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Amyloid, Tau, and ApoE: Revisiting Hypotheses of Alzheimer's Disease

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Abstract. This review provides in-depth analysis of three principal, potentially complementary hypotheses: the amyloid β (Aβ) cascade hypothesis, tau propagation hypothesis, and the apolipoprotein E (ApoE) hypothesis. We scrutinize the molecular pathways, genetic factors, and recent insights, offering a critical perspective on the current state of AD research. Based on this examination, this review offers a comprehensive understanding of interplaying mechanisms potentially subserving the onset and development of AD to further exploration into AD pathologies.

Keywords: Alzheimer's Disease (AD), Amyloid β (Aβ) cascade hypothesis, Tau propagation hypothesis, Apolipoprotein E (ApoE) hypothesis, Alzheimer's Disease (AD).

1. Introduction

A variety of diseases and injuries that affect the brain results dementia. It is now the seventh main cause of death and one of the primary causes of dependency and disability among older people around the world. The most common form of dementia is Alzheimer disease (AD), and it may contribute to 60–70% of cases[1].

German psychiatrist Alois Alzheimer first discovered and named Alzheimer's disease in 1906. He discovered abnormal deposits of proteins in the brain of a woman with progressive dementia, which later became known as "neurofibrillary tangles" and "amyloid plaques". Since then, the understanding of Alzheimer's disease has increased as medical research has progressed[2].

The research on Alzheimer's disease, as one of the great health-care challenges of the 21st century, is rapidly developing. However, little is known about the cause of AD and no curative method is developed yet. In recent years of research, many different hypotheses have been proposed regarding the pathogenesis of Alzheimer's disease. Research since the main component of tangles, tau, and the main

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component of plaques, amyloid β (Aβ) have been discovered, further information about molecular pathogenetic events were provided[3].

In addition, many causal hypotheses have been discovered, further revealing the pathogenic mechanism of AD. In this review, we critically evaluate the existing hypotheses on the pathogenesis of Alzheimer's disease, highlighting recent insights that challenge traditional views. We specifically focus on the roles of both amyloid β (Aβ), tau proteins and ApolopoproteinE (ApoE), discussing their implications in disease progression. Our aim was to provide a theoretical foundation and ideas for future research in the field of AD.

1.1. Biomarkers and Imaging in Alzheimer's Diagnosis

Alzheimer's disease is a neurodegenerative disease characterized by progression and irreversibility, which significantly affects cognition, function, and behavior. The continuum of this disease starts with preclinical stages, advances to mild cognitive impairment or mild behavioral disturbances, and ultimately leads to Alzheimer's disease dementia[4].

In the field of clinical practice, the diagnosis of Alzheimer's disease (AD) phenotypes is facilitated by a majority of biomarkers, which are divided into two main categories: pathophysiological and topographical. Pathophysiological biomarkers are indicative of the fundamental pathological mechanisms at play in AD and include amyloid positron emission tomography (PET) scans, the levels of amyloid and tau proteins in cerebrospinal fluid (CSF), and plasma concentrations of amyloid, tau, and other proteins that serve as biomarkers. Conversely, topographical biomarkers reflect the spatial consequences of the disease's pathogenesis, such as regional hypometabolism seen in fluorodeoxyglucose (FDG)-PET scans, tau PET imaging, and the visualization of regional or localized brain atrophy through structural magnetic resonance imaging (MRI). These biomarkers assist clinicians in discerning, differentiating, and confirming AD diagnoses[5]. Other studies are also investigating machine learning techniques with novel biomarkers as promising approaches to predict AD[6].

Although cognitive symptoms are one of the critical signs of AD, it is recommended that the association of both tauopathy (tau PET ligand uptake spread to neocortex or CSF) and amyloidopathy (PET evidence of AD pattern or CSF measured) defines AD even in the absence of cognitive symptoms[7].

2. Amyloid cascade hypothesis

(ACH) can date back to the 1980s where works of multiple research team summed up to the conclusion that the aggregation of Aβ, derived from the cleavage of Amyloid precursor protein (APP), into amyloid plaques is the primary cause of AD[8].

APP is a transmembrane protein with 8 different isoforms present in the human body. The three most common isoforms are APP695, which is primarily observed in neurons, while APP751 and APP770 are found in most tissues including microglia[9].The sequential cleavage of APP by different secretase produces a series of downstream products, including Aβ, which is believed to be an important part of AD pathology[10].

