to plaque formation, can be attributed to the structure of the peptide itself. The Aβ form found in the transgenic mice models, as well as the form that was used in subsequent cultures, was non-fibrillar. This toxic form of the peptide that was observed was composed of protofibrils, which are curvilinear structures that were free of both monomers and fibrils (Walsh et al. 1999). These same protofibrils, when exposed to neuronal cells in culture initiated oxidative stress and eventually death in the cultured cells (Walsh et al. 1999). This data suggests a positive correlation between the production of the Aβ42 protein and one of the hallmarks of AD: the degradation of neurons and neuronal cell death.

Whilst these studies have shown that a high concentration of Aβ42 can lead to AD
symptoms, the progression of these peptides into plaques produces even more harmful results due to the continued increase of neurotoxicity in the peptides. In human neuronal cultures, metal ions have been shown to potentiate this neurotoxicity, specifically Cu$$^{2+}$$ (Cuajungco et al. 2000) and Fe$$^{3+}$$ (Rottkamp et al. 2001). Aβ in the presence of Cu$$^{2+}$$ and Fe$$^{3+}$$ will produce H$_2$O$_2$ (Rottkamp et al. 2001) after interacting with the metal ions, generating reactive oxygen species (ROS). This then leads to lipid peroxidation and protein oxidation (Butterfield and Lauderback, 2002), which causes the neurons to undergo oxidative stress. Metal ions also lead to a higher fibrilisation rate in Aβ, even when present in very slight traces (Atwood et al. 2008). When in the presence of these metal ions, Aβ$_{42}$ will form allosterically ordered α-helical structures that can then penetrate negatively charged membranes (Curtain et al. 2003), such as the membranes of any neuron in the immediate surrounding area. Both factors together indicate how oligomerization of Aβ can lead to the formation of the characteristic plaques found in patient’s suffering from AD (Verdile, 2004).

Hormone concentration and the reduction of Aβ

Hormonal declines that result with aging have been implicated to have an effect on AD pathogenesis (Verdile et al. 2015), including the increased production of Aβ plaques. Both forms of Aβ (Aβ$_{40}$/Aβ$_{42}$) are produced neurally, and thus it is advantageous to study cell lines of neurons to examine the production of these peptides. Studies show that there is a cell line that produces APP that can be affected and have the levels of APP effectively increased when treated with physiological concentrations of 17β-estradiol (17β-E2) (Jaffe et al. 1994). During a follow up study examining this same cell line, estrogen was then used in primary cultures of rat, mouse, and human embryonic cerebral cortical neurons in order to distinguish if this route would be effective in reducing the cleavage of Aβ, and thusly lowering the risk of AD. Results from these cultures showed an increase in 17β-E2 release that was previously shown, as well as a significant decrease in the production of Aβ peptides (Xu et al. 1998). The decrease in this pathway resembled that of the increase in 17β-E2, suggesting that the pathway was regulated in a similar fashion (Xu et al. 1998). During these initial experiments, it was still debated and relatively unknown what the underlying cellular mechanism was that allowed estrogen to have this beneficial effect on AD and the Aβ plaques. What was known was that the Aβ production was reduced with estrogen treatments (Xu et al. 1998), as well as estrogen being able to block Aβ-induced neuronal cell death in vitro (Behl et al. 1995), although the mechanism remained unknown.

Estrogen is capable of exerting effects through both estrogen receptor (ER)-dependent and -independent pathways (Green et al. 1998), (Lustig et al. 1994), and via the ER-dependent pathways there are two subtypes: α and β (Kuiper et al. 1997). It is imperative to know which pathway estrogen takes in order to establish its protective effect on neurons is important in order to establish a route of treatment for AD using the hormone. To determine which pathway estrogen acts to increase the protection of neuronal cells, culturing was done with HT22 and human cells. When the human cells were treated with estrogen, it was observed that Aβ-induced death was reduced, with no reduction in induced cell death to the HT22 cells, which were not ER-expressing (Kim et al. 2001), suggesting that neuronal protection was via ER-dependent pathways. Follow up culturing with transfected human and HT22 cells was performed, using a select group with human ERα and a select group with ERβ. The HT22 cells that were transfected with ERα were able to restore the protective action of the estrogen, indicating that the effective pathway for estrogen to reduce Aβ production is ERα dependent (Kim et al. 2001). Now that this specific pathway is known, there is a possibility to better predict which types of estrogen treatments would be effective in treating AD. This is instrumental when it comes to the development of pharmaceutical drugs that may have positive effects. In addition to this benefit, the testing done on neurons with Aβ, and estrogen laid the groundwork for the examination of how testosterone may affect the levels of Aβ produced in neurons.

