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Apolipoprotein E: Linking Lipid Metabolism, Alzheimer's Disease, and Therapeutic Innovation

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Lipoproteins and apolipoproteins are essential macromolecules that maintain systemic lipid homeostasis and cellular energy balance by transporting lipids through plasma and interstitial fluids. Structurally, lipoproteins consist of hydrophobic lipid cores surrounded by amphipathic apolipoproteins, which determine their metabolic fate, receptor interactions, and physiological functions. Among apolipoproteins, apolipoprotein E (APOE) plays critical roles in lipid transport, nerve repair, and immune regulation. APOE encoded by *APOE* gene (OMIM*107741) exists in three common isoforms (APOE2, APOE3, and APOE4), which differ by cysteine/arginine substitutions at residues 112 and 158. These subtle structural changes profoundly alter receptor binding affinity, lipidation efficiency, and protein stability, resulting in distinct metabolic and pathological outcomes. In particular, APOE4 is the strongest genetic risk factor for late-onset Alzheimer's disease (AD). APOE4 promotes amyloid-β (Aβ) aggregation, impairs Aβ clearance, enhances tau hyperphosphorylation, and triggers neuroinflammatory signaling. APOE-mimetic peptides, designed to replicate key functional domains of the native protein, exhibit neuroprotective, anti-inflammatory, and lipid-modulatory effects in preclinical models of AD, stroke, and atherosclerosis. Concurrently, advances in *APOE* genotyping are expanding clinical applications in AD risk prediction, lipid-lowering therapy, and personalized prevention. Understanding the molecular mechanisms and clinical relevance of the *APOE* gene remains essential for translating genetic insights into therapeutic and diagnostic innovation across metabolic and neurodegenerative diseases. This review highlights the *APOE* gene as a pivotal link between lipid metabolism and neurodegeneration. Integration of recent advances in its structural variants, disease mechanisms, therapeutic modulation, and clinical genotyping underscores the importance of *APOE* as both a biomarker and a therapeutic target.

Key words: Apolipoproteins E, Alzheimer's disease, APOE-mimetic peptide, Lipoproteins

REVIEW ARTICLE

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INTRODUCTION

Lipid metabolism is increasingly recognized as a central determinant of both neurological health and peripheral metabolic process. Lipoproteins, which are macromolecular complexes composed of a lipid core, are essential for the systemic transport of cholesterol and triglycerides through the circulatory system [1]. In addition to their role in peripheral lipid homeostasis, lipoprotein-associated apolipoproteins influence the structure and function of the central nervous system (CNS) through membrane maintenance, lipid trafficking, and signaling [2,3]. Among apolipoproteins, apolipoprotein E (APOE) occupies a unique position in linking peripheral lipid transport to neurobiological processes such as synaptic remodeling, inflammatory regulation, and neuronal repair [2-4].

This review integrates the latest insights into lipoprotein and apolipoprotein biology, with a particular focus on APOE and its role in Alzheimer's disease (AD).

Lipid, Lipoproteins, and Apolipoproteins

Lipids, whether synthesized endogenously or absorbed from the diet, must be transported to various tissues to fulfill their metabolic functions. In the plasma, they are carried within macromolecular complexes known as lipoproteins, which are lipid-protein complexes. Lipoproteins contain one or more specific proteins,

called apolipoproteins, located on their surface. The structure of core lipids with the overlying phospholipids, cholesterol, and apolipoprotein coat is stabilized by noncovalent forces. This interaction is sufficiently loose to permit the rapid spontaneous exchange of cholesterol, which is more water-soluble than the other lipids, between plasma lipoproteins and cell membranes [1,4].

Lipoproteins are synthesized in the liver and intestines, derived from metabolic modification of precursor lipoproteins, or assembled into cell membranes from cellular lipids and exogenous lipoproteins or apolipoproteins. In the circulation, lipoproteins are highly dynamic. They undergo enzymatic modifications of their lipid components, facilitated and spontaneous lipid exchange, the transfer of soluble apolipoproteins, and structural changes in the apolipoproteins in response to changes in composition. Ultimately, lipoproteins are taken up and catabolized by the liver, kidney, and peripheral tissues via receptor-mediated endocytosis and other mechanisms [1,4].

Although the assembly, structure, metabolism, and receptor interactions of lipoproteins are largely governed by their apolipoprotein components, lipoproteins are most commonly classified according to their hydrated density or electrophoretic mobility on agarose gel. They are categorized into six major classes based on hydrated densities: chylomicron, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein(a). Each class contains a distinct combination and proportion of apolipoproteins [1,5].

