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APOE and Alzheimer's Disease: Evidence Mounts that Targeting *APOE4* may Combat Alzheimer's Pathogenesis

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Abstract

Alzheimer's disease (AD) is an immutable neurodegenerative disease featured by the two hallmark brain pathologies that are the extracellular amyloid ß (Aß) and intraneuronal tau protein. People carrying the *APOE4* allele are at high risk of AD concerning the ones carrying the *ε3* allele, while the *ε2* allele abates risk. ApoE isoforms exert a central role in controlling the transport of brain lipid, neuronal signaling, mitochondrial function, glucose metabolism, and neuroinflammation. Regardless of widespread indispensable studies, the appropriate function of *APOE* in AD etiology stays ambiguous. Existing proof recommends that the disparate outcomes of ApoE isoforms on Aβ accretion and clearance have a distinct function in AD pathogenesis. ApoE–lipoproteins combine diverse cell-surface receptors to transport lipids and moreover to lipophilic Aβ peptide, that is believed to begin deadly events that generate neurodegeneration in the AD. ApoE has great influence in tau pathogenesis, tau-mediated neurodegeneration, and neuroinflammation, as well as α-synucleinopathy, lipid metabolism, and synaptic plasticity despite the presence of Aβ pathology. ApoE4 shows the deleterious effect for AD while the lack of ApoE4 is defensive. Therapeutic strategies primarily depend on *APOE* suggest to lessen the noxious effects of ApoE4 and reestablish the protective aptitudes of ApoE. This appraisal represents the critical interactions of *APOE* and AD pathology, existing facts on ApoE levels in the central nervous system (CNS), and the credible active stratagems for AD therapy by aiming ApoE. This review also highlighted utmost ApoE targeting therapeutic tactics that are crucial for controlling Alzheimer's pathogenesis.

Keywords *APOE4* · Senile plaques · Neurofibrillary tangles · Amyloid β · Tauopathy · Alzheimer's disease

Introduction

Alzheimer's disease (AD) is the utmost common genre of dementia that often involves loss of memory and decline in other cognitive skills, which are required to maintain daily activities [1, 2]. Nearly 13% of people 65 or older and 45% of people older than 85 are projected to have Alzheimer's that causes about 60–80% of dementia cases [1, 3]. Struggling with remembering recent events or simply short-term memory deficits is the most usual symptom of patients with AD. In later stages, symptoms including disorientation; language impairment; severe memory loss; mood and behavior changes; suspicions about family, friends; and difficulty speaking, swallowing, and walking are reported. As a patient's condition deteriorates, they often isolate themselves from society and even from family. Progressively, when major physical functions are lost, a patient may even die. Though the promptness of progress of AD can differ, the ordinary life expectancy of the patients after diagnosis is usually 3 to 9 years [4].

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Increasing evidence from various studies including pathological, genetic, and functional studies have demonstrated that accretion of Aβ can take place due to the disproportion, the production, and clearance of the Aβ peptides in the brain. Toxic Aβ aggregates can be found in the form of intraneuronal Aβ, Aβ oligomers (i.e., soluble), and amyloid plaques can eventually cause neurodegeneration and dementia by injuring the synapses [3, 5]. Conversely, the incidence of microtubule-linked protein tau can lead to Aβ toxicity [6], and neurofibrillary tangles (NFTs) are aggregates of hyperphosphorylated tau protein. Aβ is usually comprised of 40 to 42 amino acids and form via proteolytic degradation of the amyloid precursor protein (APP) [7].

The actual cause of AD is not well-known and around 70% of the risk is thought to be genetic [8]. The genetic heritability of AD is based on evaluations of twin, as well as family studies ranging from 49 to 79% [9]. About 0.1% of the cases are found in the familial sorts of autosomal-prevailing inheritance, which have an onset earlier of age 65, and this disease form is named as early-onset familial AD [10]. In most of the cases, the autosomal-prevailing AD can be ascribed due to the mutations in one of three genes including those encoding *APP* and presenilins (*PSEN1* and *PSEN2*) [11]. Increased production of Aβ42, a small protein and main component of senile plaques, is seen with *PSEN* genes and most of the mutations in the *APP* [12]. Some of these mutations simply change the relation amid Aβ42 and Aβ40 without raising the levels of Aβ42 [13]. In most of the cases, AD does not show autosomal-prevailing inheritance and is characterized as the sporadic AD, wherein genetic and environmental differences may play roles as risk factors. The *ε4* allele of the apolipoprotein E (*APOE4*) is considered as the most common inherited genetic risk aspect [14]. It has been found that 40 to 80% people with AD have at least one *APOE4* [15], and it increases the risk of AD in heterozygotes and homozygotes by 3 and 15 times, respectively [16].

Although there is no remedy for AD, research is ongoing and symptomatic treatments are available [17]. While existing Alzheimer's treatments cannot halt the progression, they can slow down the deterioration of the symptoms of dementia to some extent and improve AD patients' quality of life. Currently, numerous efforts are ongoing to discover better treatment strategies based on ApoE4 to delay Alzheimer's onset, treat the disease, and to stop its progression. Therefore, the objective of this appraisal is to explore the impact of *APOE* on AD pathology and promising ApoE4 target therapeutic strategy for abating the neurodegeneration for the management of Alzheimer's pathogenesis.

APOE4 as a Strong Genetic Risk Factor for Alzheimer's Pathogenesis

ApoE is a 299 amino acid protein and primary lipid transporter abundantly found in the brain. It is synthesized mainly by astrocytes within the blood-brain barrier (BBB) [18]. There are three major ApoE polymorphic alleles in humans, *APOE2*, *APOE3*, and *APOE4*. They encode three protein isoforms such as ApoE2, ApoE3, and ApoE4 that vary by merely two amino acids cysteine/arginine polymorphisms at positions 112 or 158 in the N-terminal domain. Furthermore, early-onset familial AD characteristically builds up before 65 years and is responsible for a small portion (< 1%) of AD cases. This form of AD is mainly generated by overproduction of Aβ on account of the mutations in either the *APP* gene or genes encoding presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*). These genes are fundamental constituents of the γ-secretase complexes accountable for cleavage and release of Aβ [10, 19, 20]. On the other hand, late-onset AD (LOAD) is the most common form of AD that usually occurs at the later stage in life (> 65 years). *APOE4* is the major risk factor for the pathogenesis of LOAD commonly present in 15% of people (Fig. 1) [21, 22].

