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Chapter 5

Lipids and Lipoproteins in Alzheimer's Disease

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1. Introduction

Cholesterol is a key structural component of the brain, and cholesterol transport and distribution within the central nervous system (CNS) is mediated by a lipid metabolic cycle that includes generation of apolipoproteins as lipid carriers, lipidation by cholesterol and phospholipid transporters, enzyme remodeling of these particles and their receptor-mediated uptake and turnover in cells. It is becoming increasingly appreciated that Alzheimer's Disease (AD) patients often have comorbid conditions such as cardiovascular disease, type II diabetes mellitus, or hypertension, each of which can greatly affect lipoprotein metabolism, especially at the vessel wall and thereby possibly contribute to AD pathogenesis. Here we review the known biology of lipids and lipoproteins in the CNS and discuss how alterations in lipid metabolism may impact AD pathogenesis. Apolipoprotein E (*APOE*) is the best established genetic risk factor for AD and the major apolipoprotein expressed in the brain. In addition, genome-wide association studies (GWAS) have identified several other genes associated with AD risk that function in lipid or lipoprotein metabolism, including clusterin (*CLU*), ATP binding cassette (ABC) transporter A7 (*ABCA7*), and apoE receptors. Understanding how lipid/lipoprotein metabolism in the brain and body affect cognitive function may therefore offer new insights in developing more effective therapeutic approaches for dementia.

2. Lipid and lipoprotein metabolism in the CNS

2.1. General biology and function of lipids and lipoproteins in the CNS

The brain is the most cholesterol-rich organ in the body, with an average cholesterol content of 15-20 mg/g wet weight compared to 2 mg/g for peripheral tissues in the adult mouse [1].

The majority of the brain's sterol content is located in free cholesterol, 70-80% of which is in myelin. Cholesterol, sphingomyelin and phospholipids form the major structural components of cellular membranes, with cholesterol, phosphatidylcholine and phosphatidylethanolamine being the most abundant lipids in synaptic vesicles [2]. Many lipids also participate in important signaling pathways in the brain, with lipid-mediated second messengers derived from sphingomyelin and phosphatidylinositol, activation of G- protein coupled receptors and nuclear receptor activation being particularly important [1, 3].

Name	Major Sites of Production in the Brain	Main Functions in Healthy Brain	Potential Role in AD
ApoE	• Astrocytes • Microglia	• Lipid transport • Aβ homeostasis • BBB integrity • Cerebrovascular health • Innate immune response • Reelin signaling	• Involved in Aβ metabolism: deposition, transport across the BBB, clearance through ISF and the CSF pathways, and enzymatic degradation • Regulation of inflammation • ApoE4, the most established AD genetic risk factor, is associated with: 1. Impaired Aβ degradation and clearance 2. Increased tau phosphorylation and formation of NFT 3. Ineffective lipid transport 4. Impaired synaptic integrity 5. Reduced ability to suppress inflammation
Clusterin	• Astrocytes • Choroid plexus epithelial cells • Neurons	• Golgi chaperone • Inflammatory response • Complement regulation • Cell Cycle regulation • Reelin signaling	• Third most highly associated susceptibility locus for AD. • Potentially involved in Aβ sequestration, degradation and clearance
ApoA-I	• Not produced in the brain	• Reverse cholesterol transport • Vascular endothelial health	• AD comorbidities such as type II diabetes and hypercholesterolemia lead to apoA-I dysfunction • Reduction of CAA, neuroinflammation, and oxidative stress in mouse models of AD

Table 1. Major Apolipoproteins in the Brain

As lipids are insoluble in aqueous environments, neutral lipids are transported through bodily fluids on lipoprotein particles consisting of amphipathic apolipoproteins that surround and stabilize their lipid cargo. The general structure of mature spherical lipoproteins consists of a core of neutral cholesterol ester and triglycerides surrounded by amphipathic free cholesterol and phospholipids at the exposed surface, all of which are encapsulated by apolipoproteins

[3]. Four major lipoprotein classes, defined by their buoyant density, are found in the circulation: high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons. While LDL, VLDL and chylomicrons are triglyceride rich, HDL is triglyceride poor, and the HDL-like lipoprotein species found within the CNS contain even less triglyceride than plasma HDL. As apolipoprotein B (apoB), the major apolipoprotein of chylomicrons, VLDL, and LDL, is not found in the CNS, lipoprotein metabolism in the brain and cerebrospinal fluid (CSF) is based entirely on a lipoprotein class that most resembles plasma HDL with respect to size, shape, and density [4-11]. In rodents, astrocytes secrete apoE-containing lipoproteins that are primarily composed of phospholipids (~6 μg/ml) and cholesterol (~13 μg/ml), 0-18% of which is found in the esterified form. These nascent lipoprotein particles are discoidal, ranging from 9-17 nm in diameter with a density of 1.00-1.12 g/ml [7, 10]. Clusterin, also known as apolipoprotein J (apoJ), is also produced by astrocytes but is secreted virtually free of lipids [7, 10, 12]. Conversely, whereas lipoprotein particles found in CSF are of a similar diameter (11-20 nm) and density (1.063-1.12 g/ml) to those secreted by astrocytes, they are distinguished by their spherical shape and a greater proportion of phospholipids and cholesterol, with approximately 70% of cholesterol found as cholesterol esters [5, 7, 8, 10, 13]. ApoE and apolipoprotein A-I (apoA-I) are the major apolipoproteins present in CSF by mass, with apolipoproteins A-II, A-IV, D, CI, CIII, and clusterin also present to a lesser extent [5, 8-11]. In the healthy CNS, lipoproteins regulate the transport, delivery and distribution of lipids. In addition, lipoproteins are also thought to regulate many functions in the CNS including inflammation, oxidative stress, vascular tone, cerebral blood flow, and blood brain barrier (BBB) integrity (Table 1) [14].