Apolipoproteins are the protein components of lipoprotein particles, serving as structural scaffolds, enzyme cofactors, and receptor ligands. The prefix, "apo" derived from Greek, means "away from". Structurally, apolipoproteins are generally amphipathic proteins: hydrophobic regions interacting with lipid surfaces and hydrophilic residues exposed to aqueous surroundings. There properties enable the solubilization, transport, and metabolism of lipids in the blood and cerebrospinal fluid and are essential for the formation, stabilization, remodeling and clearance of lipoprotein particles [3,4]. However, their complete functions are not yet clear. Apolipoproteins are categorized based on their structure, genetic origin, and functional role in lipoprotein metabolism. They are primarily divided into five main classes: A, B, C, D, and E, each with several subtypes [5].

Among these, APOE plays a crucial role in neural growth, remyelination, and nerve regeneration. It is a 34-kDa plasma glycoprotein composed of 299 amino acids, encoded by the gene *APOE* (19q13.2, MIM*107741) in human. It is found on all lipoproteins, but only a small amount is on LDL. Lipoproteins containing APOE are removed from circulation by several different cellular receptors that recognize a positively charged amino acid cluster in a specific region of the protein. APOE facilitates hepatic uptake of lipoproteins by interacting with a variety of receptors, such as the chylomicron remnant receptor, low-density lipoprotein receptor, and LDL receptor-related protein [6-8].

APOE exists in three common isoforms, APOE2, APOE3, and APOE4, distinguished by amino acid substitutions at residues 112 and 158, which correspond to the three allelic variants of the *APOE* gene, ε2, ε3, and ε4, respectively [3,4]. These isoforms can be differentiated by isoelectric focusing electrophoresis:

- APOE2 encoded by *APOE* ε2, contains cysteine at both positions 112 and 158.
- APOE3 encoded by *APOE* ε3, has cysteine at 112 and arginine at 158.
- APOE4 encoded by *APOE* ε4, contains arginine at both positions.

These isoforms differ in their biophysical properties, receptor-binding affinities, and regulatory effects on lipid and energetic homeostasis [2]. APOE2 has a reduced binding affinity for the B and/or E remnant receptor compared with APOE3, which can lead to the accumulation of lipoprotein in the plasma. Conversely, APOE4-containing lipoproteins are cleared more rapidly than those containing APOE3 but can disrupt lipid homeostasis through altered receptor recycling and lipid trafficking [3,6].

Among *APOE* alleles, ε3 is the most prevalent globally, although allele frequencies vary among populations. These genetic variants contribute substantially to interindividual variability of LDL-cholesterol and ApoB-100 concentrations. Because ApoB-100 is the major apolipoprotein of LDL, its plasma concentration serves as a surrogate marker for LDL particle number [1]. Individuals carrying at least one ε2 allele generally exhibit lower ApoB-100 and LDL- cholesterol levels than ε3 homozygotes, while carriers of at least one ε4 allele tend to show higher concentrations. This is likely due to increased hepatic uptake of lipoproteins in ε4 carriers, leading to hepatic cholesterol accumulation and subsequent downregulation of the LDL receptor expression [5,6].

APOE genotype and AD

AD is a progressive neurodegenerative disorder character-

ized by cognitive decline, synaptic dysfunction, and neuronal loss, accompanied by the accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Genetic, biochemical, and neuropathological evidence indicates that APOE significantly influences the risk, onset, and progression of late-onset AD [7,9].

Among the three major APOE isoforms, *APOE* ε4 allele is the strongest known genetic risk factor for late-onset AD, while APOE ε2 confers relative protection compared with the neutral APOE ε3 allele. Individuals carrying one copy of the ε4 allele (heterozygotes) have a 3- to 4-fold increased risk of developing AD, whereas those homozygous for ε4 have a 10- to 15-fold higher risk compared to ε3 homozygotes. In contrast, the ε2 allele appears to decrease AD risk and delay onset. APOE4-associated risk is observed in both sexes but tends to be more pronounced in females [7,9-16].

Recent transcriptomic and functional studies demonstrate that APOE4 reshapes cellular and molecular networks even in asymptomatic individuals, influencing brain aging trajectories and predisposing to neurodegeneration [13,14,17-19]. Although the precise mechanisms linking *APOE* gene to AD pathogenesis remain incompletely defined, they likely involve direct and indirect interactions with Aβ plaques and tau tangles—the pathological hallmarks of the disease [13,17].

Mechanisms: Lipid Metabolism, Aβ, Tau, and Neuroinflammation

Lipidation & Astrocyte Function: APOE4 disrupts astrocytic lipid metabolism, promoting the secretion of triglyceride-rich, poorly lipidated lipoprotein particles instead of cholesterol-rich high-density lipoproteins. This alteration impairs lipid clearance and promotes intracellular lipid accumulation, astrocyte dysfunction, and lipotoxic stress [18,19].

