

Lipid metabolism in Alzheimer's disease

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Lipids play crucial roles in cell signaling and various physiological processes, especially in the brain. Impaired lipid metabolism in the brain has been implicated in neurodegenerative diseases, such as Alzheimer's disease (AD), and other central nervous system insults. The brain contains thousands of lipid species, but the complex lipid compositional diversity and the function of each of lipid species are currently poorly understood. This review integrates current knowledge about major lipid changes with the molecular mechanisms that underlie AD pathogenesis.

Keywords: brain aging; lipid metabolism; Alzheimer's disease

Introduction

Lipids are abundant in the brain. These lipids consist of glycerophospholipids (GPs), sphingolipids, and cholesterol in roughly equimolar proportions^[1]. The brain contains about 20% of the total body cholesterol^[2]. Cholesterol is primarily derived from local synthesis, whereas uptake of lipoprotein particle-derived cholesterol from the peripheral circulation is usually prevented by the blood-brain-barrier. Lipids, especially cholesterol, have recently been extensively studied in many neurodegenerative diseases. Impairment of cholesterol metabolism (synthesis, transport, and utilization by neurons) in the brain is linked to Alzheimer's disease (AD) and the aging process. In addition, lipid oxidation products accumulate at high levels in aging tissues in mice^[3]. Recent studies have demonstrated the important role of altered metabolism in AD^[4]. Sphingomyelinases promote apoptosis in human primary neurons through the generation of a proapoptotic molecule, ceramide^[5]. Moreover, upregulated arachidonic acid metabolism has been reported in hAPP-J20 AD mice as well as in the AD brain, particularly in regions having high densities of senile plaques with activated microglia^[6, 7]. Although the potential link between cholesterol and AD pathogenesis has been

intensively studied, growing evidence suggests that other lipids, such as sphingolipids and GPs, also play an important role. Here, we review some recent advances in understanding the role lipids play in the aging process and AD pathogenesis.

Major Lipid Classes and Functions in the Brain

Although most lipids serve as structural lipids in cell membranes, they are also directly involved in membrane trafficking, intracellular architecture, and the regulation of proteins and sub-compartments in membranes (lipid rafts) (Table 1). Eukaryotic organisms might contain a dozen major lipid classes, each comprising hundreds of individual molecular species^[8]. Lipids have the potential to generate 9 000–100 000 molecular species^[9, 10], and a mammalian cell may contain 1 000–2 000^[11]. The brain is one of the most lipid-enriched organs, containing several major classes, such as cholesterol, GPs, sphingolipids and fatty acids^[12]. The biological significance of the compositional complexity of lipids is poorly understood. However, the recent development of the shot-gun lipidomics technique may provide more sensitive and quantitative characterization of the lipids in the brain^[11].

Cholesterol is the major structural component of cellular membranes and myelin. It is also a precursor of oxysterols, steroid hormones, and bile acids^[2]. Brain cholesterol is essential for synapse and dendrite formation^[13, 14] and axonal guidance^[15], as well as being crucial for the development and maintenance of neuronal plasticity^[16–18], synaptic vesicle transport^[19], and neurotransmitter release^[20]. Cholesterol depletion in neurons impairs synaptic vesicle exocytosis, neuronal activity, and neurotransmission, and leads to dendritic spine and synapse degeneration^[21–23]. Abnormal cholesterol metabolism is associated with many neurodegenerative diseases such as Niemann-Pick C disease, Huntington's disease, AD, and Parkinson's disease^[24–27].

