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REVIEW PAPER

Roles of ApoE4 on the Pathogenesis in Alzheimer's Disease and the Potential Therapeutic Approaches

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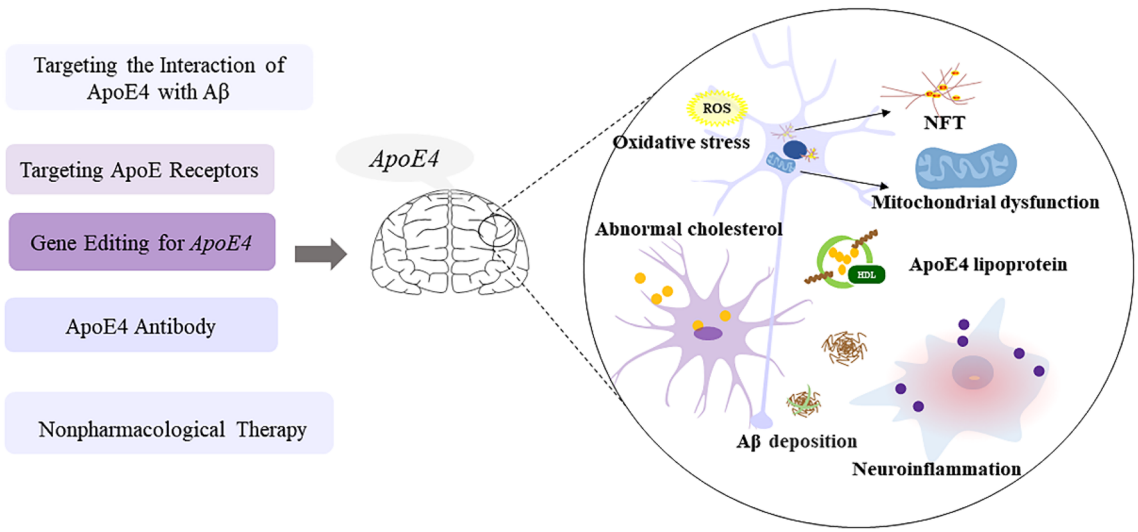
Abstract

The *Apolipoprotein E* ε4 (*ApoE* ε4) allele, encoding ApoE4, is the strongest genetic risk factor for late-onset Alzheimer's disease (LOAD). Emerging epidemiological evidence indicated that ApoE4 contributes to AD through influencing β-amyloid (Aβ) deposition and clearance. However, the molecular mechanisms of ApoE4 involved in AD pathogenesis remains unclear. Here, we introduced the structure and functions of ApoE isoforms, and then we reviewed the potential mechanisms of ApoE4 in the AD pathogenesis, including the effect of ApoE4 on Aβ pathology, and tau phosphorylation, oxidative stress; synaptic function, cholesterol transport, and mitochondrial dysfunction; sleep disturbances and cerebrovascular integrity in the AD brains. Furthermore, we discussed the available strategies for AD treatments that target to ApoE4. In general, this review overviews the potential roles of ApoE4 in the AD development and suggests some therapeutic approaches for AD.

Graphical Abstract

ApoE4 is genetic risk of AD. ApoE4 is involved in the AD pathogenesis. Aβ deposition, NFT, oxidative stress, abnormal cholesterol, mitochondrial dysfunction and neuroinflammation could be observed in the brains with ApoE4. Targeting the interaction of ApoE4 with the AD pathology is available strategy for AD treatments.



Keywords Apolipoprotein E4 (ApoE4) · Alzheimer's disease (AD) · β-Amyloid (Aβ) · Therapy

Alzheimer's disease (AD) is a progressive neurodegenerative disease affecting people over the age of 65. AD is mainly characterized by senile plaques (SPs) (Jack et al. 2010) and neurofibrillary tangles (NFTs) (Muralidar et al. 2020), constituting two major hypotheses in the pathogenesis of AD; the β-amyloid cascade hypothesis and tau protein hyperphosphorylation, respectively. Additionally, synaptic

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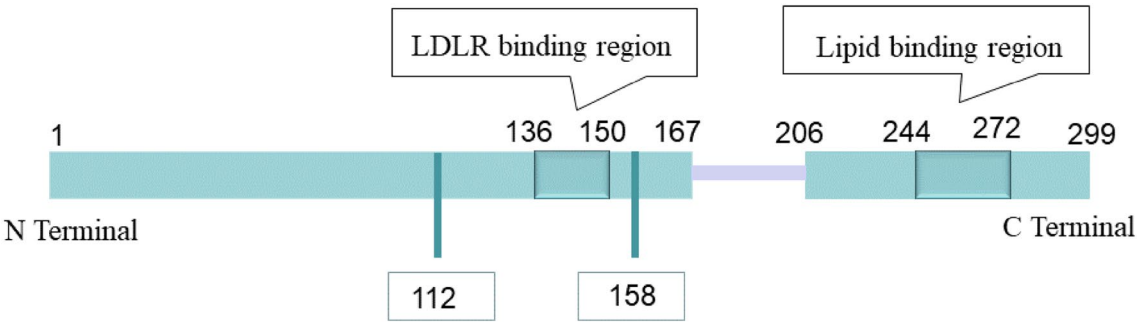
loss and synaptic damage (John and Reddy 2021) can be observed in the early stage of AD, as well as abnormal cholesterol transport (Kao et al. 2020).

Apolipoprotein E (ApoE) interacts with β-amyloid (Aβ) and regulates its aggregation and clearance in the AD brain. Furthermore, ApoE contributes to AD pathogenesis by modulating brain synaptic plasticity (Kim et al. 2014), glucose metabolism (Jiang et al. 2020), neuronal signaling (Huang et al. 2019), oxidative stress (Jofre-Monseny et al. 2008), neuroinflammation (Lanfranco et al. 2021), mitochondrial dysfunction (Yin et al. 2020) and cholesterol transportation (Jeong et al. 2019). The *ApoE* ε4 allele, encoding ApoE4, is the strongest risk factor for late-onset AD (LOAD); more than 65% of patients suffering from LOAD are found to carry at least one ε4 allele at clinical diagnosis (Saunders et al. 1993). The frequency of the ε4 allele in the population is about 15–20%, and there are some variations of this frequency among different ethnic groups. Carriers with one ε4 allele have a threefold increasing risk of AD, and carriers of both ε4 alleles have up to 90% risk of AD (Liu et al. 2013). Reversely, carriers with ε2 allele could slow the pathological process of AD. *ApoE* ε3 allele is a commonly occurring subtype in the population with a neutral risk of AD prevalence. ApoE4 has been found to be involved in AD development by mediating Aβ pathology (Tachibana et al. 2019), NFT load (Sabbagh et al. 2013), synaptic impairment (Sun et al. 2017) and abnormal cholesterol transport (Dunk and Driscoll 2022). In addition, ApoE4 mice always showed high level of reactive oxygen species (ROS) (Lauderback et al. 2002). ApoE4 is also associated with mitochondrial functions by regulating its biogenesis and dynamics (Yin et al. 2020). Furthermore, ApoE4 increases the expression of inflammatory factors and induces neuroinflammation (Iannucci et al. 2021). Currently, the therapies targeting to ApoE4 mainly concentrate on the interaction of ApoE with Aβ (Kuszczyk et al. 2013), ApoE receptors (Shi et al. 2021), ApoE4 genotype correction (Wang et al. 2018), ApoE antibody (Liao et al. 2018), and nonpharmacological therapy (Liu et al. 2014b). Therefore, understanding the link between ApoE4 and AD pathological mechanisms will help develop more strategies on diagnostic and therapy for AD patients.

Biology of ApoE

The Structure and Localization of ApoE

ApoE is a secreted glycoprotein with 299 amino acid residues (Mr = 34kd). The C-terminal domain of ApoE is responsible for binging to cholesterol and phospholipids, and the N-terminal domain comprises some receptors-binding regions (Jones et al. 2011). The three common isoforms of ApoE are ApoE2, ApoE3 and ApoE4 (Zannis et al. 1981) encoded by three allelic variants ε2, ε3 and ε4, respectively. Genetic variations of the three isoforms are induced by single nucleotide polymorphisms (SNP) that differ by two amino acid residues of ApoE at positions 112 and 158, labeled rs429358 (C > T) and rs7412 (C > T) (Weisgraber et al. 1981). ApoE3 is cysteine (Cys) at position 112 and arginine (Arg) at position 158. ApoE2 is Cys at the both positions and ApoE4 is Arg at the both positions (Fig. 1). The Arg at position 112 of ApoE4 contributes to Arg61-Glu255 and Arg112-Glu109 salt bridges, leading to interactions of domains between the N-terminal and C-terminal. Furthermore, salt bridge structure is also observed in ApoE3, showing at Arg61-Asp65. Differences in salt bridges could be one of the reasons affecting the ability of ApoE isoforms to form complexes with Aβ, and mutating ApoE4 to



ApoE2	Cys	Cys
ApoE3	Cys	Arg
ApoE4	Arg	Arg

Fig. 1 The structure of ApoE isoforms

Ala or Lys at position 112 could eliminate complex formation (Bentley et al. 2002). In general, compared with ApoE2 and ApoE3, ApoE4 is more likely to form molten globules and aggregate at 37 °C (Morrow et al. 2002), which could be implicated abnormal physiological functions.