Examining the cell pathway that estrogen takes to modulate APP, and thus its
role in the decreased secretion of Aβ from neurons, the next step to take was to observe if testosterone had similar effects and could be used as a protective treatment against AD as well. Using both rat and human cell cultures, testosterone treatments appeared to have similar effects as estrogen treatment, raising the concentration of APP and decreasing the concentration of Aβ that was released by neurons (Gouras et al. 2000). Similar to estrogen, testosterone is mediated through a receptor protein, whether through a normal androgen receptor (AR), or after 5α-reduction to a more potent dihydroxytestosterone (DHT) (Verdile et al. 2015). Unlike estrogen, testosterone currently does not have a thoroughly understood mechanism when it comes to the accumulation of Aβ, although hormone induced receptor mediated signaling pathways involving the associated luteinizing hormone (LH) appear to have an important role in APP modulation (Verdile et al. 2015). These experiments suggest that hormone treatments may be useful in the management of Aβ, and thus may prove effective in the development of new drugs and therapies to treat AD.

Butyrylcholinesterase inhibition

Selective butyrylcholinesterase (BChE) inhibition has been linked to an increase in extracellular acetylcholine (ACh) levels in the brain, which in turn leads to a decrease in secreted Aβ levels. An additional symptom of AD is the loss of enzymatic activity and the degradation of neurons that respond to ACh in the forebrain (Geula and Mesulam, 1995). Whilst AD attacks a wide variety of neurotransmitter-containing cell bodies, a majority of neurons lost are long projection neurons such as cholinergic neurons (Mufson et al. 2003; Auld et al. 2002). Many of the drugs that are currently approved to treat AD inhibit the production of cholinesterase, which terminates the activity of the neurotransmitter in the brain. These approved drugs operate via a mechanism that inhibits acetylcholinesterase (AChE), as well as BChE, although to a lesser extent (Lahiri et al. 2002). The way that these particular enzyme inhibitors work is to catalyze the hydrolysis of the ACh within the cholinergic synapses that reside in the brain and the autonomic nervous system (Taylor, 1996). Even though BChE shares similar functions to ACh, it resides primarily within glial cells, while ACh histochemically is localized to neurons (Darvesh et al. 2003).

Upon further examination of BCh and BChE, it appeared that increasing levels of BChE had a positive correlation with the development of Aβ (Geula and Mesulam, 1995). To test this association and see if the inverse also held value, a reversible BChE inhibitor comprised of cymserine analogs was used in models of the AD brain (Greig et al. 2005). During this testing process, it was found through micro dialysis that BChE inhibition led to increases in endogenous extracellular concentrations of ACh in the parietal cortex of the model brain. The maximal effect of the drug was measured at 40 minutes after administration, and the ACh levels measured were 180% and 290% depending on the dosage of the BChE inhibitor. On a more qualitative level, the BChE inhibition also improved the cognitive performance in aged rats, as they were able to navigate through a maze at an improved rate with fewer errors over their untreated counterparts after the drug administration (Greig et al. 2005). Likely causes of these results were the reduced levels of APP and Aβ levels post administration, observed in mice expressing human APP and human Aβ, both in vivo and in vitro (Greig et al. 2005). This suggests that the main causative factor for AD pathology is the Aβ plaque formation due to the reduction in plaques and the subsequent improvement in cognitive performance, as well as the increase in the levels of ACh, a critical neurotransmitter needed for basic brain functionality.