2.2. Apolipoproteins present in the CNS

ApoE is present at 2-10 μg/ml in human and mouse CSF [8, 13, 15, 16] and at 10-50 ng/ml in interstitial fluid (ISF) from both wild-type mice as well as in targeted replacement mice that express human apoE [17]. ApoE is the most abundant apolipoprotein expressed within the brain, where it is synthesized and secreted by astrocytes and, to a lesser extent, microglia [5]. Secreted apoE particles are lipid-rich, containing equal amounts of apoE and lipid, and carry cholesterol secreted by astrocytes [10, 18]. Indeed, lipidation of apoE is essential for its stability and function [19-21]. Humans express three *APOE* isoforms that differ from one another by two amino acid residues; *APOE2* (cys112, cys158), *APOE3* (cys112, arg158) and *APOE4* (arg112, arg158), with the *APOE3* allele being the most common and the *APOE2* allele being the least frequent in the general population [19]. The resulting apoE2, apoE3 and apoE4 proteins therefore have both structural differences with respect to protein folding as well as functional interactions with respect to their ability to bind to lipids and apoE receptors [22]. In addition to mediating cholesterol transport to neurons, apoE has other functions in the brain such as regulating vascular health and the innate immune system (Table 1) [23].

Brain tissue has one of the highest concentrations of clusterin, which is expressed in astrocytes, epithelial cells of the choroid plexus, and selected neuronal subsets [24]. As a result, clusterin is present in CSF at concentrations of 4-6.5 μg/ml in healthy human adults [25]. In humans, due to the presence of three alternative mRNA start sites, the clusterin gene *CLU* is expressed

as three transcriptional isoforms. At the protein level, clusterin exists in two major forms: a 50 kDa nuclear form and a 75-80 kDa glycosylated secreted form [26]. Although clusterin is best known for its role as a chaperone, it also appears to be involved in the inflammatory response and complement regulation, the cell cycle, and endocrine functions (Table 1) [27].

Unlike apoE and clusterin, apoA-I is not expressed in either murine or human brain [28-31], suggesting that its presence in the CNS reflects transport across the BBB and/or the blood-CSF-barrier (BCSFB) following its production from hepatocytes and enterocytes. Although *in vitro* experiments suggest that apoA-I can transcytose across cultured endothelial cells [32], an *in vivo* study shows that peripherally injected apoA-I rapidly localizes to choroid plexus epithelial cells with negligible association in cerebrovascular endothelial cells, suggesting that peripherally derived apoA-I may gain access to the CNS primarily by crossing the BCSFB [31]. The concentration of apoA-I in CSF is ~3-4 μg/mL, or 0.26% of plasma levels, in humans [8, 13, 15, 33] and 0.02 μg/mL, or 0.01% of plasma levels, in wild-type mice [31]. The physiological functions of apoA-I in the CNS are not well understood but are hypothesized to be similar to those of CNS apoE (Table 1) [14].

In addition to apoE, clusterin, and apoA-I, other apolipoproteins are also detected in the CNS, including apoD, apoC-I, apoC-III, apoA-II, and apoA-IV [8, 9, 11], each of which is detected in human CSF [5, 8-11]. It has been shown that apoD, an apolipoprotein with antioxidant and anti-inflammatory properties, is produced in neuroglial cells, pia mater cells, and perivascular cells in the human brain [34, 35].

2.3. Cholesterol and Phospholipid Transporters

Lipid-poor apolipoproteins receive cholesterol and phospholipids from membrane bound transporters that are part of the ABC transporter family. The ubiquitously expressed transporter ABCA1 mediates the transfer of cellular cholesterol and phospholipids from cellular membranes to lipid-poor apolipoprotein acceptors including apoA-I and apoE [36- 39], a process that is essential for the production of both plasma and CSF HDL. HDL plays a critical role in the regulation of lipid homeostasis, and is particularly important for cells such as macrophages and microglia that form part of the innate immune system. ABCA1 activity in these phagocytic cells is exquisitely sensitive to cholesterol accumulation, and by catalyzing efflux of excess cholesterol and phospholipids to apoA-I and apoE acceptors, ABCA1 activity helps to maintain intracellular cholesterol balance. In humans, mutations that block ABCA1 function cause Tangier Disease, which is characterized by a 95% loss of plasma HDL cholesterol and apoA-I levels due to rapid catabolism of lipid-poor apoA-I by the kidney. ABCA1-dependent lipidation of CNS apoE is also critical for its stability as both total body and brain-specific loss of ABCA1 in mice leads to a significant 60-80% reduction of brain and CSF apoE [20, 21, 30]. Whether ABCA1 also regulates apoE levels in the brain of Tangier Disease patients is not known. Notably, Wahrle et al. did not observe significant differences in CSF apoE levels between control subjects versus those with ten different *ABCA1* single nucleotide polymorphisms (SNPs), suggesting that these SNPs may not have a significant effect on human ABCA1 function in the CNS [16]. In mice, total body deletion of ABCA1 results in a significant and proportional reduction of apoA-I levels by 60-90% in plasma, brain tissue and CSF [40].

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Intriguingly, brain-specific deletion of ABCA1 in mice leads to a significant increase of apoA-I protein levels in brain tissue and CSF [30]. The mechanisms that regulate the distribution of apoA-I between peripheral and CNS compartments remain to be fully determined.

Highly homologous to ABCA1, ABCA7 is also abundantly expressed in microglia, oligodendrocytes, neurons, and astrocytes in both humans [41] and mice [42, 43]. Although the potential for ABCA7 to act as a cholesterol and/or phospholipid transporter in the CNS is unknown, when overexpressed in human embryonic kidney cells, ABCA7 can mediate the transfer of phospholipids and sphingomyelin, but not cholesterol, to lipid-poor apoA-I and apoE [42]. The relative contribution of ABCA7 to the *in vivo* generation of plasma HDL cholesterol appears to be minimal and may be influenced by sex, as decreases in plasma total cholesterol and HDL cholesterol are only detected in female *Abca7*-/- mice [43]. Instead, ABCA7 may be more involved is modulating the phagocytic activity of macrophages, particularly following injury or infection; whether this is also true in brain microglia will be important to address in the future [44, 45]. One critical difference between ABCA1 and ABCA7 is the distinct manner in which they are regulated by cholesterol. Whereas ABCA1 expression is induced by activation of the Liver-X-Receptor (LXR) pathway in response to increased cellular cholesterol content, ABCA7 induction is unaffected [42, 43]. Instead, ABCA7 expression is primarily regulated by sterol regulatory element binding protein 2 (SREBP-2) and is thus repressed in cholesterol-laden cells [44].