In periphery, ApoE is secreted from many cells, for example, hepatic parenchymal cells, muscle cells, adipocytes, monocytes and macrophages (Kockx et al. 2008). In the central nervous system, ApoE is synthesized mainly in astrocytes, partially in microglia, vascular wall cells and choroid plexus cells. ApoE is also expressed when neurons are stimulated or impaired (Xu et al. 2006; Polazzi et al. 2015; Huang et al. 2004). ApoE in the CSF is independent of peripheral pool, which in turn cannot cross the blood–brain barrier (BBB) (Linton et al. 1991).

Physiology Functions of ApoE

ApoE is a multifunctional protein, primarily as a ligand of cell surface receptors for the low-density lipoprotein (LDL) receptor family. ApoE is involved in lipid storage, transport and metabolism (Mahley 1988; Hauser et al. 2011); for example, clearance of cholesterol in the plasma. ApoE deficiency has been related to type III hyperlipoproteinemia, which causes early atherosclerosis and raises the level of cholesterol in plasma (Ghiselli et al. 1981). Indeed, *ApoE* mutations and abnormalities are associated with a wide range of illnesses, including atherosclerosis (Venegas-Pino et al. 2016), type 2 diabetes 2 (Chen et al. 2019), lipoprotein glomerulopathy (Yang et al. 2020), and heighten the infectious diseases susceptibility to infection, for example, AIDS, HIV and COVID-19 (Burt et al. 2008; Gkouskou et al. 2021). As a crucial apolipoprotein in the CNS, ApoE is essential for sustaining peripheral lipid metabolism, as well as lipid transport and metabolism in the brain. Cholesterol participates in maintaining neuronal plasticity, synapse growth and synaptogenesis (Mauch et al. 2001; de Chaves et al. 1997). In normal brain, ApoE is a component of lipoprotein particles, and they can transport cholesterol to neurons and increase the formation of synapse (Mauch et al. 2001). Overexpression of ApoE in astrocytes and macrophages can regulate the level of cholesterol or remove lipid debris (Poirier et al. 1991). Since the *ApoE* ε4 allele was reported as an AD risk gene, studies on the function of ApoE in the brain have focused on its genetic polymorphisms linked with AD pathology. Increasing evidence showed that ApoE2 is protective against AD. ApoE3 is risk-neutral in AD development and it is the most common isoform in the population (Lane-Donovan and Herz 2017). However, when compared to ApoE3 and ApoE2, ApoE4 is observed to increase the risk of AD development by impeding the clearance of Aβ (Castellano et al. 2011).

Although *ApoE* ε2 is considered as protective in the nervous system, individuals expressing homozygous *ApoE2/2* were found glomerulopathy (Saito et al. 2020). Therefore, more studies and cases are needed to confirm the functions and polymorphism-based gene therapy of *ApoE*.

ApoE Receptors

LDL receptor family is main class of ApoE receptors, including LDLR, very-low density lipoprotein receptor (VLDLR), low-density lipoprotein receptor-related protein (LRP)1, LRP1B, LRP2, LRP4, LRP5, LRP6, and LRP8 (ApoER2) (Carlo 2013). LDLR family is a class of transmembrane receptors with many functions, for example, lipid metabolism and cardiovascular homeostasis (Calvier et al. 2022). In the central system, LDLR is primarily associated with cholesterol regulation through binding and internalization of cholesterol-containing LDL, which in turn affects cholesterol-related BBB functions and cognitive deficits (Hong et al. 2022). The binding affinity of LDLR family depends on isomers and lipidation status of ApoE (Bu 2009). LDLR preferentially binds to lipid ApoE particles, while VLDLR preferentially binds to lipid-free ApoE. Moreover, ApoE2 has a lower affinity for LDLR compared to ApoE3 and ApoE4 (Zhao et al. 2018). LRP1 is closely associated with AD. LRP1 not only regulates the endocytosis and spread of tau (Rauch et al. 2020) but also contributes to APP processing (Ulery et al. 2000). In addition, LRP1, VLDLR and ApoER2 identified in the postsynaptic density interacts with glutamate (Nakajima et al. 2013) and Reelin signaling (Strasser et al. 2004), in turn affecting synaptic function.

In neurons, there is a novel ApoE receptor called sortilin. It has a high binding affinity with ApoE. The expression of sortilin in the CNS is restricted to neurons and it might be a major neuronal ApoE receptor for catabolism of Aβ in the brain (Carlo et al. 2013). Sortilin can help neurons to take up essential lipids by binding ApoE and by facilitating the transfer of lipids from extracellular to intracellular transport particles. In the presence of ApoE3, Sortilin and ApoE3 cycle to the cell surface properly, allowing the lipid-rich brain fatty acid binding protein 7 (FABP7, a carrier of ω3-polyunsaturated fatty acids) to be released. However, sortilin recycling would be blocked in the presence of ApoE4, which impairs FABP7 release and affects intracellular lipid transport (Asaro et al. 2021).

The triggering receptor expressed on myeloid cells 2 (TREM2) is one of the major receptors of ApoE (Yeh et al. 2016). TREM2 is associated with inflammatory response of microglia, including proliferation, transport, and phagocytosis (Wang et al. 2020). The affinity of TREM2 with ApoE shows isoforms specific: ApoE4 > ApoE3 > ApoE2 (Mai et al. 2022). This higher affinity of TREM2 with ApoE4 might be a reason for ApoE4 risk in AD. The

increased affinity of TREM2 for ApoE4 may contribute to the increased risk of ApoE4 in AD by amplifying TREM2 signaling and leading to microglia overactivation. Studies in vitro have shown that a lack of TREM2 would decrease Aβ uptake by ApoE4-treated microglia (Fitz et al. 2021). Furthermore, TREM2 variants, for example R47H, are associate with AD risk (Sayed et al. 2021). Besides, the signaling pathways triggered by the interaction between ApoE and TREM2 in AD pathogenesis are important.

In addition to the above receptors, ApoE4 can interact specifically with leukocyte immunoglobulin-like receptor B3 (LilrB3). ApoE4 can activate human microglia (HMC3) into a pro-inflammatory state, which is dependent on LilrB3 (Zhou et al. 2023). Generally, ApoE receptors play important role in the physiology function of ApoE.

Mechanism of ApoE4 in the AD Pathogenesis

Aβ Pathology

ApoE is one of the components of amyloid plaques in the brain observed by imaging. Early research studies on the roles of *ApoE4* in AD mostly focused on the interaction of ApoE with Aβ. To date, Aβ pathology is the most well-defined part of ApoE in AD pathogenesis. Aβ is produced from the transmembrane protein amyloid precursor protein (APP) by the hydrolysis of β- and γ-secretase, mainly including $Aβ_{1-40}$ and $Aβ_{1-42}$ (2020 Alzheimer's disease facts and Figs. 2020). Aβ monomers polymerize into different types of assemblies, including oligomers, protofibrils and amyloid fibrils. Amyloid fibrils are the main components of SPs in AD pathology. Aβ oligomers are soluble, so they are easy to spread throughout the brain (Chen et al. 2017). In normal brain, ApoE associated with Aβ is involved in the metabolism and clearance of Aβ. However, fragments of ApoE4 combined with Aβ could aggravate the accumulation of Aβ. Mouchard et al. showed that ApoE fragments of 18 and 16 kD are the partners of $Aβ_{1-42}$ in the brains of AD patients. These fragments of ApoE lack of C-terminus, and *ApoE4* genotype can generate more ApoE fragment of 18 kD than those with *ApoE* ε2 or ε3 (Mouchard et al. 2019). Furthermore, lower plasma $Aβ_{42}/Aβ_{40}$ in *ApoE4* carriers might predict higher cortical Aβ deposition, hippocampal atrophy and the decline of cognitive abilities (Shi et al. 2022). In normal brains, sotilin-related receptor (SORL1) can bind Aβ and target it to lysosomes for degradation. However, neural stem cells from patients carrying two *ApoE4* allele showed reduced SORL1 expression and increased levels of Aβ. This may be one of the ways in which ApoE4 affects Aβ clearance (Zollo et al. 2017).

APP transport and Aβ production can be regulated by ApoE, which correlates with the isoform specificity of ApoE. From analysis of ^{18}F-florbetapir-PET imaging, cognitively intact *ApoE4* carriers become positive on amyloid imaging at around 56 years of age, and *ApoE4* non-carriers become positive at around 76 years of age (Fleisher et al. 2013). These observations suggested that ApoE4 might increase AD risk by initiating and accelerating the accumulation, aggregation, and deposition of Aβ in the brain. However, compared with *ApoE3* and *ApoE4* carriers, individuals with *ApoE2* tend to slow cognitive decline and less pronounced Aβ pathology and NFT (Serrano-Pozo et al. 2015). ApoE4 can increase Aβ production by accelerating APP endocytosis transport mediated by low-density lipoprotein receptor-related protein (LRP) (Pietrzik et al. 2002; Tachibana et al. 2019). LRP1 plays an important role in Aβ clearance. BBB-associated pericytes clear Aβ aggregates through LRP1/ApoE interactions, affecting by *ApoE4* (Ma et al. 2018). LRP6 is an essential receptor of ApoE for Wnt signaling. LRP6 can reduce endocytic transport of APP and Aβ production. Knocking down LRP6 in neurons could increase amyloid deposition and neuroinflammation (Liu et al. 2014a). Furthermore, ApoE can act as a signaling molecule of Aβ depending on its subtype-specific. Compared with ApoE2 and ApoE3, ApoE4 binding to ApoE receptors easily leads to combination between dual leucine-zipper kinase (DLK) and ApoE receptors, activates ERK1/2 MAP kinase and induces cFos phosphorylation, which stimulates transcription factor AP-1, thereby increasing APP transcription and Aβ production (Huang et al. 2017), as shown in Fig. 2.