Oxidative stress and photosensitizers

Photosensitizers are molecules that when activated by light, will generate ROS that then damage cell structures, and have been used in various forms of healthcare such as biosensing and imaging, as well as energy conversion applications (Lee et al. 2019). This makes them particularly useful when attempting to stain Aβ plaques due to their high binding affinities. Using specific methods such as
photoxxygenation, fully mature Aβ42 aggregates were able to be deconstructed, successfully lowering their toxicity levels (Son et al. 2018). This process increased the cell’s viability from 40% to 80% and suggested that the oxidative stress generated from the treatment induced the fragmentation of the Aβ fibrils into smaller non-toxic aggregates (Lee et al. 2019).

Examining the effect that oxidative stress and the damage it can do to Aβ plaques, it is important to still consider the damage that the production of ROS can have on the surrounding molecules of the cell as well. Oxidative stress has been proven to have links to the disruption of membrane integrity, specifically the lipids that make up these membranes. One example of this is the loss of phospholipid asymmetry observed in synaptosome membranes (Castegna et al. 2004) that were created with acrolein and 4-hydroxynonenal, reactive aldehydes produced by oxidative damage of brain polyunsaturated fatty acids (Prasad et al. 1998; Lovell et al. 2001; Markesbery and Lovell, 1998). This is not the only issue that has arisen when examining oxidative stress in the brain either, as when observing transgenic mouse models for AD, there have been suggested contributions that led to the impairment of insulin signaling in the brain due to oxidative stress (Barone et al. 2016). These factors indicate that whilst oxidative stress can play a role in the clearance of Aβ plaques in neuronal synapses, the production of ROS has a negative impact on the surrounding molecular area as well.

Oxidative stress may be the answer to one of the key discrediting factors used against the ACH. A main supporting piece of evidence for NFT being the primary causative factor of AD is that in post-mortem studies, there tends to be a higher density of tau tangles that correlated more closely areas of the brain associated with AD symptoms, such as the amygdala and the hippocampus, than the concentration of Aβ plaques in the brain in those same areas (Verdile, 2004). However, oxidative stress may have been the culprit for this as opposed to tau aggregation being the main factor. When examining oxidative stress and its role in AD, it was found that an increase in oxidative stress begins early in the preclinical stages of AD development, many times alongside or even before the aggregation of Aβ to form plaques on neuronal synapses (Cheignon et al. 2018). With such an early presentation of oxidative stress, and the apparent observation that oxidative stress and Aβ plaques are not mutually exclusive to each other, it is possible that the lack of Aβ plaques that were found in areas like the frontal lobe could be due to oxidative stress and does not discredit the ACH.

**Tau centered hypotheses**

Pathogenic tau is thought to be one of the main contributors to AD pathogenesis, both by those who align with the ACH and those who believe there may be more to the picture. With the amyloid hypothesis being as prevalent as it has been, tau has generally had less focus than Aβ, and thus still has contrasting information on its mechanistic pathways and any therapeutic treatment that may be effective. The main function of tau is as a promoter of axonal microtubule assembly (Naseri et al. 2019). With this critical function, it has been suggested that the loss of tau binding to microtubules and the formation of the unbound protein into tangles at the synapse of neurons is what leads to the neurotoxicity and neuronal degradation that is often associated with AD (Naseri et al. 2019). This theory is supported by the observation of tau knockdown in the adult hippocampus of mice, which resulted in impaired muscle coordination and morphological synaptic defects (Velazquez et al. 2018), showing similar symptoms as AD presentation.