Following initial lipidation, nascent HDL lipoproteins can receive additional lipids from the cholesterol transporters ABCG1 and ABCG4 [46], which are abundantly expressed in grey and white matter of the brain [47]. Unlike ABCG4, whose expression appears to be restricted to neurons, astrocytes, and the retina, ABCG1 is widely expressed throughout the body and is found in the liver, intestine, lungs, kidney and spleen in addition to neurons, astrocytes, microglia, and choroid plexus epithelial cells [47, 48]. In addition to lipid efflux activity, ABCG1 and ABCG4 are also believed to regulate intracellular transport of cholesterol and sterols and vesicle trafficking in the brain [47, 48].

2.4. Enzymes involved in lipoprotein metabolism

Many enzymes involved in lipoprotein metabolism are found in CSF, although for most, their CNS expression patterns and functional roles have not been explored to the same extent as in the periphery. For example, lecithin cholesterol acyltransferase (LCAT), phospholipid transfer protein (PLTP), and cholesteryl ester transfer protein (CETP) are all detectable in brain tissue and CSF [13, 49-53] and, as they have established roles in plasma lipoprotein metabolism, it is of interest to understand whether they function similarly in the brain.

In plasma, LCAT is the enzyme responsible for generating the cholesterol ester core characteristic of mature circulating lipoproteins, including HDL. As the more hydrophobic cholesterol esters migrate to the core of the lipoprotein particle, the discoidal nascent particle takes on its mature spherical shape. LCAT-mediated esterification of cholesterol serves not only to generate mature HDL particles, but also to maintain the downward cholesterol gradient between the cell and the lipoprotein particle, enabling further cholesterol efflux [54]. LCAT is present in human CSF at levels corresponding to 2.2-2.5% of that in serum and migrates with

γ-like lipoproteins [13, 49]. In mice, LCAT is secreted mainly by astrocytes, can be activated by both apoA-I and apoE, and esterifies free cholesterol contained on glial-derived apoE-containing lipoproteins [55]. LCAT may therefore play a role in maturation of discoidal lipoprotein particles secreted from glia to the spherical particles that circulate in CSF by catalyzing the cholesterol esterification of immature CNS lipoprotein particles [5, 7, 56].

PLTP is another enzyme intimately involved in the maturation and turnover of lipoprotein particles within the circulation and CNS. PLTP's primary activity involves the transfer of phospholipids between HDL particles, thus modulating HDL size and composition, and transferring lipids between apoB-containing lipoproprotein particles and HDL [53]. Within the CNS, PLTP is highly expressed by neurons, astrocytes, microglia, oligodendrocytes, BBB endothelial cells, choroid plexus ependymal cells and can be found both in brain tissue and CSF in human and animals [57-61]. Within CSF, PLTP is associated with apoE-containing lipoproteins where it actively participates in phospholipid transport [13, 62, 63] with activity corresponding to 15% of plasma levels in humans [62] and 23% of plasma levels in rabbits [59]. Functionally, PLTP has been reported to regulate apoE expression and secretion by astrocytes [63] and participate in neuronal cell signalling [64].

In plasma, CETP catalyses the bi-directional transfer of cholesterol esters from HDL in exchange for triglycerides from VLDL and LDL, thereby reducing circulating HDL concentration and increasing its size [65]. CETP can potentially diffuse through the BCSFB and enter the brain from plasma. However, it is not clear whether CETP is produced in the brain. Yamada et al. reported CETP-like immunoreactivity in astrocytes in healthy human brain [51]. Albers et al. have suggested that CETP is locally produced in the brain, as they were able to detect CETP in human CSF samples at concentrations higher than what would be expected from simple diffusion of proteins across the BCSFB [66]. However, Demeester et al. were unable to detect CETP in human CSF and CETP mRNA in the human brain [13]. A few other studies have also not detected CETP mRNA in the CNS of rabbits and cynomolgus monkeys [59, 67]. Undoubtedly, more research on the production and the role of CETP in the CNS of healthy individuals is needed.

2.5. Receptors involved in lipoprotein uptake and turnover

Lipoprotein uptake and delivery of lipids into target cells of the CNS is regulated by the low density lipoprotein receptor (LDLR) family [68]. The four major apoE receptors in the CNS are LDLR, lipoprotein receptor related protein-1 (LRP1), very low density lipoprotein receptor (VLDLR), and apolipoprotein E receptor 2 (apoER2) [69]. Of these, LDLR is the only receptor that has apoE as its only known ligand in the CNS [69]. LDLR and LRP1 levels are inversely correlated with brain apoE levels as deletion or overexpression of these receptors in mice increases or decreases brain apoE levels, respectively [70-73]. VLDLR and apoER2 also serve as essential receptors for the neuromodulatory ligand Reelin, which is involved in long term potentiation, learning and memory [74-76]. Like apoE, clusterin can also bind to VLDLR and apoER2 to regulate Reelin signaling (Table 1) [77]. LDLR, LRP1, VLDLR and apoER2 are all expressed on neurons, which have a high LRP1:LDLR ratio. LRP1 and LDLR are also found on astrocytes, which have a low LRP1:LDLR ratio, and LRP1 and VLDLR are found on

microglia [78-81]. Solubilized forms of these receptors, generated via ectodomain shedding or splice variants lacking the transmembrane domain, possibly contribute to negative feedback and inhibition of lipoprotein uptake [82]. Of note, the lipoprotein related protein 2 (LRP2), also known as megalin, and the neuronal sortilin- related receptor (SORL1 receptor) are also additional apoE receptors expressed in the CNS [83, 84].