ApoE4 contributes to Aβ oligomers in the brain. *ApoE* ε4/ε4 carriers have higher levels of Aβ oligomers compared to *ApoE* ε3/ε3 carriers. The individuals expressing ApoE4 may increase dendritic spine loss and accelerate memory impairment, leading to early cognitive decline in AD (Hashimoto et al. 2012). Kara et al. (2018) found, compared with ApoE2 and ApoE3, there is a significant interaction between ApoE4 and Aβ in primary immortalized astrocytes measured by flow cytometry. This interaction makes more likely to form protein deposition complexes. Although ApoE4 affects the production, aggregation and transport of Aβ, whether APP processing correlates with ApoE subtype specificity remains unclear. In fact, a study using ApoE targeted-replacement mice suggested that ApoE isoform specificity didn't affect APP expression, full protein levels, or its processing in the brains (Novy et al. 2022). However, the different expression and processing of APP in brain regions were not detected. Therefore, the relationship between ApoE4 and APP is needed to further investigate.

Tau Phosphorylation

Hyperphosphorylated tau is a major constituent of NFTs. Studies have shown that AD patients expressing ApoE4 may

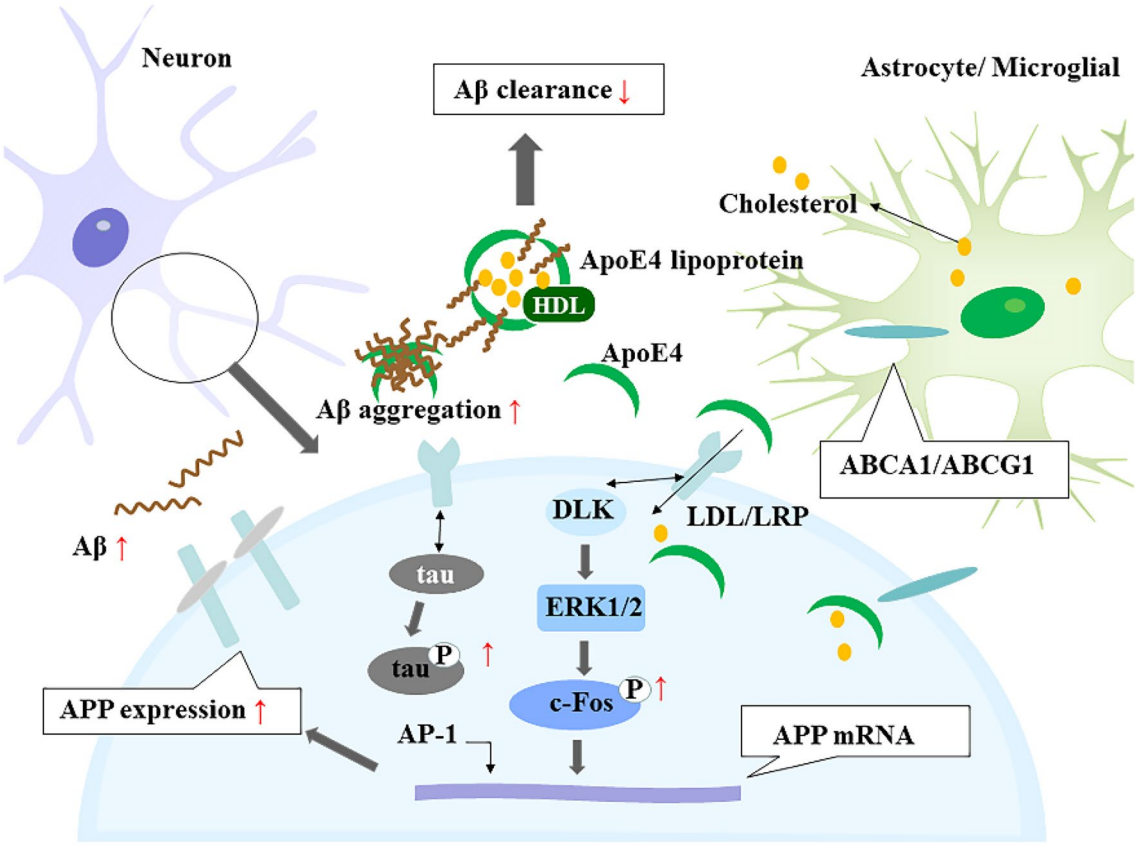


Fig. 2 Roles of ApoE4 in Aβ pathology. ApoE4 binds to Aβ and form a complex that affects Aβ clearance and accelerates its accumulation and deposition in the brain. ApoE4 makes the ApoE receptor more susceptible to binding to dual leucine-zipper kinase (DLK), activates ERK1/2 MAP kinase and induces cFos phosphorylation, stimulates transcription factor AP-1, resulting in enhanced APP transcription, increased APP expression, and consequently increased Aβ

possess relatively more NFTs in their medial temporal lobe, most notably in the entorhinal cortex (Emrani et al. 2020). The pathophysiology of NFTs in AD patients with the ε4 allele in the cortex is worsened compared to those who do not have the ε4 allele. Overexpression of ApoE4 in astrocytes can increase the phosphorylation and aggregation of tau within neurons (Jablonski et al. 2021). A study about chimeric human cerebral organoids (chCOs) also confirmed that ApoE4 astrocytes may accelerate the phosphorylation of tau in neurons, and neuron-astrocyte transport of p-tau may be impaired by neuronal ApoE4 (Huang et al. 2022). Furthermore, the extent of NFTs is greater in ε4 homozygous compared to heterozygous carriers (Sabbagh et al. 2013). Salami et al. observed a longitudinal increase of plasma p-tau level in ε4 carriers, which is related to the elevated local hippocampal connectivity at resting-state and hippocampus connectivity (Salami et al. 2022).

The correlation of ApoE and tau is likely independent of Aβ pathology. Farfel et al. (2016) identified by autopsy staining of volunteers in several regions in the internal olfactory cortex, hippocampus at CA1, entorhinal cortex, and inferior parietal cortex and found that *ApoE* ε4 and ε2 were associated with NFTs independent of Aβ. ApoE4 may have an influence on tau directly without going through Aβ. Shi et al. (2017) showed that tau-mediated neurodegeneration was exacerbated in P301S tau transgenic mice transfected with the human ApoE4 gene, but it was not associated with Aβ. The levels of tau and p-tau in CSF levels are positively associated with the number of *ApoE4* allele (Benson et al. 2022). Kang et al. revealed that ApoE4 inhibits the vesicular monoamine transporter2 (VMAT2) in the locus coeruleus and facilitate tau pathology (Kang et al. 2021). However, there is insufficient evidence that ApoE4 can act directly on tau, as few AD patients with *ApoE4* have no Aβ deposition in the brain.

NFT pathology in ApoE4-positive AD patients may be linked to tau phosphorylation. Neuron-specific proteolytic cleavage of ApoE4 is associated with increased phosphorylation of tau. ApoE fragments might play vital role in the development of neuronal deficits. ApoE fragments, extracted from brain tissue homogenates of transgenic mouse with *ApoE4* were transfected into neurons or astrocytes, study

showed that ApoE hydrolysis fragments increased phosphorylation of tau (Brecht et al. 2004). In addition, astrocyte-secreted protein glypican-4 (GPC-4), as a partner of ApoE4, could contribute to tau hyperphosphorylation (Saroja et al. 2022). LPR1 may be associated with tau propagation. Hyperphosphorylated tau binds inefficiently to LRP1, making tau internalization inefficient. ApoE4 would inhibit LRP1-mediated tau uptake, possibly because ApoE4 has a higher affinity for LRP1 (Cooper et al. 2021). Studies on ApoE4 and tau pathology are still in the preliminary stages, and evidence on whether ApoE4 bypasses Aβ and directly affects tau needs more investigations (Fig. 3).

Synaptic Impairment

In the normal brain, ApoE transports cholesterol-rich lipoproteins to neurons, promoting synaptogenesis and maintaining synaptic connections. However, *ApoE* ε4 carriers may contribute to AD risk through synaptic damage. Neurogranin (Ng) is a postsynaptic protein that is highly expressed in the hippocampus. Ng is usually involved in memory consolidation. Compared with *ApoE4* non-carriers with mild cognitive impairment, the levels of Ng in the CSF expressed *ApoE4* were significantly higher (Sun et al. 2016). This data showed that *ApoE4* contributes to early cognitive impairment and synaptic damage in AD patients. ApoE4 retains ApoER2 and glutamate receptors in endosomal compartments. Synaptic transmission mediated by Reelin is inhibited and ApoE on the surface of neurons is decreased (Chen et al. 2010). Sun et.al. (Sun et al. 2017) established model by transferring human-derived *ApoE4* and *ApoE3*. They found, compared with mice expressing *ApoE3*, mice with *ApoE4* showed shortened dendrite length, reduced dendritic spine density, and enhanced facilitation of basic synaptic transmission and paired pulses in hippocampal CA1 region neurons. This result suggested that the effects of ApoE4 on synaptic function possibly prior to AD occurrence.