In a study, Farrer et al. [23] based on the clinic- or autopsy-linked studies in Caucasian subjects reported that a copy or two copies of *APOE4* was causative for increasing the risk of AD concerning people with the *APOE3*/*APOE3* genotype. This study also stated a weak link amid *APOE4* and AD for Hispanics, as well as African American people, but a stronger correlation was reported for Japanese. The researchers reported the proof of the *APOE4* effect amid 40- to 90-year ages but abate afterward 70 years and that the risk of AD linked to a particular genotype differs concerning sex. Furthermore, Sepehrnia et al. [24] stated that Nigerian blacks have the highest frequency of *APOE4* in world populations, but their adjusted mean cholesterol level is among the lowest reported in studies of cholesterol-*APOE* linkage. In another study, Hendrie et al. [25] reported AD is pretty rare amid Africans living in Africa than in African Americans. Mounting evidence from various studies suggested that this might be due to the low cholesterol levels present in these populations [26]. Conversely, Japanese and Caucasian people who carry *APOE4* are found to have 10 to 30 times more risk of rising AD than people who are not any *APOE4*. Nonetheless, the precise mechanism of dramatic effects exerted by this allele is yet to be fully discovered; evidence from studies suggests the interaction with amyloid [27]. Though few patients with AD have minimum one copy of the *ε4* allele, as this *APOE4* is not the main contributing factors to the disease. Actually, *APOE4* is absent for one third of Alzheimer's patients. Interestingly, some *APOE4* homozygotes even never develop AD. However, people with two copies of *APOE4* have as high as 20 times the risk of rising AD [28]. In contrast, there is also evidence that supports the protective roles of *APOE2* in patients with AD [29]. People with *APOE2*/*APOE4*, *APOE3*/*APOE4*, and *APOE4*/*APOE4* are most likely to develop AD, but the odds ratios (ORs) were abated for people with genotypes *APOE2*/*APOE2* and *APOE2*/*APOE3* [23]. *APOE4* has been found to significantly upsurge the odds that a person will

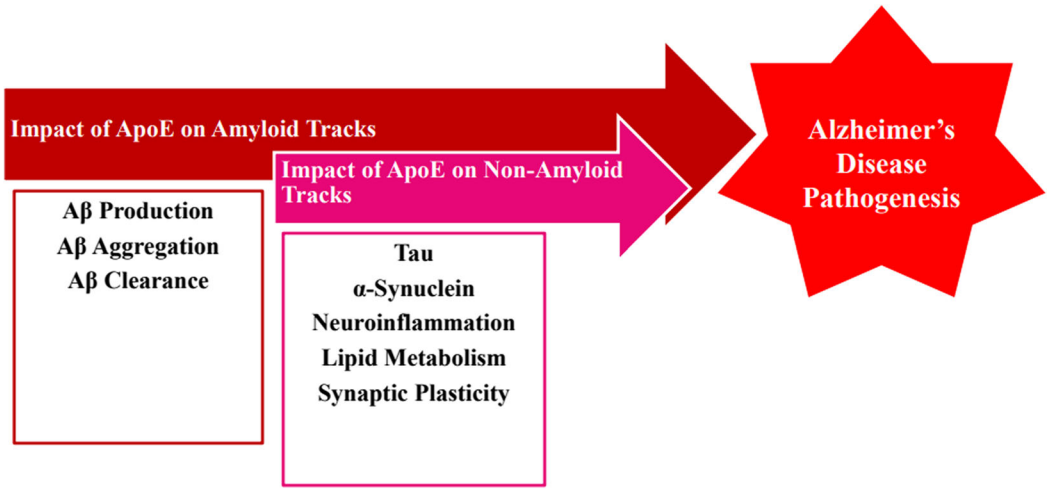

Fig. 1 The pathogenic effects of ApoE in Alzheimer's disease. Proof recommends that ApoE increases the risk of Alzheimer's by exerting its pathogenic effect on the production, aggregation, and clearance of Aβ that leads to Aβ deposition as well as other effects including tau hyperphosphorylation, α-synucleinopathy, neuroinflammation, lipid metabolism, and synaptic function also augment the disease propagation

develop AD. However, a study reported that in individuals several independent risk factors including high serum total cholesterol, any combination of *APOE* alleles, and high blood pressure in the midlife collectively could increase the risk by threefolds to develop AD at the later stage [26].

Effects of ApoE on Amyloid Pathways

ApoE and Aβ Production

Senile plaques composed primarily of the Aβ peptides are one of the neuropathological indicators of AD. Aβ is produced in an amyloidogenic path by the cleavage of β- and γ-secretases. Additionally, by influencing α-, β-, or γ-secretase activity, ApoE acts as a principal cholesterol carrier protein rises Aβ generation [30].

Previously, Ye et al. [31] inspected the effect of ApoE isoforms on APP processing and production of Aβ in rat neuroblastoma B103 cells firmly transfected with the human wild-sort APP695 (B103-APP). According to the statement of the researchers, ApoE4 seems to control the processing of APP and the generation of Aβ by using the pathway of low-density lipoprotein receptor-related protein (LRP) and domain interface. The outcomes give acumens into why ApoE4 is connected with high risk for AD and may signify a prospective therapeutic object for the drug development.

In another study, Hopkins et al. [32] reported that Aß generation rises on account of the induction of ApoE4 which could be interceded by a new ApoE-binding protein (TMCC2), recommended to expedite an interaction amid APP and the γ-secretase complex. In AD, it is clear that the interplay between TMCC2 and ApoE may also consequently make contributions to interrupt Aβ protein precursor metabolism and change Aβ genesis. Recently, using ES-cell-derived human neurons, Huang et al. [33] mentioned that ApoE isoforms (i.e., ApoE4 > ApoE3 > ApoE2) control APP transcription and Aβ production by triggering a non-canonical mitogen-activated protein kinase signaling pathway.

ApoE and Aβ Aggregation

ApoE exerts an imperative role in the Aβ levels, aggregation, and amyloid plaque loads. In the APP transgenic amyloid mice model, copious studies have demonstrated that ApoE is vital for Aβ deposition. When amyloid model PDAPP or Tg2576 mice have crossed with *APOE* knock-out (KO) mice, accumulation of Aβ in the form of amyloid plaques and the cerebral amyloid angiopathy (CAA) was drastically reduced [34, 35]. Occasionally increased accretion of Aβ in the form of diffused plaques and plaques of thioflavin-S-positive fibril were virtually lacking, especially, while there is quite substantial. Findings of these studies strongly suggest the important role of mouse ApoE in Aβ fibrillogenesis, fibrillar Aβ stabilization, and maturation of amyloid plaques [34, 35]. Nevertheless, the origin of *APOE* determines the effects of *APOE* on Aβ fibrillogenesis. In this regard, in PDAPP mice, reduced early Aβ deposition was observed by Holtzman et al. [36] with the expression of human *APOE3* and *APOE4* by astrocytes in the *APOE*-KO. Fryer et al. [37] reported that human *APOE4* changes the ratio of Aβ40 and Aβ42, as well as stimulates the genesis of CAA in Tg2576 mice. Human *APOE*-targeted replacement (TR) mice had less accumulation of Aβ in Tg2576 mice concerning control mice expressing mouse *APOE*.