3. Alterations to lipids and lipoproteins in Alzheimer's disease

The neuropathology of AD is defined by the presence of amyloid plaques and neurofibrillary tangles (NTFs), which are composed of deposited amyloid-beta (Aβ) peptides and filamentous hyperphosphorylated tau, respectively [85]. In addition to parenchymal amyloid plaques, most AD patients also have accumulation of amyloid in cerebral blood vessels, known as cerebral amyloid angiopathy (CAA) [14, 86]. Furthermore, neuronal degeneration and dysfunction, the brains of AD patients are often marked by significant signs of chronic inflammation, oxidative stress and vascular dysfunction. Not surprisingly, apolipoproteins, the lipids they carry, and the transporters responsible for their lipidation may be intimately involved in each step of the disease. In particular, the interrelationship between cerebrovascular dysfunction and AD is increasingly appreciated. Epidemiological, clinical, neuropathological and pathophysiological evidence shows that several cardiovascular risk factors also increase AD risk, including age, sex, hypertension, dyslipidemia, and type II diabetes [87-90]. Dementia progresses more rapidly in patients with cerebral infarcts [90- 93] and infarction and other forms of brain injury may potentiate AD pathophysiology [94- 96]. Importantly, many of these cardiovascular risk factors include aspects of dysfunctional lipid and lipoprotein metabolism, which likely occurs at the vessel wall. However, compared to the wealth of knowledge about lipid and lipoprotein physiology in large peripheral vessels, little is known about the mechanisms by which vascular risk factors for AD may impair the function of cerebral vessels. Importantly, BBB dysfunction may contribute to inflammatory processes in the CNS, where exacerbated inflammatory responses or failure to resolve inflammatory reactions are increasingly recognized to play important roles in AD pathogenesis [97].

3.1. Changes in brain lipid composition and their direct effects in AD

One often overlooked neuropathological observation initially reported by Alois Alzheimer is the presence of adipose inclusions in the brain, which Alzheimer defined as "extraordinarily strong accumulation of lipoid material in the ganglion cells, glia and vascular wall cells, and the particularly numerous fibril-forming glia cells in the cortex and, indeed, in the entire central nervous system" [98]. Almost all major classes of lipids have some correlation with AD pathogenesis [99]. A recent review by Kosicek and Hecimovic reported that the *post-mortem* brain levels of phosphatidylinositol, phosphatidylethanolamine, ethanolamine plasmalogen, and sulfatide are decreased in AD, while the levels of ceramide are increased [100]. Though not as extensively studied, it has been reported that CSF levels of ceramide are increased, while the levels of sulfatide are decreased in AD [101, 102]. Furthermore, studies by Soderberg et al. and Tully et al. report lower levels of n-3 and n-6 polyunsaturated fatty acids, which are major

components of phospholipids, in AD brain compared to healthy controls [103, 104]. Changes to the levels of these lipid classes affects not only the structural properties of the membranes, but also numerous signaling and trafficking pathways that are heavily involved in the normal functioning of the cells in the CNS [99, 105].

Changes to CNS lipid composition can also influence the production of Aβ peptides. As the generation of these peptides involves several lipid-associated steps, including intracellular trafficking and inter-membrane proteolytic cleavage, it is not surprising that, in addition to genetic changes that alter Aβ production, there are also indirect, lipid- dependent changes that can affect production of Aβ. Aβ peptides are derived via sequential proteolytic processing of the amyloid precursor protein (APP) by β-secretase and γ- secretase. This leads to liberation of Aβ peptides 38-46 amino acids in length into the extracellular space [106-108]. Of these, Aβ40 and Aβ42 are quantitatively the most important for amyloid deposition [109]. In healthy brains, the vast majority of APP is processed by *α*-secretase, followed by γ-secretase cleavage, which prevents toxic Aβ peptide generation [110]. All of the enzymes involved in APP processing are transmembrane proteins, raising the hypothesis that the lipid composition and lipid organization in the membrane may affect Aβ production [111]. Numerous *in vitro* studies have focused on determining the role of specific lipid classes in APP processing. For example, it has been shown that reducing membrane cholesterol lowers the levels and activity of β-secretase and reduces γ- secretase activity, decreasing Aβ production [99, 112]. Altered cholesterol content in lipid rafts, regions in the cellular membrane enriched with cholesterol and sphingolipids, affects the localization of enzymes involved in Aβ production, which can lead to changes in amyloidogenic APP processing [99]. Moreover, sphingolipids have been reported to regulate γ-secretase activity [99, 113, 114]. Interestingly, expression of familial presenilin (PS) mutations, which are mutations in components of the γ-secretase complex, affects sphingolipid metabolism, suggesting an interplay of genetics and lipid metabolism in the context of APP processing. Furthermore, *in vitro* elevation of ceramide, which is composed of sphingosine and fatty acids, increases β-secretase stability and promotes Aβ biogenesis [115].

The production of Aβ peptides is not unique to AD pathology, but a constitutive process that is a product of normal cell metabolism throughout life, confirmed by its secretion from primary cells in culture and its presence in the plasma and CSF of healthy individuals [108, 116, 117]. Therefore, it is possible that disrupted Aβ homeostasis, either via increased production or impaired degradation and clearance, leads to its net accumulation in the brain, triggering subsequent neurotoxicity. Aβ production is clearly enhanced in cases of familial early onset AD (<60 years of age), which account for 2-3% of the AD population [118]. In contrast to familial early-onset AD cases, the vast majority of AD subjects who develop cognitive impairment in late life have no genetically-determined net increase in Aβ production. For these late-onset AD patients, who account for up to 99% of the AD population [119], aging, environmental factors, or other genetic-related impairments in Aβ degradation and clearance are thought to lead to the net accumulation of Aβ within the CNS [120-122].

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3.2. Apolipoproteins and AD pathogenesis

Of the apolipoproteins present in the CNS, *APOE* has the most established genetic association with AD, influencing the risk, progression, and pathology of the disease (Table 1). The *APOE4* allele is a robust risk factor for late-onset AD and is found in 40-60% of AD subjects depending on ethnicity (the prevalence is lower in Asian compared to Northern European populations) even though its carrier frequency in the human population is approximately 15-20% [123-125]. *APOE4* increases AD risk by 3-fold when inherited in a single copy and greater than 9-fold in homozygous individuals. *APOE4* also accelerates the age of onset of AD [123, 126, 127]. A wealth of pre-clinical and clinical evidence has demonstrated that *APOE4* is associated with earlier and more extensive Aβ and amyloid deposition, which is currently believed to result from a net impairment of Aβ degradation and clearance from the CNS [120, 128]. ApoE affects Aβ metabolism through multiple mechanisms, including transport of Aβ across the BBB, modulation of interstitial fluid (ISF) and CSF clearance pathways, effects on BBB integrity, and modulating the growth of Aβ oligomers and fibrils [129, 130]. Some studies suggest that the risk and severity of CAA is also increased in *APOE4* carriers [131, 132]. Intriguingly, a patient with an ablative mutation in *APOE* was recently described to have no detectable impairment in cognitive, neurological and retinal function, with normal levels of CSF Aβ and tau despite very high plasma cholesterol levels [133], suggesting that apoE may have non-essential functions in the human brain and eye. This observation reflects the prediction made from *Apoe*-deficient mice, which also have greatly increased plasma cholesterol levels and exhibit greatly reduced Aβ retention in the CNS [134-137].