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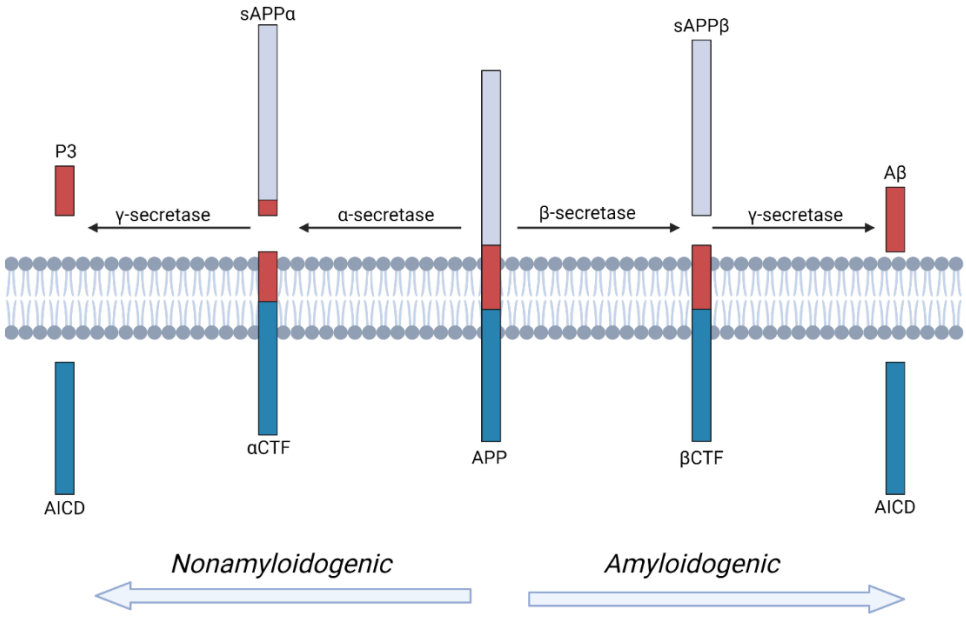


Figure 1. Schematic graph of APP processing (Created with BioRender.com)

There are two pathways by which APP can be processed (Figure 1). The non-amyloidogenic cleavage of APP initiates with α-secretase that cuts the protein within the Aβ sequence, thus preventing its production. The cleavage releases an N-terminal soluble extracellular protein(sαAPP), whereas the remaining intracellular C-terminal segment of 83 amino acid(C83/αCTF), is further processed by γ-secretase into a P3 protein which is soon degraded, and an intracellular segment called AICD[11].

By contrast, cleavage of APP by β-secretase results in a C-terminal segment of 99 amino acid(C99/βCTF) that contains the Aβ region, which will also be processed by γ-secretase to produce Aβ of varying length. Aβ monomers will naturally assemble into oligomers, fibrils, and eventually into the infamous amyloid plaques The accumulation of Aβ species due to an imbalanced production and clearance is thought to be a defining characteristics of AD progression [12]. The clear relationship between Aβ plaques and AD pathology is quite complex; Aβ oligomers and Aβ plaques interacts with astroglia, blood vessels, and microglia to induce neuroinflammation and detrimental cellular responses, eventually leading to neurodegeneration. Additionally, the toxicity of Aβ plaques is partially caused by the polymerization of hyperphosphorylated Tau protein into neurofibrillary tangles, which is heavily correlated with cognitive decline[13,14]. Therapeutics targeting Aβ plaques have also shown to be efficacious in ameliorating AD progression in clinical trials, hence further supporting the vitality of Aβ plaques in AD pathology[15].

The heterogeneity of Aβ deposits is a crucial factor that can influence the biochemical properties of amyloid plaques. Among different Aβ species, AβX-40 and AβX-42 are believed to contribute the most to AD pathology as they are the primary component of amyloid plaques[8],while Aβ42 are more hydrophobic than Aβ40, hence more toxic and forms plaque more easily. Experimentally, it has been reported that higher ratio of Aβ42-to-Aβ40 is capable of elevating plaque formation speed[16]. Moreover, research in 2018 discovered four different profiles of Aβ composition in patients with sporadic or familial AD. Amyloid profile 1(AP1) had a relatively high proportion of AβX-42 species, whereas the presence of both AβX-42 and Aβ-40 was observed in AP2. AP3 and AP4 were less common and exhibited distinct Aβ composition. Interestingly, in vitro and mice experiment revealed differentiable aggregation speed, resistance toward degradation, and overall pattern of amyloid deposition between the amyloid profiles, with AP4 presenting the most aggressive plaque deposition pattern and AP3 manifesting the mildest deposition. It was reported that there was varying seeding speed

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between Aβ species, with Aβ1-42 providing the highest rate of nucleation[17]. These Aβ species can also go through different post-translational modifications like truncation at the N-terminal and pyroglutamylation, which may impact the rate of fibril aggregation[11].