Whilst the ACH has been the primary focus in recent AD research and clinical trials, there have been opposing theories that suggest the main mechanism for AD, and thus where the focus should be when it comes to treatment, should be placed on NFTs (Stancu et al. 2014). This dissatisfaction with the ACH has come from the slow progress that has been made in clinical trials that are focused on lowering amyloid effects or minimal outcomes following marked removal of amyloid plaques (St. George-Hyslop and Morris, 2008). These theories indicate that the treatment of AD through the avenue of Aβ plaques was centered too tightly around preventative treatment rather than curative treatment, and that there was a
severe lack of knowledge when it came to tau pathogenesis. Finally, a main contributor to the tau-centered hypothesis was that the misfolding of tau was capable of active induction to distant areas of the brain (Clavaguera et al. 2009), which led to a self-propagating “prion-like” effect that would then lead to the cascade of $\alpha\beta$ plaque formation (Stancu et al. 2014), suggesting that NFTs may be the primary factor in AD development in tau-mediated neurotoxicity.

Tau-mediated neurotoxicity is characterized by a “gain of function”, or an addition of a genotype or phenotype, when soluble tau begins to aggregate in the extracellular matrix (Fath et al. 2002). This pathway stems from tau undergoing structural changes that are induced by a cumulative, high stoichiometric tau phosphorylation. These structural changes cause tau to mature and progress into NFT’s, which have been correlated to the cognitive impairment of patients with AD (Arriagada et al. 1992). However, this “gain of function” is not the only significant role that the tau protein plays in AD pathology. Coinciding with the gaining of these new toxic functions, the increased solubility of tau and the formation of NFT’s causes impaired microtubule function and axonal transport, as well as synaptic function and neuronal loss (Jaworski et al. 2010). As normal, non-phosphorylated tau has a critical function of maintaining axonal structure in healthy brains (Naseri et al. 2019), the mutation of the protein causes neuronal degradation at a rapid rate, losing the benefits of the protein whilst the same process begins to actively damage the neurons it previously supported. This rapid increase in toxicity that arises from tau mutations lends support to tau being the primary mediator in AD pathology, as opposed to $\alpha\beta$.

With all these criticisms taken into effect, the ACH was reexamined. Current and past in vitro and in vivo models, as well as newfound success in clinical trials, have shown large experimental support for the focus on $\alpha\beta$ production. However, there has been a shift in how AD pathology is modeled. The current model of AD views $\alpha\beta$ as the starting point for the pathology. In other words, the disease and the associated symptoms are the initiators for the pathogenesis and accelerate the disease progression, whereas tau is now seen as the executor of the disease. This has coined the new term “amyloid induced tau-pathology” (Stancu et al. 2014). Although the exact mechanism or molecular identity that links $\alpha\beta$ and tau has yet to be identified, interactions of $\alpha\beta$ cross-seeding with tau shows the transition of mild tau-strains to more aggressive tau-strains. This progression then triggers the prion-like spreading of the tauopathy along neuronal circuits (Stancu et al. 2014), which suggests that the amyloid plaques are necessary for the progression of tau to NFT’s, which lends support to the ACH still being the prevailing theory for the disease pathology.

Discussion

Although AD is a complicated and still minimally understood disease when it comes to curative techniques, the ACH remains the prevailing theory in the process of the disease’s pathology. The current understanding of the way that AD progresses treats the dysfunction of APP metabolism resulting in the over-production of $\alpha\beta_{42}$ as the initiate of the disease pathology. This increase in production of the toxic form of $\alpha\beta$ peptide leads to neuronal degradation independently, but the progression of AD is exacerbated when these peptides aggregate and begin to form $\alpha\beta$ plaques (Curtain et al. 2003). These plaques are non-fibrillar and have a high degree of neurotoxicity (Walsh et al. 1999). As these plaques form, the tau proteins that usually promote axonal microtubule stability begin to unbind with the neuronal axons that they are attached to. This starts the progression and transition into NFTs, which also have a high degree of neurotoxicity and begin to degrade neurons alongside the $\alpha\beta$ plaques, culminating in the presentation of AD.