In addition to modulating Aβ, apoE may also be involved in tau phosphorylation. In neurons, hyperphosphorylation of the microtubule-associated protein tau by kinases, including GSK-3β and CDK5, causes the dissociation and aggregation of tau to ultimately form neurofibrillary tangles [138]. Under conditions of stress or injury, neurons have been reported to synthesize and process apoE4 to produce neurotoxic C-terminal fragments. Release of these fragments into the neuronal cytosol has been reported to enhance tau phosphorylation and formation of NFT-like structures [139, 140].

ApoE4 has additional deleterious consequences. Compared to apoE3, apoE4 is less effective at mediating cholesterol transport in the brain; human knock-in *APOE4* homozygous mice show reduced total cholesterol and phospholipids compared to wild type mice [81, 141]. The *APOE4* allele has also been implicated in impaired synaptic integrity, as human *APOE4* transgenic mice show lower levels of excitatory synaptic activity that declines to levels comparable to *Apoe* knockout mice by 7 months of age [142]. ApoE4 has also been reported to reduce apoER2 expression at the neuronal surface, impairing the ability of Reelin to enhance synaptic glutamate receptor activity [143].

ApoE plays an integral role in inflammatory processes in the brain. Inflammation of the brain's glial supporting cells, known as neuroinflammation, is a prominent feature AD [144] and contributes to neuronal damage. In response to Aβ or lipopolysaccharide (LPS), LRP1-mediated glial cell activation increases apoE, which can limit the inflammatory response by signaling though LDL receptors to suppress c-Jun N-terminal kinase signaling [145, 146]. There is also evidence that isoform-specific apoE modulation of the innate immune response can

modulate Aβ deposition [147]. Consistent with apoE having an anti- inflammatory role, *Apoe*-deficient mice have elevated proinflammatory cytokines in the liver [148]. Importantly, isoform specific effects appear to determine the extent of cytokine induction and may also modulate progression and resolution of CNS inflammation. In mice, apoE4 has reduced ability to suppress the inflammatory response induced by LPS treatment [149] and in the EFAD model (5 familial AD mutations in the presence of human *APOE*), microglial activation in response to Aβ is augmented by the *APOE4* genotype [150]. Indeed, *Apoe*-deficient mice show a similar activation of the inflammatory response to human *APOE4* knock-in mice following LPS injection, implying that apoE4 may lack the anti- inflammatory functions of the other apoE isoforms [151]. Consistent with these findings, non- steroidal anti-inflammatory drugs are associated with a reduced risk of AD only in participants with an *APOE4* allele [152].

According to the AlzGene database, *CLU* is the third most highly associated susceptibility locus for AD following *APOE* and bridging integrator 1 (*BINI*) (www.alzgene.org). In 2009, two independent GWAS studies identified the C allele of the rs11136000 SNP in the *CLU* gene, which occurs in 88% of Caucasians, to confer a modest risk of AD development (odds ratio (OR) 1.16), whereas inheritance of the T allele is protective (OR 0.86) in Caucasians [153, 154]. Although these findings have been replicated in, and confirmed for, Caucasians of European ancestry, the association of *CLU* polymorphisms and AD risk has not been replicated in African-American, Hispanic, or Arab populations [27, 155]. Since this discovery, estensive work has been conducted in an attempt to delineate the mechanism(s) by which the rs11136000 SNP confers AD risk. Inheritance of the TT versus TC versus CC allele appears to result in either no change [156, 157] or a very subtle 8% decrease [158] of plasma clusterin levels in AD and mild cognitive impairment (MCI) patients, with small 10-17% decreases of plasma clusterin observed in cognitively normal aged-matched controls with the TT allele [156, 158]. Despite minimal effects on circulating clusterin levels with the T allele, inheritance of the C allele of the rs11136000 SNP is associated with both structural and functional changes in the CNS. In young (aged 20-30 years) cognitively normal adults, each copy of the C allele of the rs11136000 SNP is associated with lower white matter integrity [159], decreased coupling and connectivity between the hippocampus and prefrontal cortex during memory processing tasks [160], and neural hyperactivity under emotional working paradigms [161], indicative of early structural and functional abnormalities that may leave the brain more vulnerable to disease during aging. In the elderly, independent of dementia status, the CC allele is significantly associated with longitudinal increases in ventricular volume over a 2 year period [162], and increased resting regional cerebral blood flow in the hippocampus and right anterior cingulate cortex, regions which are important for memory function and default mode network activity, over an 8-year period [163]. Further, the protective T allele is associated with a reduced rate of conversion from MCI to AD (OR 0.25) [164], while the detrimental C allele is correlated with a significantly faster rate of decline in verbal but not visual memory performance in MCI and AD patients [163]. Lastly, with respect to CSF biomarkers, the *CLU* C allele is associated with significantly lower CSF Aβ42 in a Finnish [165] but not American cohort [166], with no association found for either total or phosphorylated tau.

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Although the specific mechanisms by which an individual SNP in *CLU* may confer disease risk are not well understood, there are well recognized global changes to clusterin mRNA and protein expression both in the plasma and CNS that are associated with AD pathology and clinical presentation [27]. In non-demented elderly controls and patients with subjective memory complaints, CSF clusterin is positively associated with CSF total and phosphorylated tau [167] and an elevated atrophy rate in the entorhinal cortex of older non- demented adults with low CSF Aβ42 [168]. Whereas older studies did not detect significant differences in CSF clusterin between cognitively normal aged matched controls and AD subjects [25, 169], newer studies that utilize higher sensitivity methods have reported up to a 25% increase of CSF clusterin in AD subjects [170, 171], suggesting that increased CNS clusterin may be detrimental. Within brain tissue, clusterin mRNA is increased after correcting for neuronal loss [172, 173], whereas protein levels are reportedly increased by 40-180% depending on the brain region [172, 174-177]. Within the AD brain, clusterin strongly co-stains with dystrophic neurites, neuropil threads, and intracellular NFT [176, 178, 179], with minimal to moderate co-localization observed with mature amyloid plaques [176, 178, 180, 181] and cerebrovascular amyloid [180]. Unlike the CNS, multiple studies have detected no difference between plasma clusterin levels in non-demented controls, MCI, and AD subjects [157, 182-185]. However, increased baseline plasma clusterin levels are suggestive of increased prevalence and severity of AD pathology and presentation, including brain atrophy, amyloid deposition and worsened cognitive function, with a more rapid clinical progression [186-188].