Although amyloid plaques have long been the center of countless studies regarding AD pathology, there has been many counterarguments that falsifies the correlation between senile Aβ and cognitive decline[18]. Consequently, scholars moved on to other forms of Aβ, and Aβ oligomers have likely received the most attention. Amyloid fibrils and plaques are large and insoluble, whereas Aβ oligomers are soluble and hence will be dispersed all over the brain. Cell toxicity assays have supported the view that oligomers are more cytotoxic than Aβ plaques[19]. Nevertheless, the exact molecular mechanism behind it remains to be elucidated. Some literature proposed that Aβ oligomers is capable of binding to a series of receptors including ion channels like N-methyl-D-aspartic acid receptor(NMDAR) and α subunit containing nicotinic acetylcholine receptor (α7nAChR), Aβ binding p75 neurotrophins receptor (P75NRT), low-density lipoprotein receptor-related protein (LRP), cellular prion protein (PrPc), immune globin receptors, β-adrenergic receptor (β-AR), erythropoietin-producing hepatoma cell line receptor (EphR) and some other receptors such as microglia receptors. By binding to these receptors Aβ oligomers can evoke neurotoxic signals and cause a series of harmful defects like mitochondrial dysfunction, DNA damage, synaptic dysfunction, ER stress response and in the worst-case neuronal death[20]. Other views also exist, including causing unspecific membrane perturbation, or the formation of amyloid pores and channels, leading to ion dyshomeostasis[19].

3. Expression and Function of Tau Protein

Tau protein is a microtubule-associated protein first discovered in 1975 [21]. Tau protein is encoded by a 16-exon gene located on chromosome 17 called the microtubule-associated protein tau gene (MAPT). [22]. Tau is mainly found in neurons but sometimes it will be detected in the glia as well as the outside of the cell. It seems that the level of tau protein reflects the mature state of the neuron. It is reported that in immature regions, there is lower level of tau protein while higher level is found in the mature regions. The adult cells mainly express six kinds of tau protein isomers, ranging from 352 to 441 amino acids[23]. The alternative splicing of exons 2 and 3 leads to three kinds of isomers. The other two isomers are generated by splicing of exon 10[24].

Loads of modifications take part in the expression of tau protein. Among all, phosphorylation plays a crucial role. It binds to microtubules and governs their stability and assembly[25]. Tau also undergoes several post-translational modifications, including glycation, deamidation, isomerization, nitration, methylation, ubiquitylation, sumoylation, and truncation[23].

Tau plays an important role in neuron cells reorganization. It participates in the neurite outgrowth and axonal pathfinding[26]. The importance of tau was also reported in the central neuron development. Weingarten et al, showed that post-translational modification played different roles in developing and developed brain[27].

Another role of the tau protein is axonal transport. It can accomplish this by modulating dynein and kinesin, which are motor proteins that move payloads to towards the cell body and the axonal terminus respectively[28].

In addition, Tau is required for other function, such as axonal growth and maturation. Knocking down tau in cultivated rat neurons reduces neurite production, while overexpressing tau enhances neurite formation in non-neuronal cells[29]. Further experiments are needed to confirm the functions of tau in primary neurons from different lines of Mapt-knockout mice[30]. One line showed slowed maturation and reduced neurite length, while another did not.

3.1. Tau Propagation Hypothesis

The tau propagation hypothesis was initially proposed in 2009[31]. Tau propagation became a pioneering and contentious issue that a large number of publications regarding the topic have been reviews or commentaries. The concept of disease spread by templated propagation originated from experiments using human and animal models of transmissible spongiform encephalopathies, including