Due to initial slow progress on clinical trials examining $\alpha\beta$ in patients presenting with AD, the scientific community began to focus on tau-mediated neurotoxicity. This was aided by further research that showed mutations in the tau protein that caused rapid phosphorylation, which would induce toxicity within the diseased brain.
(Fath et al. 2002). This toxicity was capable of active induction into separate regions of the brain (Clavaguera et al. 2009), potentially initiating uncontrolled and exponential spread of the neuronal degradation that mature NFT’s have been shown previously in this paper to cause. However, a contemporary model of AD pathology now addresses both Aβ- and tau-mediated neurotoxicity having a certain amount of synergy when it comes to the progression of AD (Stancu et al. 2014). Further examination and research that was conducted on Aβ plaques in diseased brains suggested that these plaques were necessary in order to initiate the phosphorylation that causes tau proteins to begin unbinding from neuronal axons. This indicated that AD possesses an “amyloid induced tau-pathology” (Stancu et al. 2014), and that the Aβ peptide deregulation and plaque formation was a precursor to the initiation and eventual maturation of NFT’s (viewing Aβ as the “initiator” of AD pathology and NFT’s as the “executor”). For AD treatments and therapies to be the most effective and to address the disease in its earliest stages, it is imperative that the primary focus of these treatments is on the regulation and management of the Aβ peptide, specifically the toxic form Aβ42, using methods previously described in this paper. This would target the perpetrator of the disease, and stop progression before the disease develops into severe AD.

Whilst the ACH may still be the consensus theory about how AD progresses, the treatment of the disease, specifically in terms of decreasing neuronal degradation, has had minimal clinical success until recently. The avenues of treatment listed above have the potential to be used in tandem with each other in order to better treat patients that present with AD. The plaques that are associated with causing the symptoms associated with AD can be diminished in multiple ways, whether that be the decreased Aβ42 or direct attacks on the plaques that have already formed. The former can be accomplished via hormone treatments in certain individuals (Gouras et al. 2000; Xu et al. 1998; Jaffe et al. 1994; Behl et al. 1995; Verdile et al. 2015), as well as using select butyrylcholinesterase inhibitors (Greig et al. 2005; Geula and Mesulam, 1995) in order to lower the secretion of the toxic peptide, while the later may be addressed using photosensitizers increasing the oxidative stress on mature plaques that have already formed (Lee et al. 2019; Son et al. 2018).

Treatments of both estrogen and testosterone in patients with AD have been shown to decrease the production of Aβ (Gouras et al. 2000; Xu et al. 1998; Jaffe et al. 1994; Verdile et al. 2015), with estrogen acting via a ERα dependent pathway (Kim et al. 2001) and being generally more understood than treatments of testosterone, which does not yet have a clearly mapped mechanistic pathway. In addition to hormone therapies, selective BChE inhibitors have been shown to increase the level of ACh in the aging brain of AD effected individuals, which in turn has caused a decrease in the secretion of Aβ peptides. Given that both of these avenues of treatment focus on the decrease in Aβ peptide production and secretion, they are likely to be useful as preventative treatments for the disease and used to slow the disease progression, as opposed to full reversal of AD.

For treatment of Aβ plaques that have already formed, techniques such as photooxygenation have proved useful, increasing the cell viability of neuronal cells that had matured Aβ plaques. The increase of oxidative stress from techniques such as this is understood to fragment the Aβ fibrils of the peptides that aggregate and form these plaques, leading to their deconstruction (Lee et al. 2019). Treatments and therapies that use avenues such as this could potentially prove useful in the secondary treatment of AD, addressing the mature plaques that have already formed as opposed to attempting to halt or decrease the production of the Aβ peptide that forms them. However, there are drawbacks to using this method to destabilize Aβ plaques, and that is that the amount of oxidative stress that is required to fragment them can have residual effects on molecular structures around the targets of the therapies and could potentially prove harmful.

In order to effectively treat AD and continue to establish progress with treatments and therapies, a few of the mechanisms previously discussed need to be further
understood. As discussed previously, the mechanism via which estrogen treatments are able to act on neurons and decrease the production of Aβ is well documented, setting a groundwork for therapies and treatments using this pathway. However, there is still a lack in understanding concerning the pathway that testosterone acts upon the production of Aβ peptides. This would allow multi-faceted treatments and could potentially allow more diverse access to hormonal treatment of AD.