ApoE4 can contribute to neuronal and synaptic dysfunction by activation of Cyclophilin-A matrix metalloproteinase-9 (CypA-MMP9) pathway (Anderson et al. 2022). In addition, Aβ burden has toxic effects on synapses. Aβ/ApoE4 complexes would lead to the accumulation of Aβ in

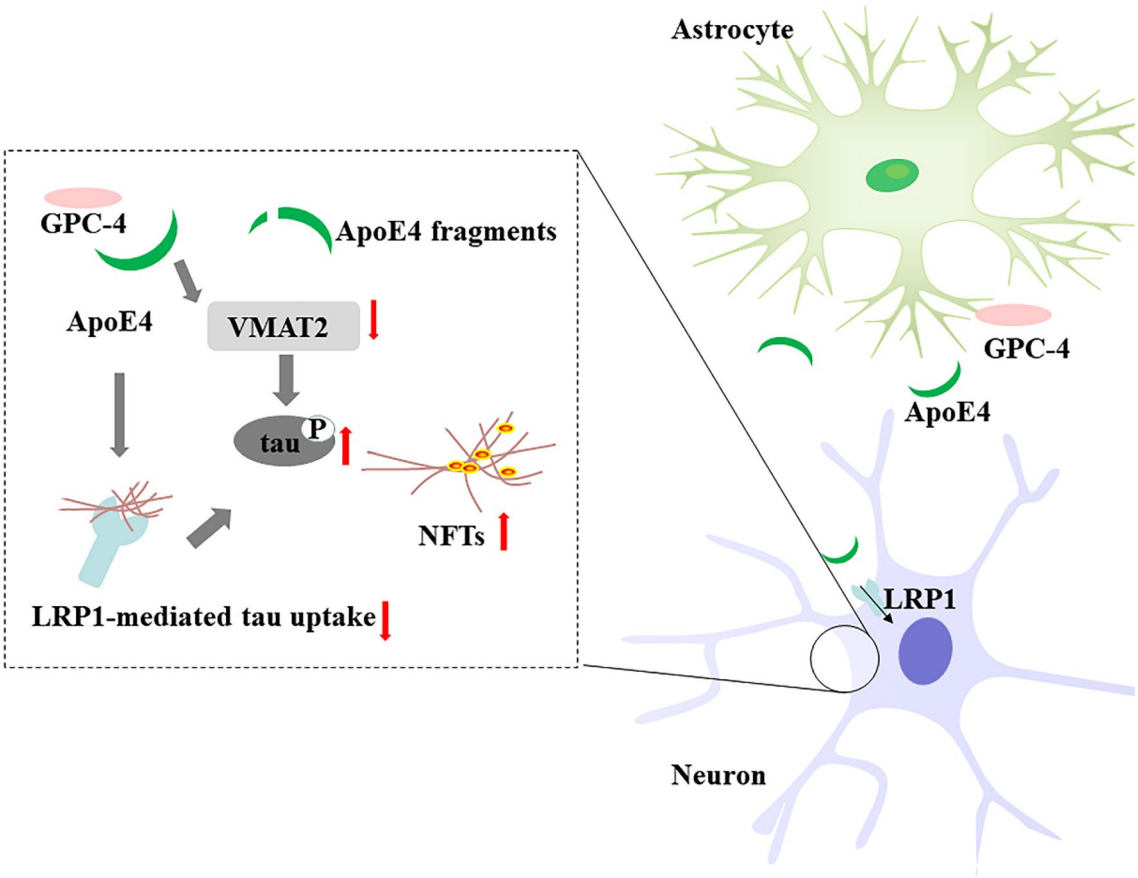


Fig. 3 Roles of ApoE4 in tau phosphorylation. Astrocytes expressing ApoE4 exacerbate the phosphorylation level of tau protein in neurons, which in turn forms NFT. The astrocytes with ApoE4 can facilitate astrocyte-secreted protein glypican-4 (GPC-4) to neurons to promote tau phosphorylation

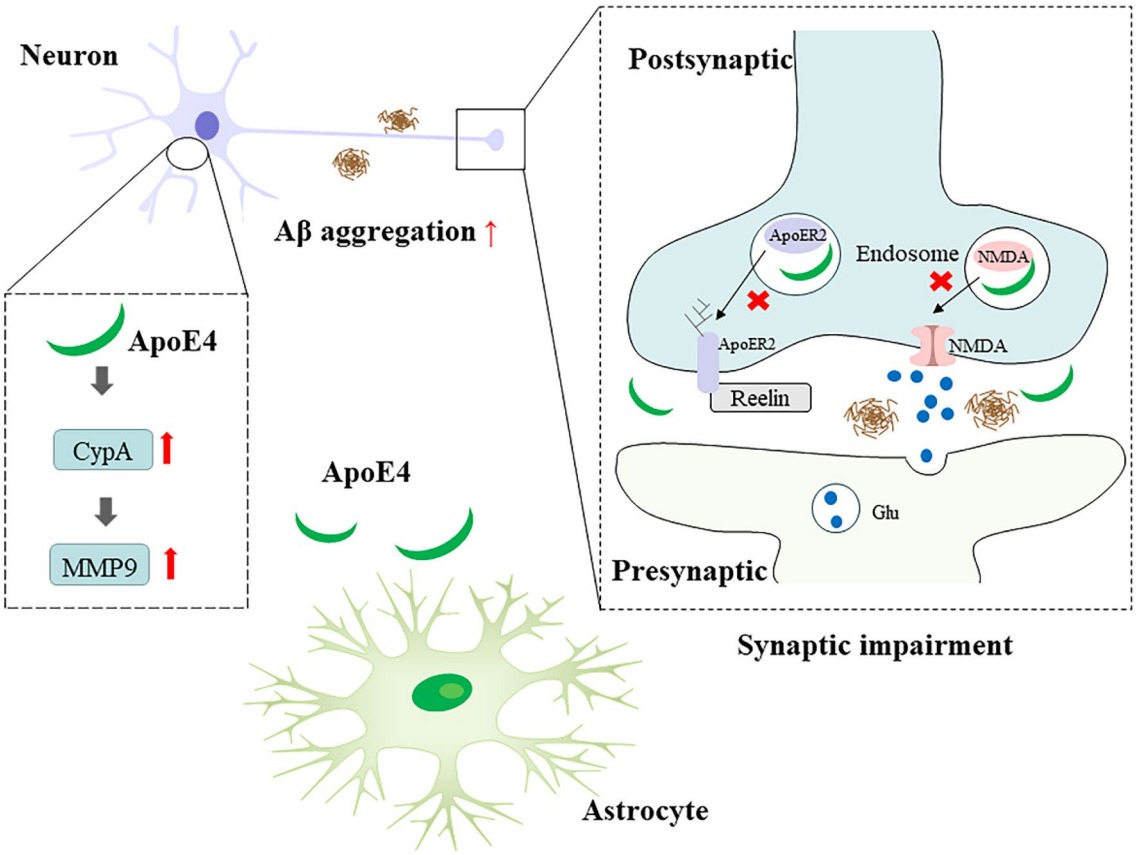


Fig. 4 Roles of ApoE4 in synaptic impairment. ApoE4 retains ApoER2 and glutamate receptors in endosomal compartments. Synaptic transmission mediated by reelin is inhibited and ApoE on the surface of neurons is decreased. ApoE4 can contribute to neuronal and synaptic dysfunction by activation of cyclophilin-A matrix metalloproteinase-9 (CypA-MMP9) pathway. ApoE4 would lead to the accumulation of Aβ, inducing synaptic impairment

the intercellular space of neurons rather than its clearance (Bilousova et al. 2019). In contrast, Aβ/ApoE2 complexes may contribute to Aβ clearance and protect synaptic function of *ApoE* transgenic (TR) mouse (Arold et al. 2012). Synaptic dysfunction is a central mechanism of cognitive impairment in AD. It is helpful for diagnosis to recognize the effect of *ApoE* ε4 on synaptic function in the early stage of AD development (Fig. 4).

Cholesterol Transportation

The brain has the highest content of cholesterol, accounting for approximately 20% of whole cholesterol in the body. Approximately 70% of cholesterol in the brain is found in myelin. The rest about 30% of cholesterol is found in the membranes of glial cells and neurons, where it is primarily circulated for neuronal repair and remodeling (Dietschy and Turley 2001, 2004). ApoE initiates the formation of high-density lipoprotein (HDL)-like particles by accepting cholesterol and phospholipids via ABCA1 and ABCG1, activating members of the ATP-binding cassette (ABC) family of transport proteins (Horiuchi et al. 2019). Lipoproteins and lipid complexes combined with ApoE interact with cell surface heparan sulfate proteoglycans and cell membrane-associated receptors to promote cellular uptake and redistribution and storage of cholesterol (Lanfranco et al. 2020).