GPs and sphingolipids are not only essential for the structural integrity of neuronal membranes, but also serve as precursors of bioactive lipid mediators in the brain^[28]. GPs bind membrane proteins to help them maintain a proper position and tight integration in the lipid bilayer. GPs are also essential for the optimal function of ion channels and neuronal surface receptors^[29]. GP-derived lipid mediators are involved in the regulation of neuronal activity and gene expression^[30]. GPs in neuronal membranes are decreased in the brains of AD patients, leading to membrane fluidity and permeability change^[31, 32]. Many of the GP degradation products are pro-inflammatory and directly involved in the activation of astrocytes and microglia, which results in the release of inflammatory cytokines, interleukin-1 β , interleukin-6, and tumor necrosis factor α ^[31, 32]. These cytokines further amplify the oxidative

stress and neuroinflammation^[33–35]. Phospholipase A2 levels are increased in the AD brain, leading to increased production of GP-derived lipid mediators such as eicosanoids, lysophospholipids, endocannabinoids, and docosanoids, eventually causing cell injury and modulating cell communications^[36–38]. An abnormal increase of lipid mediators could lead to both abnormal signal transduction and neurodegeneration in AD.

Fatty-acids are critical for mammalian cells to perform various biological functions, such as sustaining the structural integrity of cellular membranes, serving as signaling molecules, and providing energy to cells. In the brain, they are highly enriched, and actively participate in the development and maintenance of the central nervous system (CNS) during both embryonic and adult stages, but their functions under physiological and disease conditions remain elusive. According to the carbon chain length, fatty-acids are classified into short (<6 carbons), medium (6–12 carbons), long (14–22 carbons), and very long (>22 carbons). Fatty-acids in which the aliphatic chain is fully composed of single bonds between carbons are termed saturated, whereas those with one or more carbon-carbon double-bonds are termed unsaturated. During brain development, especially at the embryonic stage, polyunsaturated fatty-acids (PUFAs) are critical for cell proliferation and neuronal differentiation, and their deprivation results in apoptosis. Dietary fatty-acids not only change the lipid profiling in the brain but also alter learning and memory in mouse pups^[39]. Insufficient intake of monounsaturated fatty-acids (MUFAs) leads to age-

Table 1. Major lipid classes and functions in the brain

Lipids	Functions
Cholesterol	Major component of cellular membrane, essential for membrane structural integrity and protein function; neuronal synaptic plasticity; regeneration; lipid raft, which is important for neuronal signaling; lipoprotein particles; neuroinflammation; neurodegeneration; precursors for lipid mediators and hormones
Fatty Acids	Sustain structural integrity of cellular membrane; cellular signaling; neuronal activity and plasticity; synaptogenesis and neurogenesis; neuroinflammation; neurodegeneration; oxidative stress
Glycerophospholipids	Structural integrity of neural membrane; precursors for lipidmediators; oxidative stress; neuroinflammation; lipoprotein particles; neuronal activity; neural cell differentiation and migration; neurodegeneration
Sphingolipids	Structural integrity of neural membrane; precursors for lipid mediators; oxidative stress; neuroinflammation; lipid rafts; neuronal activity; neural cell differentiation and migration; neurodegeneration

dependent deletion of mitochondria DNA in the aged animal brain^[40]. Deregulation of fatty-acids is also involved in the pathogenesis of numerous brain disorders, such as neurodegenerative diseases, mental retardation, stroke, and trauma. The roles of fatty-acids in AD are discussed in detail below.

Cholesterol Synthesis, Transport, and Neuronal Uptake Mediated by LDL Receptor Family in the Brain

The brain is the most cholesterol-enriched organ in the body. Most of the cholesterol is present in the myelin sheaths, plasma membranes, and endocytic recycling compartments of glial cells and neurons, mainly in the unesterified form. Cholesterol plays a critical role in the development and maintenance of neuronal plasticity and function^[41]. Most of the cholesterol in the brain is synthesized *de novo*, and peripheral cholesterol cannot enter due to the low permeability of the blood-brain-barrier^[42]. In mature neurons, cholesterol is believed to be synthesized and supplied by glial cells, primarily by astrocytes^[43]. The cholesterol forms complexes with apolipoprotein E (apoE) and phospholipids, and then is delivered *via* lipoprotein receptors to neurons^[18], which use the cholesterol to form new membranes and synapses.