Amyloid β (Aβ) Pathology: APOE4 can directly bind to and alter the lipid microenvironment, thereby reducing Aβ clearance, promoting aggregation, and facilitating the formation of more toxic oligomers [11,17].

Tau Pathology: APOE4 enhances tau hyperphosphorylation and neurofibrillary tangle accumulation. Humanized mouse and iPSC-derived models demonstrated that trans-synaptic spread and cytoskeletal instability are accelerated depending on sex and age [7,20].

Microglial Dysfunction & Neuroinflammation: APOE4 reprograms microglial lipid metabolism, increasing lipid droplet accumulation, cholesterol overload, lysosomal impairment, and activating NF-κB and type-I interferon signaling. These changes reduce phagocytosis of Aβ, tau, and synaptic fragments, exacerbate neuroinflammation, and impair neuron–microglia interactions [12,21].

Brain Structure & Cognition: Cognitively normal individuals carrying ε4 allele experience brain microstructure changes, including decreased entorhinal neurite density and diffusion MRI changes [22].

Vascular/Redox and Ferroptosis Pathways: APOE4 increases neuronal vulnerability by affecting blood–brain barrier integrity, oxidative stress, lipid peroxidation, and ferroptosis [7].

APOE4's multifactorial roles have prompted therapeutic strategies beyond Aβ targeting approaches, including modulation of lipidation, correction of microglial lipid metabolism, mitigation of endoplasmic reticulum stress, and attenuation of inflammatory signaling [21]. However, measuring total APOE concentration in plasma or CSF is not enough as a diagnostic marker. The total concentration often does not reliably distinguish AD from non AD patients and does not always correlate with genotype or disease state [8,23]. However, isoform-specific quantification of APOE in CSF and plasma, combined with longitudinal monitoring of isoform ratios, may refine risk stratification and treatment response prediction [10,24]. In addition, personalized risk assessment increasingly integrates *APOE* genotype, sex, age, and metabolic context [10,13,21]. Notably, some anti-Aβ therapies exhibit differential efficacy or safety profiles in *APOE* ε4 carriers—for instance, higher incidence of amyloid-related imaging abnormalities in those with ε4 genotype [12,25]. Environmental and metabolic factors including metabolic stress, lipid dysregulation, and diet, are more influential on APOE4 toxicity. For example, astrocytes under stress produce more harmful lipid particles when expressing APOE4 [10].

Despite considerable progress, several key questions regarding APOE4's role in AD remain unresolved. First, the precise mechanisms by which APOE4 modulates tau propagation in humans require further clarification [26]. Second, it remains to be determined at which disease stages, and to what extent, altering APOE4 expression, lipidation status, or functional activity can actually reverse or slow pathology in human subjects [27]. Third, the relative contributions and therapeutic accessibility of peripheral versus central pools of APOE are not well understood—such as whether modulating brain-derived APOE or circulating APOE (or both) yields safer or more effective interventions. Finally, more detailed longitudinal human studies are needed, including tracking of APOE isoform ratios, markers of lipid metabolism, microglial function, and other

biomarkers, to distinguish causal drivers from downstream effects in the pathophysiology of AD [28].

Clinical Utility of *APOE* genotype testing

Although *APOE* genotyping was once primarily confined to research, it is increasingly applied to AD risk stratification, prognostic assessment, and therapeutic planning [13,16,25]. When combined with complementary tools, such as biomarkers, neuroimaging, and cognitive assessment, *APOE* genotyping enhances diagnostic accuracy. However, *APOE* genotyping has several limitations, including its incomplete predictive power - many ε4 carriers do not develop AD, while some non-carriers can still progress. Moreover, there are ethical concerns, such as potential discrimination and psychological stress, further complicate its use. Pharmacogenetic associations, e.g., response to statins or omega-3 fatty acids, remain inconsistent and lack clear clinical significance. Therefore, clinical implementation of *APOE* genotyping must carefully address ethical, interpretive, and logistical challenges, particularly in asymptomatic individuals.

Overall, *APOE* genotyping is most valuable for clinical trial stratification, biomarker-supported diagnostics, and individualized risk assessment, but it is not recommended as a standalone diagnostic test or for population-wide screening.

APOE-mimetic peptides: Mechanisms and therapeutic potential

There has been growing interest in therapeutic strategies that modulate APOE function. One promising approach involves APOE-mimetic peptides. In animal models of AD and acute CNS injury, APOE-mimetics have demonstrated efficacy in improving behavior, reducing amyloid and tau pathology, suppressing inflammation, and enhancing neuronal survival [15, 29,30].