A mechanistic involvement of clusterin in AD pathology is also supported by *in vivo* preclinical studies (Table 1) [27]. Clusterin appears to be directly involved in neuronal health and Aβ metabolism via a variety of mechanisms. In transgenic AD mice, genetic ablation of clusterin results in a reduction of mature fibrillar amyloid deposits and the dystrophic neurites that are associated with them [189]. Supporting this, a recent study found that co- incubation of Aβ with clusterin leads to a 60% decrease in oligomeric and 42% decrease in fibrillar Aβ binding and uptake by primary microglia, and a 72% reduction in binding and uptake of oligomeric Aβ by primary astrocytes, suggesting that clusterin can impede Aβ degradation by local glia [190]. *In vitr*o and *in vivo*, clusterin may also mediate Aβ toxicity and tau phosphorylation via dickkopf-1-driven induction of the Wnt-PCP-JNK pathway [191]. In contrast, other studies have found a beneficial role of clusterin in facilitating Aβ clearance across the BBB via LRP-2 [192] and binding to and sequestering Aβ oligomers, thereby reducing their potential toxicity [193]. Clusterin also participates in various aspects of cell signaling. *In vitro*, clusterin signals via Reelin by binding to apoER2 and VLDLR thereby increasing cell proliferation and neuroblast chain formation in the subventricular zone [77]. Clearly, more research is necessary to fully understand the pathways by which clusterin is involved in brain function and the pathogenesis of AD.

Although apoA-I is relatively abundant in CSF and brain tissue, the physiological roles of apoA-I containing lipoprotein particles in the CNS, their potential influence on AD risk and pathology, and whether they affect AD pathogenesis through actions from one or both sides of the BBB remains unknown [14]. The most established data regarding apoA-I and AD are human epidemiological studies examining the interaction between serum apoA-I and HDL-

cholesterol levels with AD risk (Table 1). At mid-life, high serum apoA-I levels resulted in a significantly lower risk (hazard ratio (HR) 0.25) of dementia later in life, [194] while high levels of serum HDL cholesterol (> 55 mg/dL) in cognitively normal elderly was associated with a significantly reduced risk (HR 0.4) of AD even after adjusting for *APOE* genotype and vascular risk factors such as heart disease, diabetes, obesity, hypertension, and lipid lowering treatment [195]. Recently, Reed et al. demonstrated that low plasma HDL cholesterol and apoA-I were associated with and predicted higher amyloid Pittsburgh compound B binding independent of *APOE4* in cognitively normal and MCI elderly subjects [196]. There also appears to be a consistent 20-30% reduction in serum apoA-I in late-onset AD subjects compared to age-matched controls [197-199], with levels of serum apoA-I positively correlating to cognitive function [199, 200]. Further, in symptomatic AD patients, plasma apoA-I levels are negatively correlated with measures of brain atrophy, including hippocampal and whole brain volume and mean entorhinal thickness [186]. Alterations to CSF apoA-I are less clear, potentially due to the small number of studies or sample size, whereas two studies reported a decrease of CSF apoA-I in AD subjects [15, 201], two other studies reported no change [13, 202]. Prospective studies designed and powered to assess the levels, and perhaps more importantly, the function of both plasma and CSF apoA-I-HDL with respect to AD onset and progression are needed to determine if apoA-I-HDL potentially contributes to AD pathology.

Although questions remain about the importance of apoA-I to AD in humans, studies in preclinical AD mouse models support a role for apoA-I in removing amyloid selectively from the cerebral vasculature, leading to reduced neuroinflammation and maintenance of cognitive function (Table 1). Specifically, genetic loss of *Apoa1* is associated with increased CAA, greater inflammation, and exacerbated cognitive impairment, whereas transgenic overexpression of human *APOA1* from its endogenous promoter (driving expression from only hepatocytes and enterocytes) prevented AD-related cognitive decline and reduced both CAA and glial activation in symptomatic APP/PS1 mice [203, 204]. Given the known roles of apoA-I-containing HDL in regulating vascular endothelial health, reducing inflammation and oxidative stress, coupled with the relative contributions of these pathologies to AD, it will be paramount to fully elucidate the function of apoA-I in the CNS and evaluate its therapeutic potential [14].

Although the roles of other CNS apolipoproteins in AD pathogenesis are not as extensively studied, apoD, apoC-I, apoA-IV, and apoC-III may play a role. The most significant change due to aging is observed in gene expression levels of *APOD* [205]; CSF and hippocampal apoD are elevated in AD [206] and correlated with disease severity [207]. ApoC-I colocalizes with Aβ plaques in human AD brain [208] and apoC-I has been suggested to influence neuroinflammation in AD [209]. The *APOC1* gene is also considered as an AD susceptibility locus, as the H2 polymorphism of *APOCI* is in linkage disequilibrium with *APOE4* [209-211]. Furthermore, heterozygosity of the *APOA4* (360:His) allele is more common in AD patients [212]. In APP transgenic mice, *Apoa4* deficiency increases Aβ load, enhances neuronal loss, accelerates cognitive dysfunction and increases mortality [213]. Lastly, apoC-III has recently been reported to be associated with Aβ levels in the periphery and is of possible interest for use as an early biomarker for AD [214].