Generally, AD brain shows abnormal cholesterol. In cultured neurons, transient increases of cholesterol in membrane are associated with early AD pathological features, for example, excessive $A\beta_{1\text{-}42}$ production, enlarged endosomes, and abnormal axonal transport (Marquer et al. 2014). ApoE4 has a low affinity and binding capacity for lipid transport (Hatters et al. 2006). Inadequate ApoE levels or impaired ApoE function in *ApoE* ε4 carriers may lead to imbalance of cholesterol homeostasis in the CNS and affect neuronal health. A study showed that the level of total cholesterol was higher in ApoE4 carriers compared to those ApoE3 and ApoE2 (Dunk and Driscoll 2022). Generally, higher total cholesterol may be a risk factor for AD pathogenesis. Previous study connected cholesterol with APP processing mediated by ApoE (Howland et al. 1998). Cholesterol clearance

depends on its catabolic derivative, 24S-hydroxycholesterol (24-OHC). Elevated 27-OHC can activate C/EBPβ at the presence ApoE4, which subsequently increases Aβ production and tau hyperphosphorylation in *ApoE4* TR mice (Wang et al. 2021). ABCA1 is involved in cholesterol transport. ApoE4 increases ABCA1 aggregation by promoting ADP-ribosylation factor 6 (ARF6) expression and reduces ABCA1 cell membrane recycling in the primary astrocytes obtained from *ApoE4* TR mice (Rawat et al. 2019). A study showed that 27-OHC might affect cholesterol transport through ABCA1-ApoE-LDLR/LRP1 proteins in the brains of *ApoE4* TR mice (Wang et al. 2022b). Lee et al. (2021) found that astrocytes expressing ApoE4 could lead to excessive cholesterol accumulation, which in turn increases the level of APP in lipid rafts, as detailed in Fig. 5. Additionally, cholesterol abnormalities induced by ApoE4 might further abnormalize glucose metabolism (Wu et al. 2018), aggregating AD process. Therefore, ApoE4 plays profound roles in cholesterol metabolism, transport, and AD development.

Oxidative Stress

When the redox balance in the brain is disrupted, oxidative stress occurs, leading to neuronal death. AD brain in a state of high oxidative stress. Nevertheless, oxidative stress is a common side effect of aging. ApoE has antioxidative properties demonstrated by *ApoE* KO mice. ApoE deficient mice may have poor learning and memory ability as a result of higher levels of diet-induced oxidation (Evola et al. 2010). Increasing evidence connected the AD induced by *ApoE* genotype with the oxidative stress. The degree of oxidative stress in AD brain is closely related to the genotype of *ApoE*: *ApoE2* < *ApoE3* < *ApoE4* (Miyata and Smith 1996). The level of reactive oxygen species (ROS) and the oxidation of protein and lipid are always increased in synaptosomes isolated from *ApoE4* mice (Lauderback et al. 2002). Compared with AD patients without *ApoE4*, AD patients carrying *ApoE4* showed higher hydroxyl radical levels in the blood (Ihara et al. 2000) and lower cerebral oxygen utilization (Robb et al. 2022). Individuals with *ApoE4* is associated with increased levels of oxidative stress, which may contribute to the earlier onset of AD. Caberlotto et.al found

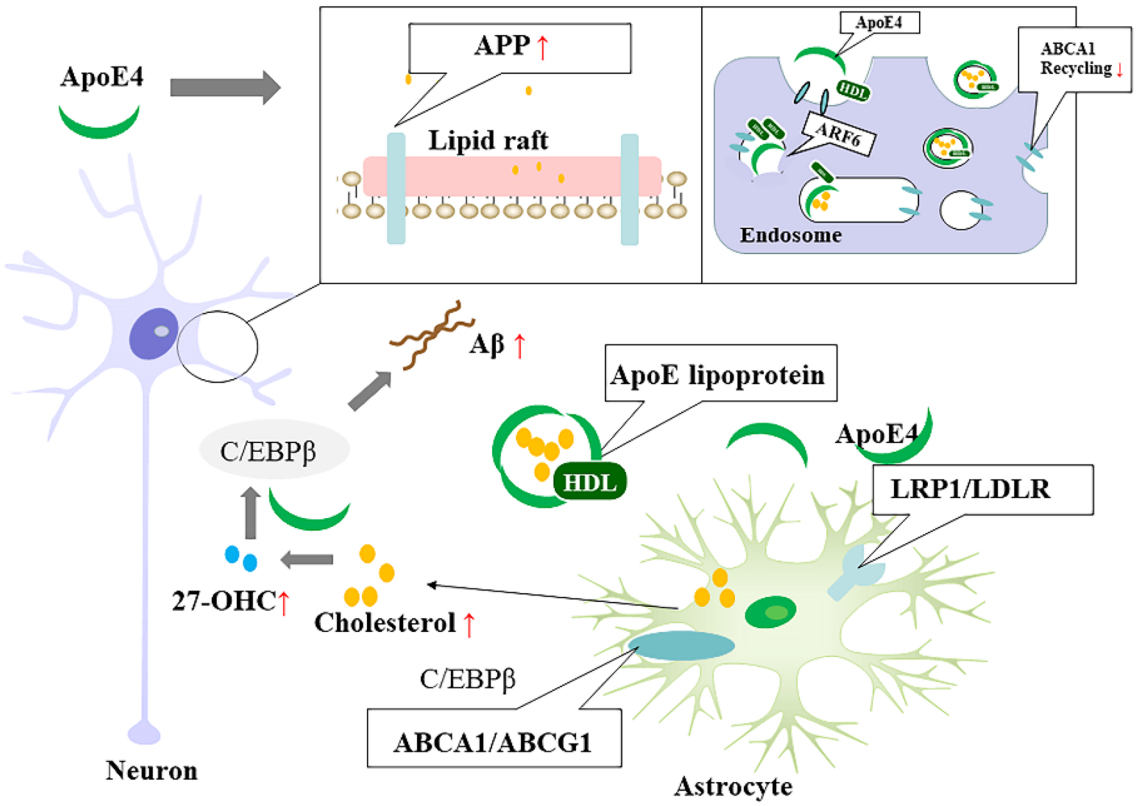


Fig. 5 Regulation of cholesterol in brain mediated by ApoE4. ApoE4 decreases ABCA1 cycling by promoting increased expression of ADP-ribosylation factor 6 (ARF6), which in turn decreases ABCA1 cycling to the cell membrane in astrocytes and affects cholesterol distribution. astrocytes with ApoE4 accumulate excess cholesterol and increase the level of APP in lipid rafts. Cholesterol clearance depends on its catabolic derivative, 24S-hydroxycholesterol (24-OHC). Elevated 27-OHC can activate C/EBPβ at the presence ApoE4, which subsequently increases Aβ production

ApoE4 is involved in oxidative stress possibly through the Notch signaling pathway suggested by transcriptomic data (Caberlotto et al. 2016).

In fact, it is still unclear how ApoE4 aggravates oxidative stress in the brain. One possible explanation related to the ApoE structure. This different amino acid composition of the three *ApoE* phenotype affects the binding with lipid peroxides; and the levels of lipid peroxides usually are used as markers of oxidative stress. A lipid peroxide, named 4-hydroxynonenal (HNE), can bind to Cys residue on ApoE2 and ApoE3 to reduce the damage. However, ApoE4 is lack of Cys residue that can clear the toxic of lipid peroxide (Butterfield and Mattson 2020). Another, ApoE4 aggravates oxidative stress and damages cerebral cortical neuron by triggering Ca^{2+} overload and CaMK II phosphorylation abnormity (Xu and Peng 2017). Although oxidative stress is thought to be a common pathomechanism involved in AD pathogenesis, it is often associated with aging and inflammation. In other word, oxidative stress is an intermediary process.

Mitochondrial Dysfunction

Mitochondrial dysfunction usually drives the early stage of AD pathogenesis. ApoE isoforms affect mitochondria-related proteins, and consequently altered mitochondrial function aggravates the AD pathological process (Fig. 6). ApoE4 could aggravate the progression of AD by impairing the respiration and increase glycolysis. When the neurons are stressed, the expression of ApoE4 will reduce the generation of ATP (Orr et al. 2019). In *ApoE4* carriers, activated receptor-gamma coactivator 1α (PGC-1α), deacetylase (Sirtuin 3, SIRT3), Mitofusin 1 (MFN1), MFN2 and dynamin-like protein 1 (DLP1) levels were lower than those in noncarriers (Yin et al. 2020). It suggested that *ApoE4* affects physiological functions, for example, mitochondrial biogenesis and dynamics. ApoE4 may be involved in mitochondrial dysfunction by damaging autophagy and mitophagy via the repression of FoxO3a in the brains of ApoE4 carriers (Sohn et al. 2021). ApoE4 could be hydrolyzed by neuron-specific proteins to produce a neurotoxic fragment (12–29 kDa). The link of the lipid and receptor-binding regions in the ApoE4 fragments leads to mitochondrial dysfunction and neurotoxicity of the Neuro-2a (N2a) cells transfected with *ApoE4* (Chang et al. 2005). In N2a cells expressing *ApoE4*, the levels of mitochondrial respiratory complexes I, IV, and V were all deregulated. However, compared to N2a cells expressed *ApoE4*, the gene transcripts of all respiratory complexes in *ApoE3* N2a cells were all downregulated (Chen et al. 2011). A recent study found that postmortem tissues from *ApoE4* carriers showed a deficiency of cytochrome oxidase (COX), complex II and III (Troutwine et al. 2022). In addition, ApoE4 was revealed to bind to α/β subunits of F1 mitochondrial ATP synthase in liver (Mahley et al. 1989). The results from proteomic analysis indicated that there was a remarkable reduction in the levels of 50% of detected F1/F0 subunits of mitochondrial respiratory complexes V (ATP synthase) (Orr et al. 2019). However, more investigates are needed to clarify the mechanism of ApoE4-driven dysfunction of respiratory complexes.