It has been found that when Aβ aggregates, soluble Aβ peptides can lead to change the conformation of these peptides into a β-sheet structure and can form nucleuses, which can also further speed up the process of fibrillogenesis to trigger the formation of insoluble fibrils with enriched β-sheet structures [38]. Several

studies explored the roles of ApoE in Aβ aggregation. Nevertheless, the assumptions of the studies are debatable, where ApoE can either accelerate or inhibit Aβ aggregation. It has been found that high concentrations of ApoE can trigger the formation of enormous co-aggregates with Aβ [39], whereas ApoE4 is expected to stimulate Aβ aggregation greater than ApoE3 [40, 41]. Furthermore, it was also observed that ApoE upsurges the level of Aβ oligomers in an isoform-reliant way (i.e., ApoE4 > ApoE3 > ApoE2) [42]. Furthermore, ApoE4 steadies Aβ oligomers greater than ApoE3 [43]. These conclusions suggest that ApoE4 detrimentally triggers Aβ aggregation in AD (Fig. 2).

In contrast, various studies have concluded that Aβ fibrillogenesis can be decreased by ApoE. Beginning of Aβ fibril formation can also be inhibited by ApoE, when investigated either with or without the addition of pre-formed Aβ aggregates as seeds [45, 46]. Since ApoE have preferences to interact with the β-sheet structure containing Aβ peptides [47], ApoE is also likely to capture Aβ nuclei and also prevents its scattering properties as well as trigger Aβ fibrillogenesis [46]. ApoE3 seems to interact with Aβ more than ApoE4 as mentioned; consequently, it is probable that Aβ fibril formation is less effectively inhibited by ApoE4. In this perspective, ApoE4 may not be that much effective to support the useful effects of ApoE to prevent Aβ fibrillation in AD. If the amount of the ApoE/Aβ complex increases as the only product of the reaction, they may form massive co-aggregates [46]. Hatters et al. [48] stated that ApoE could also aggregate with random protofilament-alike structure, where the aggregates form at extensively diverse rates which primarily depends on the isoform (i.e., ApoE4 > ApoE3 > ApoE2). Thus, through its self-aggregating tendency, ApoE4 may also be able to create more co-aggregates with Aβ. Furthermore, various experiments have also demonstrated that in the background of the amyloid model mice, *APOE3*-TR mice had less Aβ deposition than *APOE4*-TR mice [37, 49]. Instead, a more violent amyloid model mice known as 5xFAD [50], amyloid plaque deposition was far more in E4FAD mice, and E2/E3FAD mice have considerably higher diffuse plaques with E4FAD showing more dense plaques [51]. Altogether, these findings suggest that as compared to *APOE2* or *APOE3* and *APOE4*, it is either likely to stimulate Aβ fibrillogenesis or in case of prevention of Aβ aggregation it is less effective, or both. Moreover, the exact outcomes can be affected by copious factors including lipidation status, ApoE isoform, aggregation states, and the location and time of its existence during the process of disease. Furthermore, the investigation is also required to observe the effects of fibrillar plaques and diffuse on synaptic behaviors and functions in the presence of different ApoE isoforms [45]. In a current study, Hatami et al. [52] reported that most familial AD (FAD) mutations accelerated the rate of aggregation of Aβ. Moreover, declining of FAD mutations within the Aβ sequence is responsible for noticeable alterations in aggregation kinetics and finally impacts the capability of Aβ to generate immunologically and morphologically discrete amyloid assemblies.

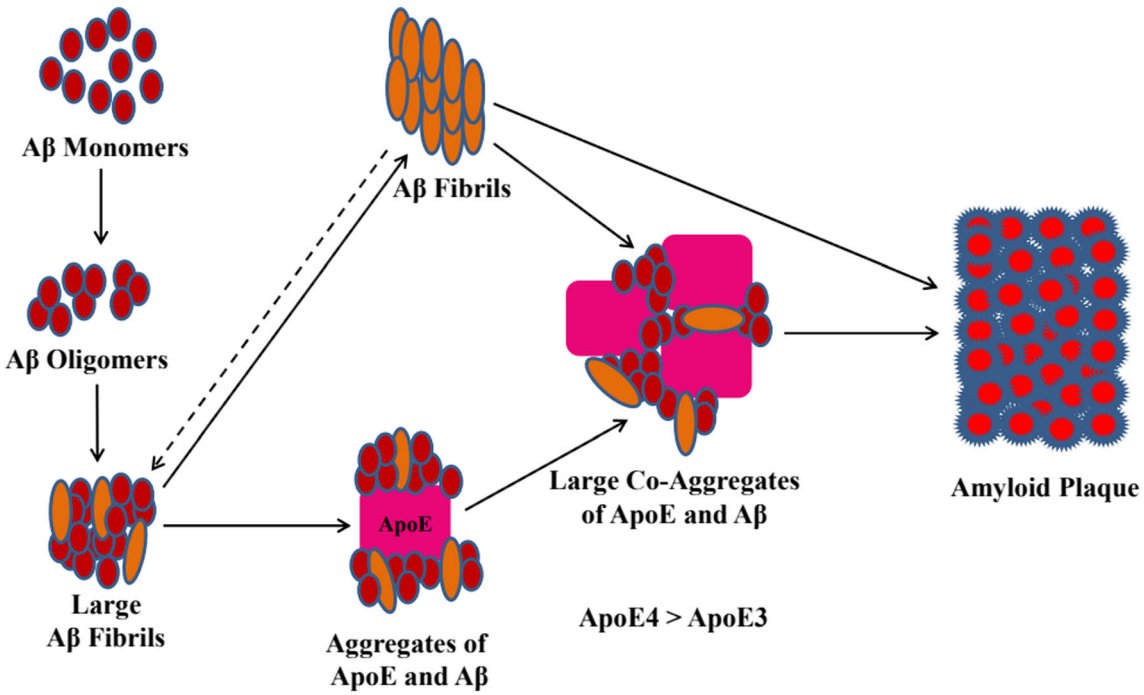

Fig. 2 The impact of ApoE on Aβ aggregation in Alzheimer's disease. Aβ monomers alter their conformation to generate oligomers and intermediate aggregates and then form large fibrils. The linkage of Aβ with ApoE generates aggregation of ApoE and Aβ as well as stimulates Aβ fibrillogenesis to form Aβ fibrils. The generated aggregates of ApoE and Aβ in conjunction with Aβ fibrils further accelerate to form larger co-aggregates. This co-aggregate deposited in the brain as amyloid plaques, Aβ fibrils also stimulate the formation of amyloid plaques [44]

ApoE and Aβ Clearance

The metabolism and transport of Aβ in the brain can be altered by ApoE. In cell culture systems, the roles of ApoE isoforms on Aβ production and processing of APP have been studied. Studies propose that lipid-free and lipid-poor ApoE4 increase LRP1- and ApoER2-reliant APP endocytosis by enhancing the production of Aβ [31, 53, 54]. Nonetheless, in other studies, no strong evidence was found to support isoform-specific effects on APP processing [55, 56]. Furthermore, there is no conclusive data to suggest that ApoE isoforms possess a different role in the Aβ production. Also, ApoE seems to exert an imperative role by numerous credible paths in the Aβ clearance [44] mentioned in Fig. 3. Sequestration of Aβ can take place via ApoE-comprising lipoprotein particles and modulation of the cellular uptake of an ApoE–Aβ complex can take place due to receptor-mediated endocytosis. Conversely, by transporting through the BBB, ApoE may control the elimination of Aβ from the brain cells to the systemic circulation. Through several sorts of neuronal cells, human ApoE helps the attachment as well as internalization of Aβ and this has been demonstrated in various studies [57–59]. No overall trend developed, although some of these studies observed ApoE isoform-reliant variances in the degree of the cellular uptake of Aβ. However, facilitation of cellular Aβ degradation was observed in few studies [60, 61], and further studies are required to establish whether ApoE helps in the uptake of Aβ into the several cell types present in the brain. Indeed, studies are also obligatory to establish and to clarify the mechanism whether this heightened uptake happens in an isoform-specific mode or not.