Cholesterol uptake by neurons is mainly through members of the low-density lipoprotein (LDL) receptor family, primarily LDL receptor (LDLR) and LDLR-related protein 1 (LRP1)^[44]. LRP1 is an endocytic and signaling receptor highly expressed in the brain. It binds to a variety of ligands, some of which are implicated in AD pathogenesis, such as apoE, amyloid precursor protein (APP), amyloid β peptide (A β), α 2-macroglobulin, and matrix metalloproteinase 9^[45]. LDLR is also a cell-surface glycoprotein and mediates apoE- and cholesterol-containing lipoprotein particle metabolism both in peripheral tissues and in the CNS^[46]. Some single-nucleotide polymorphisms in the LDLR gene are associated with a risk of AD in a gender-specific manner^[47, 48]. Interestingly, deletion of *Ldlr* in mice increases apoE levels in the brain parenchyma and cerebrospinal fluid (CSF)^[49], whereas overexpression of LDLR in the brain decreases the metabolism of apoE^[50]. Similarly, conditional deletion of

Lrp1 in forebrain neurons increases apoE metabolism^[51], while overexpression of a functional LRP1 mini-receptor in mouse brain decreases it^[52]. The major difference between LRP1 and LDLR is that the latter is more highly expressed in glial cells than in neurons, but LRP1 is expressed more in neurons than in glial cells^[53, 54]. In addition, LRP1 deletion leads to decreased cholesterol levels in the brain, whereas cholesterol levels in LDLR knockout are not changed^[51, 53]. ApoE lipoprotein particles secreted by glial cells have higher affinity for LDLR than LRP1, but CSF-isolated high-density lipoprotein (HDL) particles bind more to LRP1^[55]. The conformation and lipidation status of apoE may affect the specificity of its receptor binding.

Cholesterol is synthesized in glial cells, and then transported into apoE lipoprotein particles *via* ATP-binding cassette (ABC) transporters, such as ABCA1 and ABCG1. ABC transporters use ATP to drive the transport of various molecules including lipids across cellular membranes^[56, 57], and include 49 known ABC transporters and 7 classes. ABCA and ABCG are the major classes in the brain, critical for lipid homeostasis^[58-60]. ABCA1 is an important lipid transporter in the brain, and it transports not only cholesterol but also other lipids like phospholipids to lipid-poor apolipoproteins including apoE. Deletion of ABCA1 leads to poor lipidation of apoE, and significantly reduced apoE levels in the brain and CSF^[61, 62], suggesting that poorly lipidated apoE is more rapidly cleared. ABCA1 catalyzes the initial transfer of lipids onto lipid-free apolipoproteins, including apoE, to form nascent particles, which are then fully lipidated in a second phase of efflux mediated by ABCG1^[63, 64]. Deletion of ABCG1 results in the accumulation of neutral lipids in peripheral tissues, and ABCG1 shows a better correlation with cholesterol efflux from primary glial cells than ABCA1^[65-67].

Apolipoprotein E and the Pathogenesis of AD

AD, especially late-onset AD (LOAD), is the most common cause of dementia in the population >60 years old. Mutations in the genes for Presenilin 1, Presenilin 2, and APP can cause early-onset, autosomal dominant familial AD, but these cases only account for <1% of the total AD cases^[68]. AD is characterized clinically by progressive decline in memory, and pathologically by extracellular accumulation of amyloid plaques, intracellular formation

of neurofibrillary tangles, synapse and neuron loss, inflammation, and brain atrophy. Accumulation of the A β peptide, the major component of amyloid plaques, is hypothesized to initiate a pathogenic cascade that eventually leads to AD^[69]. The sequential proteolytic processing of APP by β -secretase (BACE1) and γ -secretase produces several A β species, including the most abundant 40 amino-acid (A β 40) and 42 amino-acid (A β 42) species^[70]. Genetic and biochemical evidence suggests that increases in A β levels, the A β 42/A β 40 ratio, or mutant forms with a greater amyloidogenic propensity are the main mechanisms for the rare familial AD, but for LOAD other mechanisms are involved^[70]. ApoE is still the major risk factor for LOAD, and apoE-mediated lipid metabolism in the brain may play a critical role in its pathogenesis. Another key pathological feature of AD is the intracellular accumulation of the hyperphosphorylated microtubule-associated protein tau, which forms neurofibrillary tangles in neurons. Neurofibrillary tangles are present not only in the cell body but also in the dystrophic neurites. Hyperphosphorylated tau aggregates tend to have ubiquitin modification in the tangles, so the degradation of ubiquitinated tau in the proteasome may be defective in AD^[68, 69]. Although no tau mutations have been identified in AD, the neurofibrillary tangle density is correlated with cognitive decline, which supports the tau hypothesis of AD. Amyloid and tau pathology are prevalent in AD pathogenesis, but the mechanistic link between A β and tau is not fully understood. The current view holds that aggregation of A β initiates some intracellular events that cause tau hyperphosphorylation and accumulation.