3.3. Cholesterol and phospholipid transporters in AD

There is a growing body of pre-clinical and clinical evidence that supports the involvement of ABCA1, and recently ABCA7, in the pathogenesis of AD [215]. In mice, ABCA1-mediated lipidation of apoE correlates with a net increase in Aβ clearance [216]. For example, total body deficiency of *Abca1* markedly decreases soluble apoE and increases amyloid plaque-associated insoluble apoE, decreases plasma and CSF apoA-I, and increases Aβ deposits in both parenchymal and vascular compartments, with no net change in APP production or processing [217-220]. Recently, Fitz et al. demonstrated that haploinsufficiency of *Abca1* significantly exacerbated cognitive deficits, increased Aβ and amyloid deposits, and reduced Aβ clearance in ISF of *APOE4* but not *APOE3* APP/PS1 *Abca1*-/+ mice, suggesting a particularly deleterious state of poorly-lipidated apoE4 compared to apoE3 [221]. Of interest, the presence of apoE4 with *Abca1* hemizygosity leads to a modest but statistically significant decrease in CNS apoE (~10%), decreased CNS and plasma apoA-I by approximately 50 and 20%, respectively, and decreased plasma Aβ42 and HDL cholesterol, with a strong inverse correlation between plasma HDL cholesterol levels and amyloid burden [221]. Both genetic and pharmacological approaches that increase brain ABCA1 activity also increase functional CNS apoE [40, 222] and improve learning and memory with [222-227] or without [228-232] changes in Aβ and/or amyloid burden. Importantly, ABCA1 was required to observe an improvement in cognitive function in APP/PS1 mice treated with the LXR agonist GW3965, suggesting that ABCA1 lipidation of lipid-poor apolipoproteins is essential for cognitive function [229]. It is important to note, however, that these manipulations will affect ABCA1-mediated lipidation of apoE in the brain as well as ABCA1-mediated lipidation of apoA-I in the periphery and potentially the CNS, of which the relative contributions are unknown.

The association of *ABCA1* genetic variants and AD risk in human subjects is not as clear despite more than a dozen studies [216]. In 2013, a meta-analysis was conducted on 13 independent studies totaling 6034 controls and 6214 AD patients that examined whether the *ABCA1* variants R219K rs2230806, I883M rs4149313 and R1587K rs2230808 were associated with AD risk. No significant association was found even after adjusting by ethnicity and sample size [233]. This is consistent with *ABCA1* failing to appear in GWAS [216]. It is important to note, however, that most of the *ABCA1* gene variants in heterozygous patients translate to a relatively small reduction in plasma HDL cholesterol that may or may not increase the relative risk of ischemic heart disease [234, 235], raising the caveat that these variants may not be severe enough to impact brain physiology. As Tangier Disease, in which patients completely lack functional ABCA1, is extremely rare and most patients die before 70 years of age, it is not known whether human ABCA1 deficiency is associated with neuropathological changes relevant to AD [236].

In contrast to ABCA1, numerous independent GWAS have identified associations between multiple *ABCA7* SNPs and AD risk [237-244]. ABCA7 expression has been reported to be increased in the brains of AD subjects, with the magnitude of the increase correlating with greater cognitive decline [239, 241]. In 2011, the first two major SNPs of *ABCA7*, rs2764650 [244] and rs3752246 [237], were associated with increased risk of late-onset AD. Two subsequent GWAS found that the rs2764650 SNP was significantly associated with increased neuritic plaque burden [242, 243]. However, both Larch et al. and Vas-

quez et al. found that the minor allele of the rs2764650 SNP conferred protection from AD by delaying onset and decreasing disease duration, despite increased ABCA7 expression, whereas another study found that rs2764650 neither altered ABCA7 expression or AD risk [238]. In African Americans, the *ABCA7* rs115550680 SNP was shown to increase AD risk by 1.79 even after adjusting for *APOE* genotype, which itself conferred a relative risk of 2.31 [240]. With more *ABCA7* SNPs identified by GWAS to confer AD risk [238], it will be increasingly important to identify the functional consequences of *ABCA7* polymorphisms. In transgenic APP mice, total body loss of *Abca7* increases hippocampal Aβ and amyloid burden with no changes in APP processing or brain levels of ABCA1, apoE, LDLR, or markers of neurodegeneration or synaptic loss [245]. However, increased Aβ and amyloid did not significantly impair any measure of cognitive function, including spatial memory, object recognition, short-term recognition, or fear conditioning [245]. Intriguingly, bone marrow derived macrophages obtained from *Abca7*-/- mice displayed a 50% reduction in Aβ uptake compared to wild type controls, suggesting that phagocytosis may be compromised; however, there were no change to either the number or distribution of microglia or macrophages within the brain parenchyma in AD *Abca7*-/- mice [245].

Despite high expression in the brain, ABCG1 does not appear to have a marked role in AD pathogenesis, as ABCG1 overexpression in AD mice does not significantly change Aβ or amyloid burden [246]. Although a recent GWAS study reported that *ABCG1* SNPs were correlated with neuritic plaque burden in AD subjects [243], the relative risk of *ABCG1* variants has yet to be confirmed.

3.4. LCAT, PLTP and CETP in AD

Although better characterized with respect to their involvement in atherosclerosis, research is emerging regarding the potential role of the lipoprotein modifying enzymes LCAT, PLTP and CETP in AD [53, 65, 247]. One early study in a small group of symptomatic AD patients suggested that CSF LCAT activity was reduced by 50% compared to cognitively normal age-matched controls [13], raising the possibility that aging may influence LCAT activity or LCAT activity may influence AD pathogenesis. Stukas et al. recently tested this hypothesis in mice and found that the abundance and activity of LCAT in liver, cortex and plasma is unaltered by aging or the presence of amyloid deposits [14]. Furthermore, total loss of *Lcat* does not impact apoE levels or lipidation, or Aβ or amyloid metabolism in symptomatic APP/PS1 mice, despite a 70-90% decrease in circulating and CNS levels of apoA-I [14]. These results suggest that CNS lipoproteins need not be in a mature spherical form containing cholesterol esters to participate normally in Aβ metabolism.

PLTP may also be involved in the pathogenesis of AD. Intriguingly, whereas PLTP synthesis by neurons and glia is increased in the early stages of AD [62], its levels, and more importantly, its activity are reduced in brain tissue and CSF of AD patients in later stages [57, 63]. In mice, deletion of *Pltp* increases cerebral oxidative stress, elevates Aβ42, reduces synaptophysin expression, increases BBB permeability and decreases expression of tight junction proteins under basal conditions [61, 248]. Further, intracerebroventricular injection of an oligomeric Aβ peptide leads to exacerbated cognitive impairment in *Pltp*-/- mice compared to wild-type

controls [248]. In aged *Pltp*-/- mice, enhanced cognitive impairment is accompanied by increased cortical Aβ42, APP expression, and both β- and γ-secretase activity with decreases in cortical Aβ40 and apoE [249]. These preclinical studies suggest a role for PLTP not only in phospholipid transport, but Aβ homeostasis, neuronal function, barrier integrity, and oxidative stress.