It is still unclear that how exactly this denouement is related to the observed results, where deficiency of ApoE can lead to an intense decrease in a load of thioflavin-S-positive amyloid [34, 36, 62]. Fascinatingly, it has been found that in young PDAPP mice, before the onset of accretion of Aβ, soluble Aβ levels may be increased due to the lack of ApoE and this result is consistent with outcome obtained from cell culture data [63]. This finding was also confirmed in an experiment in which microdialysis was used to examine the Aβ level in interstitial fluid of the brain [64]. Some studies also support that cellular Aβ degradation and uptake are enhanced by ApoE, Indeed, it also needs to be considered that BBB can act as an effective pathway of clearance of Aβ in the brain and particularly by LRP1 [65].

The clearance of Aβ is yet to be extensively studied in the presence of human ApoE. Recent findings from a study have demonstrated that in the brain of the mouse, brain to blood clearance of lapidated ApoE4 is considerably lower than the ApoE3 and ApoE2 clearance [66]. However, this tendency is quite reversed for what is detected for the entire human ApoE levels in the brain especially when the *APOE* are expressed in knock-in (KI) mice. Thus, whether BBB shows any crucial part in case of controlling the brain's ApoE levels yet needs to be established. Growing current findings strongly recommends that when a composite in between human ApoE and Aβ is formed, the brain to blood elimination of Aβ is essentially abated concerning free

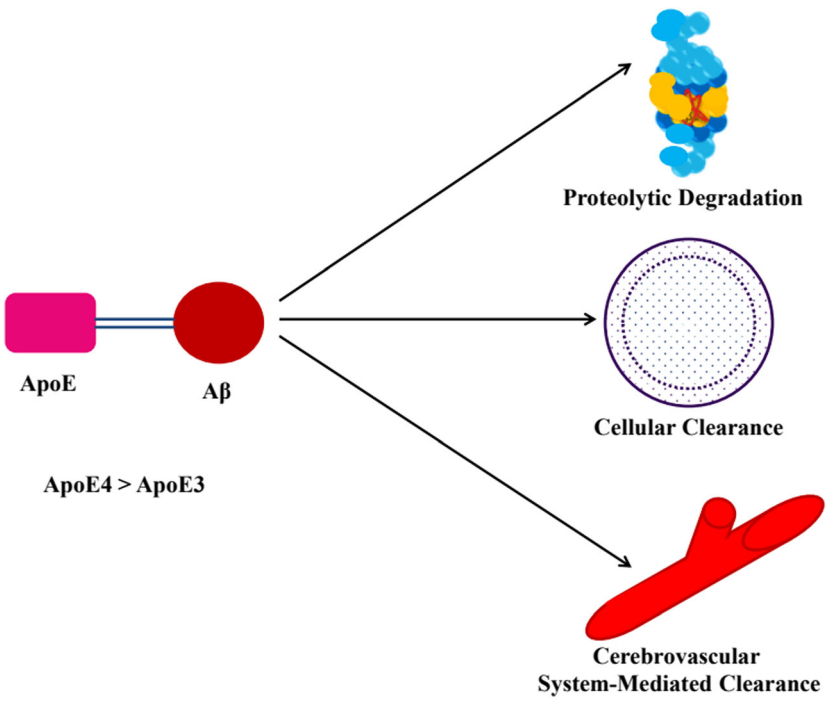

Fig. 3 The impact of ApoE on Aβ clearance in Alzheimer's disease. The Aβ is cleared from the brain by the proteolytic degradation, cellular clearance, and cerebrovascular system-linked clearance. ApoE likely facilitates Aβ clearance by triggering the aforementioned pathways. The Aβ clearance is also suppressed by ApoE through competing with either Aβ receptor or by blocking Aβ clearance [44]

Aβ [66–68]. Moreover, Aβ composite to ApoE2 and ApoE3 is less more likely to be removed from the brain at a considerably quicker degree than Aβ composite to ApoE4 [66]. Ji et al. [69] observed at BBB transference of Aβ in transgenic mice for either human ApoE4 or ApoE3 did not exhibit any significant variances regarding Aβ removal from the brain. Lastly, in brain capillaries, an ApoE4–Aβ complex found in the periphery is far more sequestered as compared to the Aβ bound to ApoE2 or ApoE3. This denouement further suggests that ApoE4-facilitated blood to brain transportation of Aβ can play an important role in the accretion of amyloid in the brain [70]. In addition to these studies, further work is required to decipher the precise roles played by BBB in mediating clearance of Aβ, how exactly ApoE contributes in this process, and also whether isoform-explicit roles be existent or not. Presently, a study by Liu et al. [71] reported that astrocytic low-density lipoprotein receptor-related protein 1 (LRP1) exerts a pivotal role in Aβ metabolism. Moreover, it also accounts for restoring LRP1 expression and function in the brain could be a fruitful approach to expedite Aβ clearance and counter amyloid pathology in AD.