APOE-mimetics are short peptides derived from functional motifs of the APOE protein, particularly receptor-binding and anti-inflammatory domains. Most APOE-mimetics mimic the receptor-binding domain of APOE protein (amino acids 141–149), facilitating interactions with members of the LDL receptor family. They also promote APOE lipidation via ABCA1 transporters, which enhances lipid trafficking and amyloid clearance in the brain. These peptides have been shown to shift amyloid precursor protein processing towards the non-amyloidogenic α-secretase pathway, thereby reducing Aβ production [31-34] (Table 1).

APOE-mimetic peptides show therapeutic promise in reducing Aβ and tau pathology, as well as improving cognition—evidenced by CS-6253 treatment in APOE3 mice, which increased APOE lipidation, lowered soluble and insoluble Aβ, reduced amyloid deposits, and improved memory when given before pathology onset. They have also been shown to attenuate neuroinflammation: in transgenic AD models, administration of APOE receptor-binding region peptides led to reduced inflammatory cytokines (e.g. IL-6), fewer plaque and tangle pathologies, and improved behavior. In dyslipidemia and metabolic disorder settings, the lipid-efflux-promoting action of mimetic peptides (via ABCA1 or similar pathways) yields antioxidant benefits and improved lipid handling in peripher-

Table 1. Key APOE-mimetic peptides: types, domains, and experimental findings

APOE-mimetic peptide	Feature	Key Experimental Findings
CS 6253 [31]	Small α-helical peptide derived from the C-terminal lipid-binding domain of *APOE* gene: it stabilizes ABCA1 and maintains its plasma membrane localization.	In APOE3-expressing transgenic mice, early treatment increased brain APOE levels, reduced Aβ pathology, and improved memory. Late treatment showed limited benefit.
Monomer, dimer, trimer of "LRKLRKRLL" motif [32]	Peptides containing a double or triple tandem repeat of the APOE receptor-binding region, LRKLRKRLL (residues 141–149): Binding effect increases with repeat units.	Reduced Aβ production and increased sAPP levels. Trimer peptides showed greater efficacy than monomers or dimers (trimer > dimer > monomer).
COG1410, COG112, COG133 [33]	Peptides derived from APOE receptor binding domain residues 130-150 of *APOE* gene; it bound to the SET protein which is a potent physiological inhibitor of PP2A	APOE and APOE-mimetic peptides antagonize SET, thereby enhancing endogenous PP2A phosphatase activity, which reduces levels of phosphorylated kinases, signaling, and inflammatory response. Improved cognition and reduced Aβ/tau pathology in mouse models.
Ac hE18A NH_2 and related [34]	Lipid-modulating and anti-inflammatory mimetics with modified amphipathic α-helical structures.	Lowered lipid hydroperoxide levels, reduced oxidative and inflammatory stress, promoted autophagy. Promising in models of diabetes and dyslipidemia.

ABCA1, ATP-binding cassette transporter A1; Aβ, amyloid-β; sAPP, surface amyloid precursor protein; PP2A, protein phosphatase 2A.

al and glial cells.

However, despite encouraging preclinical data, their translation to humans is still at an early stage. Human trials are lacking, and several critical issues remain unresolved: long-term safety, effective blood–brain barrier permeability, isoform-specific efficacy—especially for *APOE* ε4 carriers—and immunogenicity are not yet well characterized. Evidence also suggests that timing is crucial: the CS-6253 peptide was effective only when administered before or early in pathology in male mice that express APOE3, with little or no effect if administered later or in *APOE* ε4 animals [31].

In summary, APOE-mimetic peptides represent a novel therapeutic direction targeting lipid metabolism, amyloid/tau accumulation, and neuroinflammation in neurological and metabolic diseases. For clinical application, further investigation is required into their pharmacokinetics, isoform-specific activity, safety in humans, and optimal timing of treatment relative to disease stage.

SUMMARY

The *APOE* ε4 allele is consistently and strongly associated with increased risk of AD through multiple interconnected pathways. These include impaired Aβ clearance and enhanced aggregation, altered tau kinetics, dysregulated lipid metabolism, particularly in astrocytes and microglia, and heightened neuroinflammatory responses. Recent evidence further indicates that these effects are modulated by isoform concentration, age, sex, and environmental factors. Treatment strategies targeting these mechanisms show considerable promise, while biomarker-based studies are advancing clinical understanding of *APOE* status as a dynamic biological system rather than merely a static genetic risk factor.

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