The primary focus of future research, however, should be focused on the interactions between the different types of treatment that have previously been discussed in this paper. In order to effectively treat AD, treatments need to effectively mediate the amount of Aβ peptides produced by neurons, as well as manage the accumulation of these peptides when plaques begin to matriculate and mature. This would require using multiple different approaches when it comes to therapies and treatments. Specifically, further studies should be conducted on how therapies such as testosterone/estrogen treatment and butyrylcholinesterase inhibition, which can be viewed as more preemptive treatments (Xu et al. 1998; Gouras et al. 2000; Greig et al. 2005), interact with treatments that focus on photooxygenation and oxidative stress (Son et al. 2018), which are treatments that focus on the correction and the reversal of symptoms such as plaque buildup. Upon combination of these treatments, it could potentially reveal increased effectiveness and reliability, with the breakdown of already accumulated Aβ plaques and the prevention of any subsequent new toxic peptide secretion.

The first step of this process would be examining the effects of these combined therapies in mice, similar to previous experiments such as the estrogen and the butryrylcholinesterase trials that were previously mentioned in this paper. The goal of these experiments is to first confirm that the noted effects are shown to be consistent prior to any further experimentation, then to implement additional variables into the experiments and observe any effects. The primary subjects should be mice with noted neurological deficits and substantial plaque buildup, and they should first be treated with methods of photooxygenation, which begin to degrade the neuronal plaques that exist in the synapses of the subject’s neurons. After continued observation, the mice should then be treated to hormone therapies such as estrogen or testosterone treatments, which have been shown to decrease the secretion of the toxic Aβ peptide. This paired treatment could potentially set groundwork on new methods of AD treatment, with a combined curative and preventative model. Trials such as these are necessary in order to determine if these types of treatments can result in additive effects, or if the combination of these therapies could potentially be harmful. Similar trials should be implemented using BChE inhibitors in place of hormone treatments as the preventative component.

However, clinical progression from mouse subjects to human trials has continually been shown to yield relatively poor results due to the limitations of any animal model (Webster et al., 2014). The majority of mouse models that are used to observe AD effects are of the familial form of AD, which may alter the effectiveness of results due to this form being only a small percentage of noted AD diagnoses (Campion et al. 1999). These animal models do not completely reflect how AD presents in humans due to animal models needing to be induced via mutation (Qin et al. 2020), and this could be the source of the differences in effectiveness and mechanisms of certain treatments when progressed from mouse models to clinical trials. This signifies the importance of clinical trials when it comes to AD research, which involves the development of aducanumab, the only FDA approved curative AD drug that was mentioned previously in this paper. This drug was shown to have positive findings in phase III clinical trials when administered to patients (Schneider, 2019), with results showing drastically increased Aβ plaques in these patients when examining cortical brain regions (Haddad et al. 2022). Even though this drug was only tested in clinical trials on patients with mild forms of AD (Haddad et al. 2022), and there have been claims that the methods used were only statistically significant and not clinically significant (Schneider, 2019; Sevigny et al. 2016), the mechanistic pathway showed promising results for further research.
Aducanumab selectively binds to Aβ aggregates rather than individual Aβ monomers, which provides unique amino acid interactions. These interactions in turn facilitate the compact and shallow binding of the drug to these aggregates, which results in the decrease of Aβ plagues and restores neurological function (Haddad et al. 2022).

**Conclusion**

The ACH has been shown to have positive effects (i.e., the restoration of neurological function) via the novel drug aducanumab (Haddad et al. 2022). Although these findings are heavily debated over whether they warranted FDA approval (Karlawish and Grill, 2021), the mechanism has produced results, whereas there is no currently approved therapies or treatments for AD that attack tau pathology and also produce curative effects (Ferrero et al. 2016). This progress, considered with the multitude of avenues that allow for treatment of Aβ plaques in diseased patients, suggest that the ACH should remain the prevailing theory when it comes to AD research and should guide the future directions in the understanding and treatment of AD.

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