Effects of ApoE on Non-amyloid Pathways

ApoE and Tau

ApoE might also affect processes involved in neurodegeneration, in which, there is a link of tau pathology. Interestingly, overrepresentation of the *APOE4* allele has been noticed in most of the clinical studies in case of both AD and frontotemporal dementia, whereas histopathologic examinations showed a substantial positive correlation between stage of neurofibrillary pathology and *APOE* genotype [72]. For instance, even following the correction of their levels of Aβ42, Alzheimer's patients having ApoE4 allele normally contain more tau in the cerebrospinal fluid [73]. Agosta et al. [74] performed a study in 31 patients with behavioral and variant frontotemporal dementia and 51 patients with a probable AD, in comparison with 56 healthy controls, to explore the effect of *ε4* allele carrier status on the disease severity pattern and atrophy of gray matter. It was found that the frequency of *ε4* allele was notably higher in the patients with AD ($P < 0.001$) as compared to healthy controls, but not in the patients with variant frontotemporal dementia. No differences were noticed in terms of cognitive and demographic profiles between noncarriers and *ε4* allele carriers within any of the diagnostic groups. Nonetheless, marked brain atrophy in disease-specific regions in comparison with noncarriers in both AD and variant frontotemporal dementia was linked with *ε4* carrier status. AD *ε4* carriers exhibited noticeable atrophy in the right hippocampus and bilateral parietal cortex. On the other hand, variant frontotemporal dementia *ε4* carriers showed marked atrophy in the dorsolateral, bilateral medial, and frontal cortex, anterior insula and cingulate cortex with right predominance. This regional effect of *ε4* is consistent with the hypothesis that in different neurodegenerative diseases ApoE may possibly alter the morphologic expression in a unique way. The patterns of atrophy in carriers of *ε4* might specify that they are at significant danger for further clinical progression. However, Riemenschneider et al. [75] found that there is no noteworthy difference between the groups containing either *ε2/ε4* allele frequency. Patients with the *ε2/ε3* genotype (i.e., 61.3 years) showed the highest age at onset. In contrast, patients with the *ε3/ε3* (i.e., 58.3 years) had the lower age at onset than the patients with the *ε2/ε3* genotype and *ε3/ε4* genotype (i.e., 56.4 years). Nonetheless, these differences had no statistical significance. Another study conducted by Srinivasan et al. [76] showed that frontotemporal dementia is not related to tau gene mutations. They also found that *APOE4* allele possessions in men can approximately double the chances of developing the disease, while this type of possession has no impact upon disease risk in women.

Strittmatter et al. [77] stated the isoform-specific interactions of ApoE with microtubule-associated protein tau. They found in an in vitro binding assay that ApoE3 rather than ApoE4 mainly interacts with tau. Furthermore, isoform-specific interactions of ApoE with tau perhaps play a role in the regulation of intraneuronal tau metabolism in AD and also in the alteration of the rate of NFTs and paired helical filaments [77]. Phosphorylation of tau prevented the interaction between ApoE3 and tau, which suggests that ApoE3 binds preferably to non-phosphorylated tau. In another study, Chang et al., [78] mentioned that ApoE4 (1–272) was neurotoxic, however full-length ApoE4 (1–240) and ApoE4 (1–299) were not. These findings suggest that the lipid-binding region (i.e., amino acids 241–272) facilitates the neurotoxicity, besides that amino acids 273–299 are protective. The neurotoxicity of ApoE4 (1–272) was found to be abolished by a quadruple mutation in the lipid-binding regions mainly such as W264R, F257A, V269A, and I250A. In addition, neurotoxicity of full-length ApoE4 is associated with the single mutations in the amino acid regions 273–299 (i.e., Q284A, L279Q, or K282A). Study via immunofluorescence staining revealed that in some cells ApoE4 (1–272) made filamentous inclusions comprising phosphorylated tau and interacted with mitochondria in others, which can further lead to mitochondrial dysfunction as determined by flow cytometry and MitoTracker staining. Neurotoxicity or mitochondrial dysfunction was not caused by ApoE4 (241–272), which suggests that only the lipid-binding region is inadequate to cause neurotoxicity. Instead, neurotoxicity of ApoE4 (1–272) and the mitochondrial interaction were abolished upon truncation of N-terminal sequences (i.e., amino acids 1–170) having the receptor-binding region (i.e., amino acids 135–150) and triple mutations within that region (i.e., R142A, R147A, and K146A). Further studies revealed that the receptor-binding

region is essential to escape from the secretory pathway and that the lipid-binding region facilitated mitochondrial interaction. Hence, the receptor- and lipid-binding regions in fragments of ApoE4 work together to facilitate neurotoxicity and dysfunction of mitochondria, which might be crucial in the pathogenesis of AD. A study conducted by Harris et al. [79] in ApoE4 transgenic mice showed that Erk activation was linked with the increased tau phosphorylation, and this might be modified by zinc, which suggests that zinc and ApoE4 work together to contribute to the AD pathogenesis. Hoe et al. [80] showed that a number of signaling cascades in neurons are affected by ApoE including increased level of disabled phosphorylation, ERK1/2 pathway activation pathway (i.e., reliant on calcium influx through the NMDA receptor) and the c-Jun N-terminal kinase 1/2 pathway inhibition (i.e., reliant on γ-secretase and G-proteins). Nevertheless, in another study, Huang et al. [81] stated that ApoE4 preferentially go through intracellular processing, generating a bioactive fragment that interacts with cytoskeletal components and induces NFT-like inclusions comprising phosphorylated neurofilaments and phosphorylated tau of high molecular weight in neurons.

Recently, Shi et al. [82] revealed a promising new role of *APOE4* in the development of AD. A mouse model was designed by the researchers, in which the modified form of human tau was observed in the rodents, influencing them to form tangle. These researchers genetically modified the mice to contain human versions of the *APOE* genotypes (i.e., *ε2*, *ε3*, and *ε4*) instead of their mouse-specific *APOE*. They observed the mice for 9 months and in the meantime, the mice that had *APOE2* showed the least neurodegeneration and the *APOE4* showed the most neurodegeneration. The hippocampus and entorhinal cortex are the brain areas that play a pivotal role in memory were found to have atrophied in case of *APOE* variations containing mice. Furthermore, brain damage was also noticed in these mice with the significant number of dead brain cells. The study also showed that tau tangles were not that much harmful, particularly when *APOE* was absent. Conversely, no brain damage was observed in the mice that lacked *APOE*. The researchers also noticed a profound inflammatory response by observing the immune cells in the brains of mice with *APOE4* were activated; in contrast, immune cell activation was not noticed in case of mice that lacked *APOE4*. To find out the functions of in human brains, these researchers also investigated autopsy samples, which were collected from the 79 dead people who primarily died due to tau pathologies and made a database of the ApoE variants that these dead people had. These studies also showed that people who had *APOE4* experienced more severe damage concerning those without the variant. The denouements further recommend that *APOE4* can interfere with neuroinflammation, tau pathogenesis as well as neurodegeneration mediated by tau which is independent of Aβ pathology [82].

ApoE and α-Synuclein

AD and synucleinopathies are found to share similar pathological mechanisms. ApoE4, which is known as the most common genetic risk factor for AD, also upsurges the risk for dementia in the context of pure synucleinopathies. However, the molecular mechanisms of the role of α-synuclein are yet to be fully revealed. On the other hand, pathologic effects of α-synuclein are generated by a gain-of-function toxic mechanism triggered by the accumulation of this molecule and this finding is found to have strong evidence. Nevertheless, it has also been recommended that loss of the normal α-synuclein physiological functions might play a crucial role [83]. Remarkably, up to 50% of patients with dementia and α-synucleinopathy also have Aβ plaques, whereas a smaller subset also has associated NFTs [84]. Gallardo et al. [85] using transgenic mice reported neurodegeneration induced by α-synuclein involving ubiquitin/proteasome system activation, the buildup of insoluble mouse Aβ, and an enormous upsurge in ApoE levels. ApoE was injurious and was not protective, since ApoE deletion caused the delay in neurodegeneration caused by α-synuclein and suppression of the Aβ accumulation. The results show a molecular link between central pathogenic mechanisms involved in AD and Parkinson's disease. Furthermore, it also suggests that intracellular α-synuclein is pathogenic, at least partly due to the activation of ApoE involved extracellular signaling pathways.