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Creutzfeldt–Jakob disease in humans and scrapie in sheep[32]. Prion is a kind of protein that is misfold and becomes highly infectious. In the hypothesis, it is said that the neuron will generate prion-like tau protein. Such misfold protein will eventually spread the whole brain of the human, leading to the large number of neurons to die. According to the hypothesis, it is the abnormal phosphorylation of tau protein that will lead to the depolymerize of the microtubules[32]. Besides, the inter-neuron transmission will also be affected[33]. The prion-like tau protein is generated by hyperphosphorylation. The level of tau phosphorylation is maintained under normal level through the regulation of a series of enzyme including glycogen-synthase kinase-3β(GSK-3β), cyclin-dependent protein kinase 5 (cdk5), cAMP-dependent protein kinase (PKA), stress-activated protein kinases and tau phosphatases[34]. Though we understand the way of regulation of phosphorylation of tau protein, it is still a mystery why hyperphosphorylation occurs. It is reported that cdk5 level increased in Alzheimer's disease patient's brain, though such observation was challenged since such result was only shown in one experiment[35]. Abnormal level of PKA was also observed in a few cases. Apart from the enzymes, hyperphosphorylation and aggregation of tau can also be affected by alterations to the protein itself. Some studies have shown that tau may be modified by β-N-acetylglucosamine (GlcNAc), which is called O-GlcNAcylation. Decrease in Tau O-GlcNAcylation was observed in AD brain, which is correlated to tau hyperphosphorylation[36].

What happens next is the transportation of the tau prions. Compared with mysterious generation of hyperphosphorylated tau protein, such process is much clearer. First, the generated tau-prion is released by the pre-synapse through the vesicles. Then, the healthy post neurons will take up the vesicles through endocytosis or fusion of extracellular vesicles with the plasma membrane[37]. The prions will therefore escape from the vesicles and leads to the growth of the fibrils and propagation of the aggregation process. This will lead to the growth in the region of the death neurons[38].

So, loads of treatments are based on such hypothesis, including treatments targeting cdk 5. Inhibitors of cdk 5 are found across multiple structural classes. Although it is unclear whether these inhibitors are specific for cdk 5 over other cdk kinase that play important physiological role, administration of roscovitine did lower the level of hyperphosphorylation of tau in transgenic mice models[39].

Another treatment is based on the Tau O-GlcNAcylation. Recently, small inhibitory compounds that is capable of selectively inhibiting O-GlcNAcase, which removes O-GlcNAc from proteins, have been developed. By increasing tau O-GlcNAcylation, these inhibitors and their future derivate can potentially inhibit tau hyperphosphorylation[40]. In general, Alzheimer's disease remains largely mysterious. The tau propagation hypothesis offers a novel approach to potential treatments, but further research is required to thoroughly evaluate and validate this theory.

4. ApolopoproteinE in AD

APOE, coding ApolopoproteinE (ApoE), is discerned as a key genetic strand for sporadic AD, modulating both the onset age and the chance of developing AD[41]. The two singe-nucleotide polymorphisms as residue 112 and residue 158 in the APOE variant result in three alleles: ε2, ε3 and ε4. As the most common allele, APOEε3 is used as the yardstick. The APOEε4 accentuates the possibility of developing AD[42], whereas APOEε2 offer protection against developing AD [43]. Indeed, as mentioned previously, Aβ accumulation is observed to precede the progression of other AD phenotypes and may play a part in AD onset and progression, with genetic evidence supporting its involvement. However, >99% of AD cases are sporadic[44], in presence of various pathologies in AD brains. This challenges the practical relevance of the infamous "Amyloid Cascade Hypothesis". Furthermore, when various therapeutic Aβ-targeting approaches reduces brain Aβ deposition, intended cognitive improvements are limited[45]. Therefore, pathways other than Aβ deposition are posited to play a role, and APOE stands out since mounting evidence has supported that the APOE isoforms subserve comprehensive molecular and cellular mechanisms in different brain cell types and are correlated with Aβ plaque, tau pathology, neuroinflammation, and energy metabolism failure.

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4.1. The Normal Function and Structure of ApoE

Typically, ApoE is an extracellular protein, acting as a lipid transporter[46]. Cerebral ApoE is manufactured primarily by astrocytes, but also in lesser quantities by reactive microglia, stressed neurons, and other glial cells [47]. To transport lipid, membrane-spanning ATP-binding cassette transporters [48] first load lipids onto ApoE. Subsequently, the lipidated ApoE transport lipids between cells by attaching to ApoE receptors[49] on cell surface. Since residue 122 is attached to lipid-binding site and residue 158 is positioned adjacent to the lipid binding domain [50], the differences among ApoE isoforms by merely two amino acid residues lead to different binding rates with lipoparticles, partially influencing their affinity for lipoparticles of varying sizes[51]. In such way, both the types and amount of lipids transported and the affinity of ApoE to diverse receptors[52] are significantly influenced. APOE2 has been reported as a better lipid acceptor and transporter[53]. Receptor bindings are postulated as a key mechanism contributing to AD risk regulation, since ApoE receptors has been shown to modulate AD neuropathology[54].