Another enzyme that plays a central role in lipid homeostasis that can potentially affect dementia outcome is CETP. As reduced CETP activity in humans is associated with reduced cardiovascular disease risk, the functions of CETP in atherosclerosis and the potential of CETP inhibitors for cardiovascular disease have been of intense interest [65]. The *CETP* 405V allele, which results in low plasma CETP levels in *CETP* 405V homozygotes [250], is associated with longevity. However, the direction and the magnitude of this effect is not clear as some studies have found a positive association, some a negative association, and some no association with longevity [251-256]. It has also been shown that in young adults, this allele is associated with higher fractional anisotropy, a measure of myelination in brain's white matter [257]. In older subjects, however, this effect is reversed [257]. Furthermore, genetic studies have proposed a relationship between C629A, I405V, and D442G *CETP* polymorphisms and AD risk. Intriguingly, the effects that are exerted by these polymorphisms may be dependent on the presence of the *APOE4* allele. Rodriguez et al. reported that in *APOE4* carriers, the AA genotype of the C629A *CETP* polymorphism is associated with lower AD risk [258]. It has also been shown that in the Northern Han Chinese population, there is an association between the G allele of the D442G *CETP* polymorphism and lower AD risk, an effect that was abolished in the absence of *APOE4* [259]. Additionally, Murphy et al. reported that in *APOE4* non-carriers, the I allele of the I405V polymorphism is protective, whereas the V allele is associated with higher AD risk [260]. Interestingly, these associations are reversed in *APOE4* carriers [260]. These results are replicated by the Rotterdam study [250]. However, the Einstein Aging Study reported an association between the VV genotype and slower memory decline and AD risk, and a recent meta-analysis by Li et al. reported no association between AD and the 1405V *CETP* polymorphism [253, 261]. Clearly, more research is required to elucidate the specific role of CETP in the brain and its contribution to AD.

3.5. ApoE receptors

APP endocytosis is regulated by several members of the lipoprotein receptor family leading to increased or reduced Aβ generation [74]. These receptors are also critical for Aβ clearance. LRP1 can bind Aβ directly or bind apoE-associated Aβ to internalize and transport soluble Aβ across the BBB to plasma for eventual degradation, or mediate degradation within cell lysosomes [262-266]. *APOE* genotype impacts clearance of Aβ-apoE complexes with Aβ-apoE4 having the slowest net clearance rate [267]. Findings in knockout mice imply LDLR may also enhance Aβ clearance [268, 269]. Other apolipoproteins such as clusterin may play a role in mediating Aβ degradation and clearance though the LDLR family of receptors [83]. In addition to Aβ removal, apoE receptors also regulate tau phosphorylation. Reelin signaling through apoER2 and VLDLR inhibits the activity of GSK- 3β and blockade of this pathway increases hyperphosphorylated tau in the brain [270, 271]. Although apoE receptors are clearly impli-

cated in AD pathogenesis by a number of mechanisms, genetic evidence for their role is not robust, despite mutations in *LDLR* being highly associated with hypercholesterolemia in humans [272]. For example, a polymorphism in exon 3 of the *LRP1* gene (rs1799986) has been weakly correlated with increased risk of AD, although subjects with both this *LRP1* allele and a tau polymorphism (*MAPT*, intron 9, rs2471738) have 6.2-fold higher risk of developing AD than those without this genotype [273-275]. A polymorphism in *LRP2* (rs3755166) has also been reported to be associated with AD [276, 277]. By contrast, the neuronal sortilin-related receptor (*SORL1*, also known as *LR11)* is an apoE receptor that has been shown to be significantly associated with AD risk by multiple groups and in a GWAS [278, 279]. SORL1 levels are reduced in AD brains [280] and risk variants that decrease SORL1 expression, particularly in childhood and adolescence, predict increases in amyloid pathology [281].

4. Conclusions and future directions

ApoE is the major apolipoprotein produced within the CNS and is intimately involved in the risk, progression, and pathogenesis of AD. Allelic differences in *APOE* appear to confer isoform specific effects with respect to Aβ deposition, degradation and clearance, tau phosphorylation, neuronal injury and inflammation. Given its gain of toxic or loss of beneficial function, strategies aimed at increasing functional apoE may be of therapeutic interest, although it is possible that elevated levels of dysfunctional apoE4 may actually be detrimental for *APOE4* carriers. However, as over 50% of AD patients carry at least one *APOE4* allele, development of future therapies must take into account the structural and functional differences of this lipoprotein isoform, and seek to develop ways to either correct or bypass the "dysfunction" of apoE4. Long ignored, the importance of clusterin in CNS health and disease is now rapidly expanding. While clinical evidence is mounting that clusterin may be involved in AD disease risk, severity, and rate of decline both with respect to cognitive function and Aβ metabolism, the mechanism(s) by which clusterin confers these roles is poorly understood. ApoA-I may also influence AD pathology, potentially by modulating cerebrovascular integrity and function by assisting in the removal of Aβ peptides from cerebrovascular smooth muscle cells and decreasing inflammation. Indeed, the known effects of common AD comorbidities such as type II diabetes and hypercholesterolemia, on apoA-I function, should be taken into account in clinical studies on dementia risk and potential therapeutic approaches.

In the cardiovascular field, many preclinical and clinical studies have endeavored to increase the net concentration of circulating HDL to protect against cardiovascular disease. Many of these studies may also have implications for CNS function. However, as some of these approaches, such as the inhibition of CETP, have failed to meet their primary endpoints for cardiovascular disease despite significantly increasing HDL cholesterol levels, the lipoprotein field is now deeply invested in understanding the functional complexities of HDL. Therapeutic interventions aimed at increasing the function of HDL particles and their cargo may be of much greater importance than increasing its net levels, in both the peripheral and CNS compartments. Given the complexity of the HDL proteome and lipidome, it will be critical to divest the same details in the CNS to allow for therapeutic development targeting lipoprotein species.

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