In a recent study, Emamzadeh et al. [86] studied the effects of different isoforms of ApoE (i.e., ApoE2, ApoE3, ApoE4) on the α-synuclein aggregation. The results also showed that ApoE concentration influences α-synuclein aggregation. At low ApoE concentrations (< 15 nM), all of the isoforms were capable of increasing the α-synuclein aggregation (50 μM), among the isoforms ApoE4 showed the greatest stimulatory effect. On the contrary, a decrease in the α-synuclein aggregation was observed with the higher concentration (> 15 nM) of these isoforms. The denouements demonstrate that exceptionally low levels of ApoE may possibly seed α-synuclein aggregation, which could possibly lead to the pathogenesis of neurodegeneration induced by α-synuclein. Conversely, higher ApoE levels could possibly reduce the degree of aggregation of α-synuclein and confer protection. The differential effects observed with ApoE4 could clarify why ApoE4 results in onset for neurodegeneration in an earlier age [86].

Deficiency of α-synuclein can result in the shortfalls in the nigrostriatal system, impaired disrupted activity-dependent regulation of nondopaminergic and dopaminergic transmission [87], along with the synaptic proteins loss, for example synaptotagmin, in the course of aging [88]. In addition, impairment of the synaptic response to repetitive stimulation is initiated due to the deficiency of α-synuclein, which was linked with a noticeable decrease in the reserve pool of synaptic vesicles, especially reduced glutamate mobilization from

the reserve pools [89]. Henceforth, these findings denote that α-synuclein binds precisely to different presynaptic proteins including Rab3 and vesicle-associated membrane protein 2 (VAMP2)/synaptobrevin, which suggests that an important role is played by α-synuclein in the function and maintenance of the release machinery and the nerve terminal [90]. Nerve terminals are predominantly found to be susceptible to ApoE4, which is revealed by the previous studies [91, 92].

Recently Bar et al. [93] stated that in TR mice, the pathologic effects of ApoE4 are heightened by the deficiency of α-synuclein and the ApoE4 effects are gene dose dependent and in the female the effects are more noticeable. In terms of accumulation of Aβ, it has been found that α-synuclein absence at old age can lead to the increased level of amyloid plaques, which suggests that α-synuclein possibly plays a role as a chaperone to help the cells to remove deposits of protein. This has been found to be consistent with the currently noticed Aβ42 accumulation in the ApoE4 mice lacking α-synuclein, which might be the synergistic outcome of two faulty mechanisms of clearance of Aβ. Ultimately, this may cause tau hyperphosphorylation, typically either by ApoE4-mediated mechanisms [81] or by the Aβ peptide [94].

Another probable mechanism is based on the interaction among α-synuclein and ApoE and their effects on microglial pro-inflammatory activation. In a study, Austin et al. [95] reported that, after stimulation, Scna−/− microglia secreted increased levels of interleukin 6 (IL-6), pro-inflammatory cytokines, and tumor necrosis factor alpha (TNFα), in comparison with wild-type. Nonetheless, Scna−/− cells exhibited impaired phagocytic ability, in spite of the reactive phenotype. These effects have been suggested to be facilitated by a subset of lipid-signaling-associated enzymes expression and through α-synuclein-mediated microglial secretory behavior regulation [96]. In addition, Li et al. [97] specified that the innate immune suppressor, triggering receptor expressed on myeloid cells 2, exhibited markedly reduced expression of microglia in ApoE4 cells in comparison with ApoE3. It was reported by Ouberai et al. [98] that the α-synuclein binding strength is associated with the specificity of the lipid environment such as the chemistry of lipid and steric properties inside a bilayer structure and to the capacity of the membranes to remodel and accommodate upon the interaction between lipid membranes and α-synuclein. In another study, Castagnet et al. [99] stated that disrupted uptake and trafficking of astrocyte fatty acid is related to the α-synuclein deficiency, with a significantly increased trafficking of fatty acid to triacylglycerols and cholesteryl esters and decreased phospholipids trafficking, as well as phosphatidylinositol. Nevertheless, ApoE is the foremost brain lipid transporter. Hu et al. [100] in a study described that ApoE4 can enhance accumulation of Aβ and decrease lipidation of ApoE, while ApoE2 has been found to have the opposite effects. These findings recommended that increasing ApoE2 in carriers of *APOE4* could be a useful strategy in the treatment of AD, while increasing ApoE4 in carriers of *APOE4* is likely to cause harm.

ApoE and Neuroinflammation

In the development and progression of AD, an inflammatory reaction in the brain due to glial activation plays a crucial role [101]. Increased ApoE has functional significance to limit the inflammatory response. Actually, in comparison with wild-type mice, glial cells cultured from ApoE KO mice show an increased production of several pro-inflammatory markers in response to treatment with Aβ and other activating stimuli [102]. Lynch et al. [103] stated in their study that ApoE can modulate the endogenous CNS inflammatory response and glial activation. Another study further recommended that animals who expressed the *ε4* allele had considerably increased systemic and brain elevations of the pro-inflammatory cytokines IL-6 and TNFα in comparison with their ApoE3 counterparts, which suggest an isoform-specific effect of the immunomodulatory properties of ApoE [104]. Moreover, in mice, intravenous administration of a small ApoE mimetic peptide likewise suppressed both brain and systemic inflammatory responses following administration of lipopolysaccharide. Lowest levels of ApoE were observed with the *APOE4* carriers. Ringman et al. [105] mentioned in their study that although young *ε4* carriers possess increased inflammatory markers, that decrease with age. They confirmed altered inflammatory responses in *ε4* carriers during young and middle adulthood, which may relate to Alzheimer's risk later stages of life. Interestingly, Szekely et al. [106] stated that for nonsteroidal anti-inflammatory drugs (NSAIDs), the user has reduced the risk of AD, nonetheless this association was found only in the *APOE4* allele and no specific advantage was found for Aβ (42)-lowering NSAIDs. *APOE* interactions particularly with molecules, which are significant for lipid endocytosis and lipid efflux, trigger effects of the *APOE* genotype on lipoprotein composition and neuroinflammation [72]. These effects suggest important targets for new therapies to reduce the risk of AD before the exhibition of any signs of pathogenesis.