Additionally, lipid-free forms of ApoE with misfolding and self-oligomerization tendecies because they are not conformationally stable[55]. Depending on the isoforms, ApoE inclines to produce soluble amyloid protofilaments exhibiting a distinct alpha-helical structure in vitro (ApoE4 > ApoE3 > ApoE2)[56]. In human brains, ApoE4 has also been observed to possess greater aggregation propensity[57]. Together, the isoform-dependent properties in lipidation of ApoE, receptor binding and oligomerization significantly modify its normal functioning, ultimately initiating a series of cellular and systemic processes that influence AD.

4.2. ApoE interactions

Being observed to accumulate together with amyloid deposits, ApoE has been suggested to as a molecular chaperon that promotes the initiation and accumulation of Aβ[58]. ApoE4 accentuates Aβ's propensity to oligomerize, increasing AD risk. In compact plaques in different mouse models of humanized APOE knock-in and murine APOE knock-out, compared to ApoE3, ApoE4 increases Aβ fibrillization and aggregation. On the other hand, ApoE2 remarkably postpones the initiation while mitigating the severity of Aβ plaque formation[59]. Of note, the binding strength of ApoE4–Aβ complexes with ApoE receptors is significantly lower and attributes to a less efficient clearance mediated by receptors and an increase in half-life of Aβ[60]. Aside from inducing Aβ deposits and hindering its removal, APOE variants can significantly regulate the transcription of Aβ precursor protein and the production of Aβ: APOE4 increases these variables more than APOE3 does, both dwarfing APOE2[61]. In APOE knockout plaque-depositing mice, Aβ deposits into plaques. However, when APOE is intact, plaques are less compact and no synaptic and cognitive deficits is observed, highlight the complicated interaction between ApoE and Aβ[60]. Such preclinical data and a case involving a person with APOE deficiency and hyper-lipoproteinaemia type III who yet exhibits normal cognitive function support that downregulating APOE expression could have attenuate cognitive impairments caused by Aβ deposition[62].

The distinguishable effect of ApoE isoforms on Aβ's aggregating tendency in cerebral fibrils rich in β-pleated sheets is the mechanism behind ApoE4's facilitating misfolding most effectively[63]. As mentioned previously, in its lipid-free form, ApoE itself has the propensity to oligomerize. Of note, ApoE oligomerization is suggested to be biologically detrimental and facilitate Aβ oligomerization[40]: a benefactory variant of APOE known as the Jacksonville mutation has been identified to lessen ApoE aggregation and Aβ accumulation; an antibody against lipid-free ApoE, prone to aggregate, has demonstrated potential in various AD mouse models[64].

It is discovered in animal and cell models that independent of Aβ, ApoE4 is positively correlated with not only a burden of induce misfolded and hyperphosphorylated tau but also more acute tau-driven neurodegeneration[65]. Of note, despite of similar extent of tau accumulation in reference to APOE3/PS19 mice, APOE-removed/PS19 mice were protected against loss of neuronal and hippocampal volume relative to other APOE-expressing mice[66]. Resembling its effect on Aβ, ApoE4 not only accentuate the propensity of tau to deposit but also modulate the cerebral response to those

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deposits[67]. These mechanisms will be further clarified in a subsequent discussion on the cell-specific effects of APOE, such as on astrocytes and microglia.

4.3. ApoE Cellular Effects

Astrocytes predominantly produce cholesterol for mature neurons and ApoE for effective cholesterol transport[68]. Astrocytes derived From APOE4 human-inducible pluripotent stem cells (hiPSCs) demonstrate dysfunction in secreting lipidated ApoE and cholesterol metabolism in contrast with APOE3 hiPSC-derived astrocytes[69]. Such malfunctioning is possibly detrimental to astrocytes and neurons and could induce neurodegeneration[70]. Supporting this hypothesis, APOE4 astrocytes have more exhibit increased lipid droplet accumulation, glucose underutilization and mitochondrial dysfunction. [71]. As the key producers of cerebral, ApoE production in astrocytes regulates downstream pathways operating both autonomously within cells and externally. In APOE knock-in plaque-depositing mice, astrocytic APOE3 and APOE4 deletions spare Aβ aggregation: plaque decreased to the same extent observed in APOE knockout mice[72]. In contrast, in the tauopathy equivalent, astrocytic APOE4 removal exclusively substantially reduce tau neurofibrillary tangle deposits[73]. Intriguingly, the data showed that astrocytic APOE deletion hinder the microglial response to Aβ plaques and neurofibrillary tangles, but astrocytic reaction was largely unaltered[72,73]. Therefore, it is postulated astrocytic APOE effect astrocyte–microglia communication.