ApoE plays a critical role in regulating cholesterol metabolism in the brain. It has three isoforms in humans (alleles ϵ 2, ϵ 3, and ϵ 4)^[71], differing only in a single amino-acid (arginine or cysteine) at residues 112 and 158. The most common allele in humans is ϵ 3, followed by ϵ 4 and ϵ 2^[72]. These apoE isoforms have different effects on cholesterol metabolism (such as its mobilization and distribution). Glial cells, mainly astrocytes, produce much more apoE than microglia^[73]. In some conditions, neurons can also generate apoE, albeit at much lower levels^[74]. ApoE functions as a ligand in the receptor-mediated endocytosis of lipoprotein particles in the brain. The *APOE* ϵ 4 allele is the strongest risk factor for sporadic AD^[75]. Compared to individuals without ϵ 4 allele, the increased

risk for AD is 2- to 3-fold in people with only one ϵ 4 allele and ~12-fold in those with two ϵ 4 alleles^[76, 77]. The ϵ 4 allele is also associated with an early onset of AD^[78, 79]. *APOE* ϵ 4 alleles are associated with higher cholesterol levels, whereas *APOE* ϵ 2 alleles are associated with lower cholesterol levels; the difference may be due to the structural differences among apoE isoforms.

Role of Cholesterol Metabolism in AD Pathogenesis

Mounting evidence indicates that cholesterol actively participates in AD pathogenesis. Cholesterol alters A β production by regulating secretase activity^[23]. Reducing the membrane cholesterol levels can also decrease the activity of BACE1 and γ -secretase, and lead to reduced A β production^[80–83]. In addition, inhibition of 3-hydroxy-3-methylglutaryl-CoA-reductase and 7-dehydro-cholesterol-reductase^[84], both key enzymes in cholesterol synthesis, reduces both intracellular and extracellular A β levels^[80, 81].

Cholesterol efflux plays a significant role in A β production in the brain. ABCA1 serves as an important regulator of the efflux of excess intracellular cholesterol to extracellular lipid acceptors such as apoE. Increased levels of ABCA1 reduce A β production^[85], whereas deprivation of ABCA1 greatly increases A β deposition^[86]. Further studies have shown that poor apoE lipidation may promote amyloidogenesis^[87].

The conversion from soluble and nontoxic monomeric A β to insoluble and toxic oligomeric A β is a critical step in AD pathogenesis. Cholesterol facilitates the formation of more neurotoxic aggregates of A β ^[88]. Increased cholesterol levels in the lipid bilayers enhance A β conformation changes from a helix-rich to a beta-sheet-rich structure, which facilitates amyloid accumulation^[89]. In contrast, lowering the membrane cholesterol with statin causes decreased A β production due to cholesterol interfering with glycosylation in the protein secretory pathway^[90]. However, moderate reduction of membrane cholesterol in hippocampal neurons from rodent models causes an increase in A β production, suggesting a delicate balance between cholesterol and A β levels^[91].