Increasing studies focus on the mitochondrial dysfunction and endoplasmic reticulum (ER) related to high level of ROS. Astrocyte-conditioned media (ACM) containing ApoE4 showed increases of mitochondrial-associated membrane (MAM) function compared to ApoE3 (Tambini et al. 2016). In N2a cells and female ApoE4 (Δ272–299) TR mice, ApoE4 (Δ272–299) significantly induces mitochondrial dysfunction by triggering ER stress and increasing the expression of GRP75, which promotes the formation of mitochondrial-associated membrane (MAM) and mitochondrial calcium overload (Liang et al. 2021). ApoE4 (Δ1-272) could induce the activities of mitochondrial respiratory

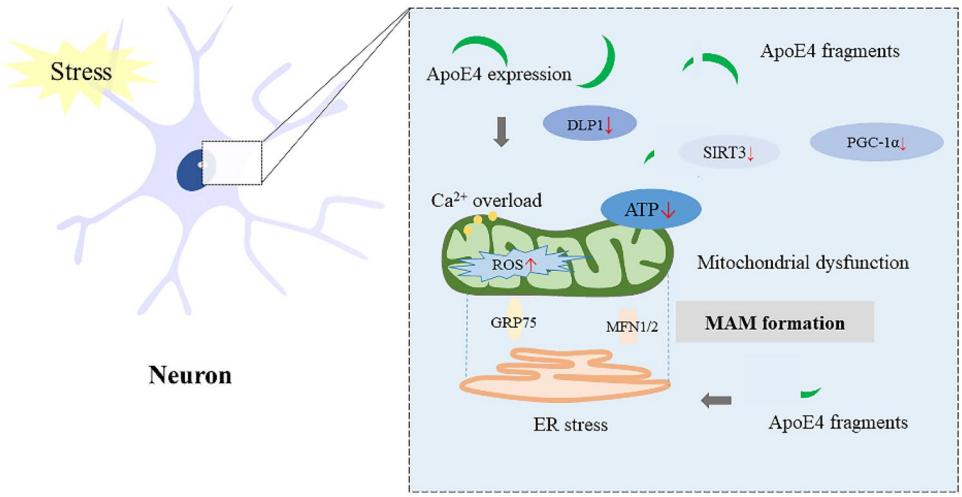


Fig. 6 Influence of ApoE4 in mitochondrial dysfunction. When the neurons are stressed, ApoE4 expression in neuron cells would inhibit the generation of ATP, increase the reactive oxygen species (ROS) level and promotes calcium overload. Some proteins about mitochondrial biogenesis and dynamics could be reduced when ApoE4 presents. ApoE4 fragments also lead to mitochondrial dysfunction and endoplasmic reticulum (ER) stress, as well as the formation of mitochondrial-associated membrane (MAM)

complex III and IV, which triggered mitochondrial dysfunction (Nakamura et al. 2009). In fact, MAM activity mediated by ApoE4 on AD development is still unclear, but it can be determined that ApoE4 may contribute to the development of AD by affecting mitochondria-related functions.

Neuroinflammation

ApoE4 may be involved in neuroinflammation. The inflammatory factors in the brain are mainly produced from microglia and astrocytes. Similarly, ApoE protein is normally synthesized by microglia and astrocytes. Lynch et al. (2003) used human-derived *ApoE4* and *ApoE3* transgenic mice and administered lipopolysaccharide intravenously. They found a significant increase in TNF-α and IL-6 present in the brains of *ApoE4* mice compared to *ApoE3* mice. These results also found in the cells that ApoE4 increases the expression of inflammatory factors in human astrocytes (Iannucci et al. 2021). Moreover, ApoE4 genotype also alters immunometabolism of microglia. A study indicated that aerobic glycolysis and level of hypoxia inducible factor 1α (Hif1α) are increased in microglia expressing ApoE4. Furthermore, ApoE4 could aggravate plaque-induced microglial reactivity and lipid metabolism (Lee et al. 2023).

Apparently, *ApoE4* exacerbates neuroinflammation. ApoE is a ligand for triggering receptor expressed on myeloid cells 2 (TREM2). TREM2, expressed on microglia, is an immune receptor. TREM2 is important in microglia-related functions. A study showed that microglia could be activated by TREM2 through spleen tyrosine kinase (SYK) or DAP10-dependent pathways. SYK could guild signaling and effector functions downstream of TREM2. Phagocytosis of Aβ by microglia is also associated with SYK. Moreover, Akt-GSK-3β signaling could be affected by the combination between DAP10 and TREM2. Deficiency in SYK can lead to the development of disease-associated microglia and the onset of the prodromal stage of ApoE expression, which occurs via DAP10-dependent pathways (Ennerfelt et al. 2022; Wang et al. 2022a).

TREM2-mediated signaling pathways for neuroprotection can be affected by ApoE (Ulrich and Holtzman 2016). In fact, TREM2 is also a major genetic risk factor for AD development. ApoE-TREM2 interaction is related to AD. The interaction between ApoE and TREM2 is affected by ApoE polymorphisms, and ApoE4 shows the highest affinity with TREM2 compared to ApoE2 and ApoE3 (Kober et al. 2020). Krasemann et al. reported that ApoE-TREM2 pathway could be activated when neuronal apoptosis happened, inducing microglia homeostatic imbalance (Krasemann et al. 2017). However, this study was conducted in mice and could not account for genetic subtype differences of ApoE in relation to TREM2. In the microglia expressing ApoE4, lacking of TREM2 would reduce Aβ uptake by microglia (Fitz et al. 2021) (Fig. 7). A study showed that ApoE4 induces neuroinflammation through activating the proinflammatory PGE2 pathway or inhibiting the TREM2 pathway (Li et al. 2015). Furthermore, the

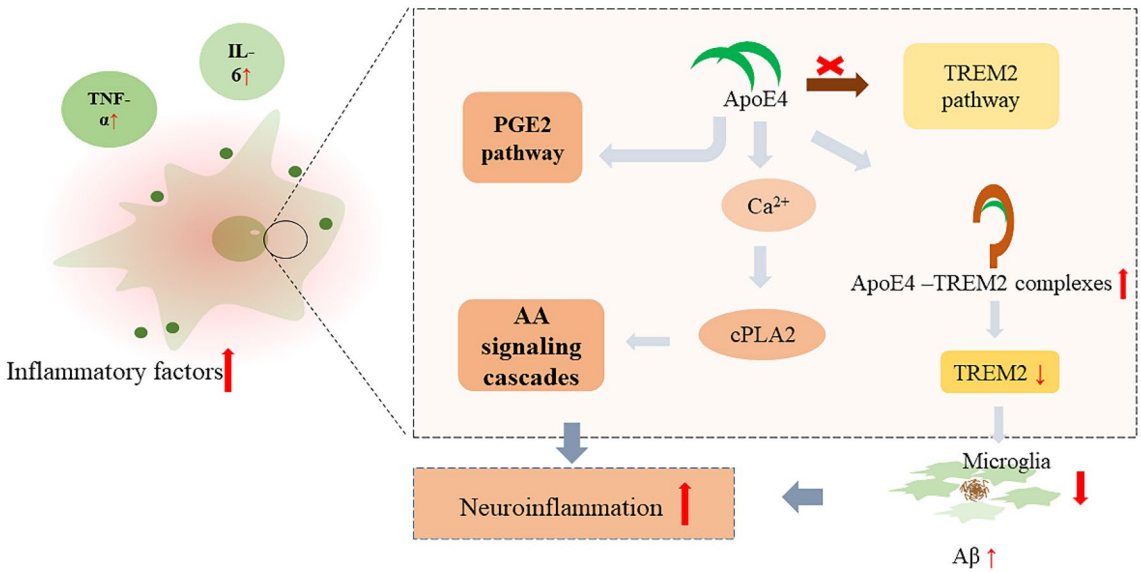


Fig. 7 Neuroinflammation effects of ApoE4 in AD pathogenesis. ApoE4 induces the increase of inflammatory factors, including TNF-α and IL-6. ApoE4 could exacerbate neuroinflammation through activating the proinflammatory PGE2 pathway or inhibiting the anti-inflammatory TREM2 pathway. ApoE4 also can contribute to neuroinflammation through inducing Ca^{2+} dependent phospholipase A2 (cPLA2) activations and changes on arachidonic acid (AA) signaling cascades. Further, ApoE4 affects Aβ clearance mediated by the interaction between ApoE4 and TREM2

molecular mechanism of interaction between ApoE4 and TREM2 deserves to be further investigated.

In addition, ApoE4 can induce Ca^{2+} dependent phospholipase A2 (cPLA2) activations and contributes to the changes on arachidonic acid (AA) signaling cascades. AA changes are generally related to the chronic brain inflammation (Duro et al. 2022).

Sleep Disturbances

ApoE4 may also be associated with sleep disturbances in AD patients. The older with cognitive impairment and expressing ApoE4 generally showed long sleep duration (Basta et al. 2021). Carriers containing two ε4 alleles showed more sleep abnormalities compared to ε4 noncarriers or AD patients with one ε4 allele (Koo et al. 2019). A study of 698 community dwelling older adults without dementia showed that improving sleep quality reduced the negative effects of ApoE4 on NFTs (Lim et al. 2013). Furthermore, ApoE4 effects on sleep might be independent of Aβ and tau stages and ApoE4 might regulate the level of melatonin. AD patients with two ε4 alleles was associated with significantly reduced post-mortem CSF melatonin compared to AD patients with one ε4 allele (Blackman et al. 2022). Furthermore, sleep disorders could activate microglial and even contribute to neuroinflammation (Hu et al. 2021).