ApoE and Lipid Metabolism

ApoE mediates neuronal delivery of cholesterol, as brain cholesterol levels are found to be considerably reduced in hippocampal and cortical areas in patients with Alzheimer's in comparison with age-matched controls [107]. Riddell et al. [108] stated that astrocytes specifically damage ApoE4, which can lead to reduced secretion of ApoE4 and can ultimately reduce ApoE levels in the brain. Furthermore, the genotype-dependent decrease in ApoE levels in the CNS mirror the comparative risk in the development of AD and propose that low levels of total ApoE showed by *APOE4* allele carriers

might directly contribute to the progression of the disease, possibly by reducing the ApoE capacity to facilitate Aβ clearance and/or synaptic repair. A decreased ApoE4-bound cholesterol uptake was found by Rapp et al. [109] in hippocampal neurons. On the contrary, hippocampal astrocytes exhibit diminished internalization of ApoE2-bound cholesterol. Furthermore, lipidated ApoE4 is slightly related with neurites in hippocampal neurons in comparison with the other two isoforms. Hamanaka et al. [110] in their study stated altered lipid and cholesterol metabolism in human *APOE4* KI mice. In a recent study, Moser and Pike [111] stated that obesity most likely accelerate AD-related pathology in *APOE4* but not in the case of *APOE3* mice.

ApoE and Synaptic Plasticity

Synaptic failure is considered as an early pathological feature of Alzheimer's and variation in the regulation of synaptic plasticity is observed with ApoE isoforms [112]. Moreover, Buttini et al. [113] stated that old ApoE-deficient transgenic mice expressing in their brains human APP (hAPP)/ApoE3 and hAPP/ApoE4 had comparable cholinergic/synaptic deficits, and these deficits were observed not only in the hippocampus region but also in the neocortex, which in most mice did not contain any plaques. Another study conducted by Sen et al. [114] reported that ApoE3 but not ApoE4 provides protection against synaptic loss via greater expression of protein kinase Cε. Additionally, mean age-of-onset of dementia is significantly reduced by the ApoE4 isoform. Instead, Chen et al. [112] described that ApoE4 mediates reduction of synaptic plasticity and glutamate receptor function through specific impairment of ApoE receptor recycling. These observations implicate an isoform-specific role of ApoE in the intracellular trafficking and localization of glutamate receptors and lipoprotein, and thus suggest the existence of an alternative mechanism through which ApoE4 may accelerate the onset of neuronal degeneration and dementia by differential impairment of the maintenance of synaptic stability.

The effects of ApoE4 particularly on the long-term synaptic plasticity were examined by Qiao et al. [115]. The findings for the first time confirmed that ApoE4 could alter hippocampal late-phase long-term potentiation through the reduction of phosphorylated Ca^{2+}/calmodulin-dependent protein kinase IIα (p-CaMKIIα) and phosphorylated cAMP response element-binding protein (p-CREB), which suggests that ApoE4 can induce the suppression of hippocampal long-term synaptic plasticity, and may possibly contribute to the cognitive impairments in genetic AD. Both of these CREB and CaMKIIα are vital intracellular targets of the neurotoxic ApoE4 [115]. In another study, Hwang et al. reported that acute treatment of PKR inhibitor can reinstate the shortfalls in long-term memory, synaptic plasticity, and long-term potentiation in case of both mouse models without disturbing the load of Aβ in the hippocampus [116].

ApoE Levels in the Central Nervous System of Alzheimer's Disease

Studies examining the ApoE levels on AD suggest that *APOE* (Table 1) exerts a foremost role in developing AD. Moreover, the advancement of AD is also connected with the existence of *APOE*4 undoubtedly as a result of interactions with the Aß [123].

Copious analyses examined ApoE levels in the brain and cerebrospinal fluid (CSF) about the *APOE* genotypes has produced variable outcomes. Fukumoto et al. [124] stated that in *APOE3*/*APOE4* people, the relation of ApoE4 to entire ApoE levels was 30 to 40% in plasma, signifying a reduced genesis or an augmented metabolism of ApoE4 concerning ApoE3. Astoundingly, the proportion in the CSF was opposing, with ApoE4 estimated for 60 to 70% of the entire ApoE. Nevertheless, a study by Bekris et al. [125] reported that it is esoteric to forecast the levels of CSF ApoE by *APOE4*. The *APOE* genotype, AD statement, gender, and race do not influence levels of CSF ApoE; however, normal CSF ApoE levels rise with age according to the study of Wahrle et al. [126]. A meta-analysis that comprised 1064 AD cases and 1338 non-demented control groups specified the perspective of ApoE levels of CSF as a hallmark of AD [127].

Controversial results were also reported for levels of ApoE isoforms in the parenchyma of the brain [128]. The contradictory findings from brain parenchyma researches might also stem from the comparatively minor number of sample size then heterogeneity in people, stages of the people as well as the period of the disease. Furthermore, the levels of ApoE may be affectedly changed by autopsy related delay [129]. Conversely,

Table 1 *APOE* frequencies and odds ratios in normal persons and Alzheimer's patients of worldwide populations

Parameter	*APOE* allele (%)			Odds ratios		
	ε2	*ε3*	*ε4*	*ε2/ε4*	*ε3/ε4*	*ε4/ε4*
Typical people [23]	8.4	77.9	13.7			
Nigeria [16]	10.2	63.8	26.0			
Norway [117]				3.2	4.2	12.9
Chile [118]					2.4	12.8
Korea [119]					2.9	24.7
Japan [120]					3.9	21.8
Iran [121]	0.95		21			
Tunisia [122]					2.9	5.4

the amount of ApoE differs in diverse brain areas and numerous factors associated with the genesis and metabolism of ApoE may be fundamental in the pathogenesis of AD [130].

ApoE as a Therapeutic Target for Alzheimer's Pathogenesis

ApoE is an important risk factor in AD pathogenesis; ApoE might suggest a smart target for AD therapy. In Table 2, ApoE-based therapeutic target in controlling AD is represented.

Cramer et al. [171] stated that the expression of ApoE is prompted transcriptionally by the act of the peroxisome proliferator-activated receptor gamma as well as LXRs that generate heterodimers in allocation to RXRs. In a mouse model of Alzheimer's, bexarotene, an RXR agonist, caused a swift clearance of Aβ, especially soluble Aβ in ApoE-reliant mode within hours. In fact, more than 50% reduction of Aβ plaque was reported for 72 h [171]. Similarly, Riddell et al. [172] stated that the LXR agonist for example, TO901317, abates Aβ42 of hippocampal and expands memory in the Tg2576 mouse model of AD. Therefore, a surge in the levels of ApoE in the brain is

Table 2 Potential ApoE-targeted therapeutic approaches for the management of Alzheimer's pathogenesis