Free cellular cholesterol can be converted into cholesteryl esters by the enzyme sterol O-acyltransferase 1 (ACAT1). Cholesteryl ester levels are well correlated with

A β production: A β release increases with cholesteryl ester levels in cultured cells^[92]; and A β release and cholesteryl ester levels are significantly reduced after inhibiting ACAT activity^[93]. Free cholesterol can also be converted into 24(S)-hydroxycholesterol (24-OH cholesterol)^[1, 94-96], which can then be transported into the peripheral circulation and tissues through the blood-brain barrier. Converted free brain cholesterol results in reduced brain cholesterol levels. Accumulating evidence indicates that AD patients during the early stage normally have higher levels of 24-OH cholesterol in the peripheral circulation and CSF than unaffected individuals^[97-99], suggesting that cholesterol turnover in the brain is enhanced in AD patients. Thus, 24-OH cholesterol can be used as a clinical biomarker for early diagnosis. This evidence indicates that the balance between free cholesterol and cholesterol esters is essential for regulating amyloidogenesis in AD pathogenesis.

Cholesterol metabolism also has a significant impact on tau phosphorylation and aggregation in AD. Inhibiting cholesterol biosynthesis in cultured neurons results in hyperphosphorylation of tau and axonal degeneration^[100]. A cholesterol-enriched diet enhances tau phosphorylation and aggregation in a Tau mutant mouse model^[101]. Deletion of NPC1, involved in cholesterol transport and esterification, leads to the accumulation of free cholesterol and increased levels of hyperphosphorylated tau^[102]. Further, kinases for tau, such as CDK5, are upregulated in NPC1-deficient cells^[103, 104].

Role of Fatty-Acid Metabolism in AD Pathogenesis

Fatty-acids have been intensively studied in diabetes and other metabolic diseases, but in neurodegenerative diseases, especially in AD, little is known about their roles. Some *in vitro* studies have shown that they affect A β secretion, especially palmitic acid and PUFA^[105]. However, recent *in vivo* studies using an APP mutant AD mouse model showed that both extraneously supplied and endogenous PUFAs suppress A β production and the formation of amyloid plaques^[106]. Similarly, MUFAs, mainly oleic acid, inhibit the production of A β and amyloid plaque formation both *in vitro* and *in vivo*^[90]. In contrast, arachidonic acid increases A β production and the formation of amyloid plaques and other neuropathology^[91]. Some studies have confirmed the animal results and shown

decreased levels of PUFAs and MUFAs in the AD brain^[107]. However, there are reports showing that PUFAs do not change significantly in the AD brain compared to the healthy brain^[108]. In addition, overexpression of *Fat-1*, enhancing endogenous production of *n*-3 PUFAs, in 3 $\times$ Tg-AD mice significantly reduces phosphorylated tau and improves brain function^[106]. Although the reasons for these disparities are unclear, it is probable that different stages of AD have different effects on fatty-acid metabolism, or gene expression for fatty-acid synthesis differs during different stages.

Role of Sphingolipid Metabolism in AD Pathogenesis

Sphingolipids are a class of lipids containing a backbone of sphingoid bases, which are a set of aliphatic amino-alcohols that include sphingosine. It is the major structural lipid of CNS membranes and highly expressed in the myelin sheath. The simplest sphingolipids are ceramides (sphingosine plus a fatty-acid), and the most complex are sphingomyelins and glycosphingolipids, such as cerebroside, sulfatide, and ganglioside. The brain contains a large amount of sphingolipids, which play critical roles in synaptic stability and transmission, signaling pathways, and neuronal survival, and have essential biological functions.

The role of sphingolipids in AD has been studied since the last two decades. Several reports, including post-mortem studies, have shown that ceramide levels are elevated in cortical regions of the AD brain^[109-111] and CSF^[112] and this increase is accompanied by decreased sulfatide levels in the same regions. Given that ceramide results from sulfatide degradation, these results indicate decreased sulfatide metabolism in the AD brain. Immunohistochemical studies have shown that the ceramide levels are increased mainly in astrocytes^[113], suggesting that neurons may have a lipid metabolism different from that of glial cells. White-matter ceramides are increased 3-fold in the AD temporal cortex and cerebellum during the early stage of the disease^[109]. In the late stages, ceramides remain elevated about 2-fold compared to age-matched controls. However, gray-matter ceramides are unchanged at all stages of AD^[109]. Recently, a study showed that hippocampal ceramide levels are decreased^[113]. *In*

vitro studies indicated that A β activates sphingomyelin hydrolysis and causes ceramide accumulation^[110–114], and ceramide in turn influences A β production by stabilizing β -secretase and promoting the amyloidogenic pathway of APP processing^[115, 116].