Cerebrovascular Integrity

The contribution of cerebrovascular integrity to AD is increasingly recognized. ApoE4 can exacerbate the deposition of Aβ in the brain to form cerebral amyloid angiopathy (CAA), which can severely damage vascular integrity and BBB functions. Although CAA is not clinically identical to AD pathology, it has a similar molecular basis with AD. (Safieh et al. 2019). Reducing ApoE4 in astrocytes from 5XFAD ApoE4 knock-in mice could decrease overall Aβ-mediated gliosis and increase cerebrovascular integrity in CAA-containing vessels (Xiong et al. 2023). Cerebrovascular integrity and function are also regulated by fibrinogen, which is also dependent on the subtype specificity of ApoE. AD patients with *ApoE* ε4/ε4 genotype exhibit increased fibrinogen deposition in CAA and oligomeric Aβ-positive vessels (Hultman et al. 2013). Data from recent years suggested that ApoE4 expression could exert detrimental effects on the cerebrovascular system, including BBB impairments. BBB integrity is critical in the pathology of neurodegeneration and cognitive impairment. Compared with ApoE3, ApoE4 could accelerate BBB catabolism, neuronal loss and behavioral deficits, which can be independent of Aβ (Montagne et al. 2021). ApoE4 activates the CypA-MMP9 pathway in the cerebrospinal fluid and thereby accelerates BBB catabolism, leading to neuronal and synaptic dysfunction (Montagne et al. 2020).

Others

ApoE4 plays an important role in many aspects of AD pathogenesis. In addition to the mechanisms described above, intracerebral glucose metabolism, transactive response DNA binding protein (TDP-43) pathology, and the relationship with other non-AD diseases still require more investigations. In addition, astrocytes expressing ApoE4 showed high glycolytic activity, low oxygen consumption, and reduced rate of glucose oxidation in the presence of lactate (Farmer et al. 2021). Diabetes is a risk factor for AD (Shinohara et al. 2020). Atherosclerosis is related to LDLR and ApoE (Zhao et al. 2022). Therefore, studies related to these two diseases may provide the investigation of the mechanisms and treatment for AD. Furthermore, the AD risk for *ApoE4* carriers might differ between sexes. The activity of BACE1 is associated with ApoE4, which female showed higher BACE1 expression than male, using the mice with ApoE4 or AD risk factors (*APPSwe*, *PS1*M146V, *tau*P301L; 3xTg) (Hou et al. 2015). Astrocyte coverage of plaques was the poorest in ApoE4 females (Stephen et al. 2022). Compared with primary microglia in ApoE4 males, the levels of IL1b, TNFa, IL6, and NOS2 were higher in ApoE4 female primary microglia (Mhatre-Winters et al. 2022). The interaction between sex and ApoE4 in AD pathogenesis remains unclear. In addition, AD brains have another pathological deposition, that is TDP-43 pathology. TDP-43 is a 43 kDa heterogeneous nuclear ribonuclear protein, which regulates gene expression and RNA processing (Stover et al. 2004; Higashi et al. 2013). Some evidence showed an association between *ApoE4* and increased TDP-43 pathology. Two community-based cohort studies of ageing and dementia indicated that *ApoE4* seemed to interact with increased TDP-43 burden, and high levels of TDP-43 might induce hippocampal atrophy (Yang et al. 2018). A study on 738 older adults with AD also showed that TDP-43 are associated with *ApoE4* directly (mediated by Aβ and tau) or indirectly (Wennberg et al. 2018). Furthermore, brains with limbic-predominant TDP-43 pathology were more likely to carry ε4 allele and had higher possibility of AD (Teylan et al. 2021). In addition, TREM2 deficiency could damage phagocytic clearance of pathological TDP-43 by microglia, inducing neuronal damage (Xie et al. 2022).

Therapeutic Approaches Targeting to ApoE

To date, AD remains far from cure, and there are a few classes of drugs approved for the AD treatment; for example, cholinesterase inhibitors (Tacrine, Donepezil, Rivastigmine,

Galanthaminone) NMDA receptor antagonists (Memantine), and Aβ monoclonal antibody (Aducanumab). The genotype of *ApoE* determines the degree of LOAD risk, and ApoE plays a crucial role in the brain. Therefore, targeting ApoE4 is a highly promising therapy for AD. Considering the roles of ApoE4 in the LOAD pathogenesis, the current research studies on ApoE4-targeted AD therapy can be divided into the following categories: targeting the interaction of ApoE with Aβ, targeting ApoE receptors, correcting the *ApoE4* genotype or its function by gene editing, ApoE antibody, and nonpharmacological therapy (Fig. 8). The research on ApoE-targeted therapy can be helpful in the early intervention and treatment of LOAD. Furthermore, there are several drugs targeting ApoE to improve AD pathology in trials are shown in Tab. 1.

Targeting the Interaction of ApoE with Aβ

In *ApoE4* carriers, ApoE-Aβ interaction contributes to Aβ more susceptible to deposition into amyloid plaques. Blocking the interaction between ApoE and Aβ could reduce intraneuronal accumulation of Aβ and inhibit synaptic degeneration. $Aβ_{12-28}P$ is mimics of Aβ. $Aβ_{12-28}P$ can reduce neurotoxicity induced by Aβ through blocking the binding between ApoE and Aβ at residues 12–28. $Aβ_{12-28}P$ can also attenuate Aβ deposition and insoluble tau accumulation and inhibit synaptic degeneration in AD mice model (Sadowski et al. 2004; Kuszczyk et al. 2013; Liu et al. 2014b). The enoxaparin molecule has a strong energetic affinity for ApoE4 and disrupt the interaction between ApoE4 and Aβ (Aguilar-Pineda et al. 2022). Therefore, amyloid load can be reduced by regulating ApoE levels in the brain.

Targeting ApoE Receptors

ApoE participates in different physiological process mediated by its receptors. *ApoE4* will reduce the expression of LRP8 (ApoER2) (Chen et al. 2010); this receptor can prevent the loss of corticospinal neurons with aging (Beffert et al. 2006). Overexpression of ApoER2 may reduce the risk of *ApoE4*. LRP1 also plays an important role in mediating the involvement of ApoE4 in AD pathogenesis, mainly associated with Aβ signaling (Pietrzik et al. 2002). Regulating the expression of ApoE receptors can restore lipid homeostasis and synaptic plasticity and increase Aβ clearance. In addition, overexpression of LDLR in microglia can inhibit ApoE expression and reduce tau-associated neurodegeneration mediated by ApoE (Shi et al. 2021).

Gene Editing for *ApoE4* Gene

The function of ApoE is dependent of its heterodimer. Therefore, it might be effective for suppressing the risk of *ApoE4* to modify *ApoE* from ε4 to ε3 or ε2 by gene editing. When iPSC-derived neurons were converted from *ApoE* ε4 to ε3 using zinc finger nucleases, there were reductions in

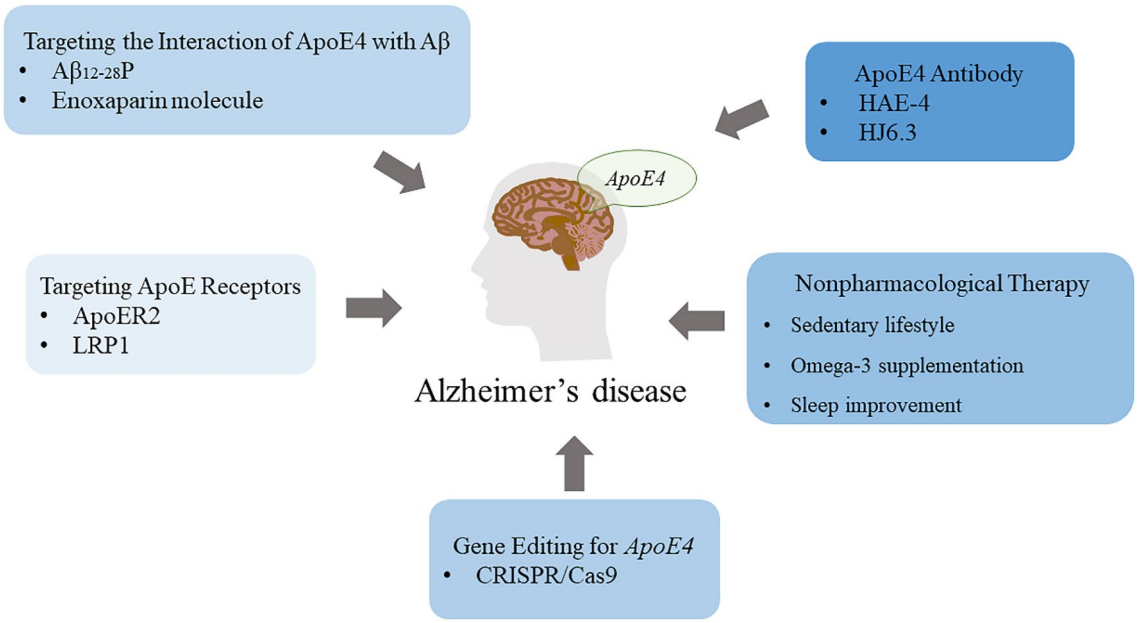


Fig. 8 AD therapy targeting to ApoE. Targeting ApoE4 is highly promising for AD treatment and improvement. Considering the roles of ApoE4 in the LOAD pathogenesis, the therapeutic approaches can be subdivided into the following categories: targeting the interaction of ApoE with Aβ, targeting ApoE receptors, correcting the *ApoE4* genotype by gene editing (CRISPR/Cas9), ApoE antibody, and nonpharmacological therapy