Although normally astrocytes produce the majority of cerebral ApoE, with AD, ApoE expression is distinctively increase by reactive microglia [74] responding to Aβ plaques and neurofibrillary tangles. This disease-associated microglial (DAM) response is modulated in an isoform-dependent fashion, likely via their various affinity to specific surface microglial receptors. Reactive microglia move toward Aβ plaques, envelop plaques and increase the production of ApoE, which attaches to receptors and propels plaque compaction. This response potentially account for reduced microglial reactivity against and compactness of Aβ plaques in ApoE knockout plaque-depositing mice[75]. HiPSCs with an APOE4 microglial profile downregulates phagocytic activity and upregulates inflammatory genes relative to those with an APOE3 profile [76]. Along the line, in microglia of APOE4/PS19 model, APOE4 deletion retains a neuroprotective microglial response in originally tauopathy mice[77].

Compared to microglia, neurons under stress produce less ApoE [47]. In hIPSC-derived neurons, ApoE4 affects synaptic function, fatty acid accumulation and hyperexcitability[75]. Either astrocytic or neuronal APOE3/APOE4 mouse models indicate that APOE3 is protective against neuronal hyperexcitability, whereas APOE4 in neurons is detrimental[78]. A separate study using a tauopathy mouse model has found that removing neuron-derived APOE4 significantly mitigates tau pathology and tau-induced neurodegeneration[79].

Post-mortem analysis of brain tissue has linked the APOEε4 allele and fewer oligodendrocytes in the frontal cortex in controlled AD patients[80]. ApoE is posited to mediate oligodendrocyte number and function. Research of APOE knock-in mice both in postmortem brain studies and in vivo research has attributed damaged myelination of oligodendrocytes to cholesterol transport mediated by ApoE4 [81].

ApoE4 has a higher propensity of breakdown or cleavage. Therefore, ApoE4 has more fragments of ApoE than ApoE3. This increased abundance can induce mitochondrial dysfunction and impaired regulation of cellular lipid content in neurons[82]. Moreover, in vitro studies in APOE4 carriers shows lysosomal impairment regulated by ApoE4 results in an accumulation of impaired and hindered mitochondrial. This mitochondrial dysfunction partially results from to mitophagy blockade[83]. APOE4 also affect proteins expression for mitochondrial fission and fusion. This expression alters mitochondrial dynamics and thereby regulates the moderating and storage of calcium ions[84]. In vitro studies in an APOE4-expressing neuron showed undermined calcium flux compared to APOE3-expressing neurons. The impaired calcium flux is suggested to explain the hyperexcitability in APOE4 neurons [85].

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5. Discussion

Mounting evidence indicates that AD has more than one pathway. No existing hypothesis, by itself, can fully explain the pathology. Therefore, it is crucial to examine all the prominent hypotheses to build groundwork for in-depth investigation. Here, with details ranging from molecular mechanisms to cellular interactions, we not only scrutinize the Aβ cascade hypothesis, which remains widely accepted, but also analyze the tau propagation hypothesis and the ApoE hypothesis as complementary.

Though recent studies question the primacy of Aβ due to inconsistent therapeutic efficacy, Aβ remains in the spotlight, and more research on a molecular level is necessary to understand the initiation and and progression of AD. Tau pathology is of great importance to neurodegenerative processes, yet its exact role in AD progression requires further investigation. ApoE, particularly APOEε4, is emphasized as a key genetic risk factor influencing Aβ deposition and tau pathology and more investigations focusing on the multifaceted role of ApoE is necessary. By and large, further investigation into these three hypotheses is needed to understand the initiation and development of AD is needed.

6. Conclusion

This paper mainly focuses on the three hypotheses of the Alzheimer's disease: amyloid hypothesis, tau propagation hypothesis and ApoE hypothesis. All the three hypothesizes provided strong proof and different therapies were developed based on these hypothesizes. However, given the complexity of this disease, additional molecular experiments are necessary to assess the viability of the hypothesis.

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