Viewpoint	Approaches	Logics	Examples
Controlling the levels of ApoE	Modulating the levels of ApoE	▪ Stimulates the clearance of Aβ ▪ Maintain lipid homeostasis ▪ Enhances synaptic function	Adeno-associated virus-mediated gene delivery, ApoE gene silencing, retinoid X receptor (RXR) agonists, liver X receptor (LXR) agonists [131–137]
	ApoE mimetic peptides	▪ Reduces inflammation ▪ Decrease neurotoxicity ▪ Rises ApoE3-linked defensive roles	Small peptides comprising the receptor-binding area in ApoE [138–142]
Alternating the roles of ApoE	Increasing the lipidation of ApoE	▪ Decrease the deposition of Aβ ▪ Improve cognition	RXR agonists, LXR agonists, small molecules [60, 132, 143–145]
	Blocking the interaction of ApoE and Aβ	▪ Abates the accretion of Aβ ▪ Improve memory deficits	ApoE-specific antibody, Aβ12–28P, ApoE peptides [146–150]
	Blocking aggregation of ApoE	▪ Reduce Aβ aggregation ▪ Prevent ApoE4-related toxicity	Anti-ApoE antibody, small molecules [151–154]
	Alteration of ApoE4 to ApoE3	▪ Rises the protective effects of ApoE3 ▪ Disrupt ApoE4 domain interaction ▪ Reduces the noxious impacts of ApoE4	CRISPR/Cas9, ApoE structure correctors [155–158]
	Restoring the roles of ApoE	▪ Rises the protective effects of ApoE ▪ Reduces neuroinflammation	ApoE mimetic peptides [140]
	Blocking the disintegration of ApoE	▪ Subsides tau pathology ▪ Abate mitochondria toxicity	Inhibitors for proteolysis of ApoE [3, 159]
Modifying the receptors	Restoring the roles of ApoE receptor	▪ Promote cholesterol transport ▪ Augments the clearance of Aβ ▪ Increase signaling and synaptic plasticity	Small molecules [160–162]
	Regulating ApoE and receptor trafficking	▪ Restore function of ApoE and synapses	Small molecules [112]
	Increasing the levels of low-density lipoprotein receptor-related protein 1 and low-density lipoprotein receptor	▪ Augments the clearance of Aβ ▪ Cholesterol transport and synaptic plasticity	Small molecules [160–162]
	Increasing the apolipoprotein E receptor 2 and the levels of very-low-density lipoprotein receptor	▪ Upsurges ApoE signaling and synaptic plasticity	Small molecules [3, 163, 164]
Targeting insulin	Controlling insulin signaling	▪ Improve cognitive function in AD	Insulin [165]
	Increasing the brain glucose metabolism	▪ Induces hyperketonemia that raises the brain's normal reliance on glucose and mitochondrial efficiency	Ketogenic agent (ketone monoester), the ketogenic diet (high carbohydrate or very low carbohydrate diet) [166, 167]
Miscellaneous	Promoting cerebrovascular integrity	▪ Enhance Aβ clearance ▪ Inhibit ApoE4-facilitated BBB breakdown	Cyclosporine A [168]
	APOE genotype and immunotherapy	▪ Aids to forecast clinical consequence for Aβ-linked or other treatments	Aβ immunotherapy [169, 170]

probably advantageous in AD therapy. Nevertheless, huge caution is necessary for this concept since ApoE4 is also pathogenic. It also has been suggested that increasing ApoE lipidation perhaps be the key for ApoE-based therapy rather than focusing on increasing ApoE. The lipidation of ApoE is facilitated by ATP-binding cassette transporter A1, ABCA1 [132]. In case of PDAPP transgenic mouse model of AD, Wahrle et al. [173] stated that ABCA1 deletion could upsurge the deposition of Aβ peptide. The same researcher also reported that overexpression of ABCA1 suppresses Aβ deposition. These findings further advocate the deductions that increased ABCA1-mediated lipidation of ApoE in the CNS can reduce the load of amyloid. This enhancing the function of ABCA1 might have a beneficial effect on AD.

The dispute regarding the reduction in ApoE expression to treat AD is supported by the fact that Aβ deposition is primarily triggered by ApoE as mentioned above. On the other hand, Bien-Ly et al. [151] mentioned that abating human ApoE levels weaken the accumulation of age-dependent Aβ particularly in mutant human APP transgenic mice. Kim et al. [174] stated that in a mouse model of Aβ amyloidosis, haploinsufficiency of human *APOE* could reduce amyloid deposition. Further, immunotherapy for ApoE also reduces Aβ accumulation. In another study, Kim et al. [175] stated that anti-ApoE immunotherapy inhibits amyloid accumulation in a transgenic mouse model of Aβ amyloidosis. These results suggest that decreasing ApoE levels has beneficial effects and that anti-ApoE immunization can be explored as a novel therapeutic tool, at least from the perspective of Aβ deposition. Furthermore, the interaction amid ApoE and Aβ can also be considered as therapy. ApoE can perform as a neurotic chaperone of Aβ, endorsing its morphological alteration from solvable Aβ into pathogenic aggregates. Sadowski et al. [176] reported that in the existence of ApoE, Aβ12-28P, a synthetic peptide, decreases the fibrillogenesis of Aβ and Aβ/ApoE toxicity in cell culture. This study avowed that 1-month treatment of transgenic mice by Aβ12-28P reduced 63.3 and 59.5% Aβ burden in the cortex and hippocampus, respectively, concerning control, transgenic mice. In another study, Shinohara et al. [177] found that a hydroxymethylglutaryl-CoA reductase inhibitor, for example, fluvastatin, abated the level of Aβ by an isoprenoid-reliant mode. Augmenting the roles of ApoE receptors can be an auspicious therapy for AD. In a current study, Luz et al. [178] examined the magnitude to which the roles of ApoE4 can be offset with an anti-ApoE4-specific monoclonal antibody (mAb), 9D11. The researcher reported that 9D11 stopped the ApoE4-focused accretion of Aβ in the hippocampus, caused the reverse of the cognitive deficiencies, and reversed the hyperphosphorylation of tau-mediated by ApoE4 as well as abated the expression of the ApoER2 receptor.

The tau protein mediates the transportation of nutrients and other necessary supplies to neurons in the brain of a healthy person. However, in case of a brain of an AD patient, this essential transport system does not function properly as tau forms tangles. Recently Shi et al. [82] reported that ApoE4 significantly worsens tau-facilitated neurodegeneration in a mouse model of tauopathy. The researchers avowed that the absence of ApoE is found to be protective, whereas ApoE4 shows noxious effects in AD. Therefore, targeting ApoE, particularly ApoE4, is an auspicious therapeutic tactic in controlling AD.

Conclusion

ApoE4 is the most powerful genetic risk factor for formation and propagation of the late-onset AD. Typically, ApoE4 enhances brain Aβ pathology concerning other ApoE isoforms. The existence of the *APOE4* allele is related to more intense neurodegeneration in people with a sporadic primary tauopathy. Furthermore, in people with Aβ pathology with the symptomatic AD, as well as tau pathology *ε4*-carriers play a superior degree of disease progression. ApoE isoforms have diverse functions in regulating α-synuclein aggregation, neuroinflammation, lipid metabolism, and maintenance of synaptic plasticity. Exploring the exact impact of ApoE4 on AD pathogenesis is a great dispute, but ApoE4-targeted therapeutic strategies are an auspicious area of existing research in combating AD pathogenesis.

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Abbreviations AD, Alzheimer's disease; Aβ, Amyloid β; NFTs, Neurofibrillary tangles; ApoE, Apolipoprotein E

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