Table 1 Drugs to improve AD targeting ApoE

Drug	Mechanism	Subject	Result	References
Bexarotene	Raising ApoE levels and mediating Aβ-ApoE interactions to clear Aβ	*APP/PS1* mouse	Aβ plaques were cleared in the cortex and hippocampus. Expression of ApoE and ABCA1 and ABCG1 gradually increased. The level of LDL increased	Cramer et al. (2012)
Ondansetron	Regulating LXR-ABCA1 pathways	Astrocyte of human *ApoE3*-TR mice Human astrocyte	The level of ApoE secretion increased	Shinohara et al. (2019)
Probucol	Increasing the ApoE levels and decreasing the level of cholesterol	AD mice injecting in the single to aggregated $A\beta_{1\text{-}40}$	The deleterious effects of $A\beta_{1\text{-}40}$ on learning memory capacity and hippocampus are attenuated. The degree of lipid peroxidation in hippocampal are reduced	Santos et al. (2012)
ApoE mimetic CN-105	Mimicking ApoE binding to LRP1 on microglia and neurons	*APP/PS1/ApoE* TR mice	Administering early in the course of disease can reduce Aβ pathology and attenuate memory deficits in male mice	Krishnamurthy et al. (2020)
Candesartan	Evaluating the therapeutic potential of angiotensin receptor blockers (ARBs)	human ApoE4 mice	Short-term memory and higher levels of synaptic protein can be improved in female mice	Scheinman et al. (2021)
Imipramine and Olanzapine	Inhibitors of the apoE4-Aβ interaction	5X FAD TR mice and primary neuron cell model from 5X FAD mice, data from the National Alzheimer's Coordinating Center (NACC)	Aβ fibrillization was reversed. AD subjects taken imipramine or olanzapine demonstrated better cognitive performance as measured by the MMSE	Johnson et al. (2022)

ApoE fragments, Aβ production, and tau phosphorylation. This research study suggested gene editing can eliminate the deleterious effects of *ApoE4* (Wang et al. 2018). CRISPR/Cas9, the third-generation gene editing technology, has shown great potential in modifying ApoE genotypes. The technology has proven successful at the cellular level, where cells from healthy *ApoE3/E4* individuals can be transformed into *ApoE2/E2*, *ApoE3/E3*, *ApoE4/E4* or *ApoE* KO (Schmid et al. 2019). In recent studies, CRISPR/Cas9 gene editing technology is mostly used to establish models with *ApoE4* to study the effects of this gene on synaptic function and lipid metabolism (Lin et al. 2018). However, whether CRISPR/Cas9 gene editing technology can be used for gene therapy of *ApoE4* remains to be investigated. Notably, there are ethical issues and risks associated with gene editing therapies, so whether they can be administered to AD patients remains highly controversial.

ApoE Antibody

An anti-human ApoE antibody (HAE-4) which recognizes human ApoE4 and ApoE3. It preferentially binds to non-lipidated forms of ApoE and ApoE in plaques. HAE-4 has been reported to suppress Aβ plaques (Liao et al. 2018) and tau spreading driven by Aβ. This clearance abilities of HAE-4 might depend on microglial activation. HAE-4 could increase microglial activation (Gratuze et al. 2022). Furthermore, HAE-4 not only reduces Aβ deposition including CAA but also inhibits reactive microglia, astrocytes and pro-inflammatory related genes in the cortex (Xiong et al. 2021a). HJ6.3, a monoclonal antibody against ApoE, could block the interaction of ApoE with Aβ. Liao et al. treated 7-month-old *APP/PS1* mice with HJ6.3 for 21 weeks. They found HJ6.3 could reduce the formation and aggregation of Aβ and improve the spatial learning abilities of mice (Liao et al. 2014). Although ApoE antibodies are effective, more investigations are needed to determine whether these antibodies have side effects.

Nonpharmacological Therapy

ApoE4 carriers have a high probability of AD development, but early intervention can still delay the onset of AD or even prevent it from occurring. The individuals carrying *ApoE4* can prevent AD through diet, such as using a low glycemic index and low carbohydrate diet structure. This diet could be helpful in preventing the glycation of ApoE and brain lipid metabolism for AD patients. Nevertheless, this diet could prevent the effects of ApoE4 on the insulin cascade (Norwitz et al. 2021). Ketogenic diet is an option of low glycemic index and low carbohydrate diet structure for patients. A ketogenic diet for *ApoE4* carriers can make their metabolism dependent on ketones rather than glucose (Wu et al. 2018), thereby reducing the metabolic burden and improving cognition of *ApoE4* carriers with AD (Morrill and Gibas 2019). Long-term omega-3 supplementation improved the cognition abilities and lowered Aβ burden in *ApoE4* carriers (Li et al. 2022). DHA-containing fish oil supplementation improved novel object recognition memory, increased BDNF protein, and improved abnormal Erβ, Cldn1 and Glut-5 expression (Pontifex et al. 2022) in *ApoE4* mice treated with VCD (4-vinylcyclohexene diepoxide). Additionally, a poor lifestyle in *ApoE4* carriers, such as sedentary lifestyle, might increase the risk of amyloid deposition; active physical activity might prevent the AD risk associated with *ApoE4* (Liu et al. 2014b). Notably, improvement on sleep disturbance might reduce the risk of probable AD patients for individuals carrying *ApoE4* allele.

Summary and Prospect

AD is a neurodegenerative disease influenced by genetic and the environmental factors, but there is still no cure for AD patients. Given the discovery of *ApoE4* as an AD risk gene, it is expected that more insights can be gained into the pathogenesis and treatment of AD by investigating the mechanism followed by the role of this allele in AD pathogenesis. ApoE plays an important role in the AD brain. Although ApoE4 is not inevitable in the induction of AD, it remains possible for this genetic isoform to accelerate AD progression. Mechanistically, ApoE4 could increase the risk of cognitive decline by initiating and accelerating the accumulation, aggregation, and deposition of Aβ in the brain, as well as increasing the level of Aβ oligomers in the brain. Additionally, ApoE4 could affect tau phosphorylation and the density of NFTs in the brain directly or indirectly. Compared with ApoE3 and ApoE2, ApoE4 shows a lower level of efficiency not only in providing cholesterol but also in maintaining synaptic integrity and plasticity. These reviews are similar to the previous reviews, for example Koutsodendris et al. (2022) and Serrano-Pozo et al. (2021). In addition, we further reviewed that ApoE4 exacerbates the level of oxidative stress in the AD brain. Definitely, it is also suspected that ApoE4 may also be associated with mitochondrial dysfunction, neuroinflammation, and sleep disturbances in AD pathogenesis. Notably, the fragments generated by hydrolysis of ApoE4 are linked to several pathological features of AD, such as tau. Therefore, understanding the involvement of *ApoE* ε4 allele in the AD pathogenesis is not only conducive to preventing or delaying the onset of AD, but also contributory to developing the therapeutic strategies for AD targeting ApoE4. The current studies targeting to ApoE4 focus on ApoE-Aβ interactions, ApoE

receptors, correcting the *ApoE4* genotype or its function through gene editing. ApoE antibody might be a possible treatment for AD. Furthermore, nonpharmacological therapy could be effective in prevention. However, ApoE4-targeted therapy can only slow down the progression of AD and reduce the probability of AD occurrence in populations with *ApoE4*. Therefore, ApoE4-related therapies are recommended for early treatment of AD in individuals who carry the *ApoE4* gene or for preventing AD pathology before it occurs. Furthermore, although recent studies have reviewed about ApoE degradation and structural correctors (Safieh et al. 2019), our review do not cover these topics. Because we believe that preserving the physiological function of ApoE is crucial and that relevant therapies should not be utilized in a manner that compromises its original function. The functions performed by ApoE4 vary in different cells. In addition to microglia and astrocytes, it is also worthwhile to study the expression of ApoE4 in vascular wall cells. The expression of ApoE4 in blood vessels not only reduces the blood flow in small arteries but also impairs the ability of spatial learning (Yamazaki et al. 2021). Therefore, to reveal the different roles of ApoE4 in different cells is beneficial to understand AD pathogenesis. Furthermore, ApoE4 is related to COVID-19 (Xiong et al. 2021b), dementia with lewy bodies (Zhao et al. 2020), and diabetes mellitus type, and all of which have a close link to AD. It is suggested that the connection between ApoE4 and other pathological proteins characteristic of these disease can be found in the pathogenesis of AD. AD pathogenesis can be understood from different perspectives. Notably, ApoE4 can exacerbate or induce inflammation, which may be a commonality between these diseases. In conclusion, most studies are still focused on the connection between ApoE4 and Aβ, and we believe that this study about ApoE4-Aβ interval is a promising target for AD treatment. In addition, diet improvement might be a better treatment for ApoE4 carrier without AD. Furthermore, there are some new perspectives, for example, tau propagation, vascular dysfunction. Lipid homeostasis related to the function of ApoE is also well worth an in-depth discussion.

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Data Availability Enquiries about data availability should be directed to the authors

Declarations

Conflict of interest All authors declare that there is no potential conflict of interests.

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