Total ganglioside levels in the AD brain are significantly reduced, mainly in the temporal and frontal cortices, and the nucleus basalis of Meynert^[117, 118]. They remain constant in the frontal and temporal cortices between 20 and 70 years^[119]. Recently, some studies have shown that the levels of b-series gangliosides such as GD1b and GT1b appear to be reduced in the AD brain^[120], whereas other studies have shown that a-series gangliosides are affected even more^[118].

The sulfatide levels are depleted up to 92% in gray-matter and 58% in white-matter of all examined brain regions in the early stage of AD^[109]. Post-mortem studies also suggest that sulfatide levels decrease significantly in the early stage^[109], but no further reduction occurs as the disease develops into the late stage, suggesting that sulfatides may be a good diagnostic marker for early AD. Moreover, sulfatide levels are higher in AD patients who are APOE ϵ 4 allele carriers, compared to non- ϵ 4 allele carriers^[121]. Although sulfatide levels are decreased in the AD cortex, the compositional distribution of their subtypes remains unchanged^[122]. Sulfatide loss is very specific for AD because it does not occur in individuals with Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, or multiple sclerosis^[123]. Interestingly, during aging, sulfatide levels are reduced by ~35% in centenarians compared with 20-year-olds^[119].

Besides the lipids in cells, CSF lipid levels have also been investigated. One study reported a 40% decrease in sulfatide levels, and other studies showed a 40% increase in ceramide levels in AD patients^[112]. These studies also demonstrated that sulfatides are associated with apoE particles in the CSF, and the modulation of sulfatide content depends on the apoE isoform. This seems to be particularly important for A β -binding to apoE-associated particles. Moreover, A β 42 levels correlate with sulfatides in the CSF and sulfatides enhance the uptake of A β ^[109]. Sulfatides may provide a potential link between apoE, A β , and AD pathology^[121].

In addition to structural maintenance of cell membranes, glycosphingolipids are also implicated in

regulating the proteolytic processing and subcellular transport of APP^[124]. Inhibition of glycosphingolipid biosynthesis reduces the secretion of APP and A β , whereas addition of exogenous gangliosides reverses these effects^[124]. There is a large and growing number of reports covering the role of sphingolipid metabolites, especially ceramide and sphingosine-1-phosphate (S1P) in neuronal signaling and function. This important aspect has recently been extensively reviewed by Colombari and Garcia-Gil^[125].

Recent studies showed that the levels of acid sphingomyelinase, the hydrolysis of sphingomyelins, and the generation of ceramide are positively correlated with hyperphosphorylated tau and A β levels in the AD brain^[111], suggesting that ceramide generated by acid sphingomyelinase mediates the toxic effects of hyperphosphorylated tau and A β . S1P accumulation promotes tau hyperphosphorylation by increasing calpain and CDK5, which induces cell-cycle reactivation and neurotoxicity^[126]. In addition, inhibition of serine palmitoyltransferase reduces hyperphosphorylated tau levels^[127].

Role of Glycerophospholipid Metabolism in AD Pathogenesis

GPs are amphipathic molecules that play active roles in the function of neuronal membranes, receptors, transporters, ion channels, and storage depots for lipid mediators. GP levels are lower in AD brains than in age-matched controls^[128], and accordingly, the levels of the metabolites of phospholipid degradation are elevated^[129].

GPs are important components of neuronal membranes. GP composition indicates that levels of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol are significantly decreased in the neuronal membranes of AD patients compared to age-matched control humans; these changes occur in several regions^[32, 130–134]. This leads to changes in membrane fluidity and permeability and ion homeostasis, which then lead to oxidative stress.

GP degradation products are pro-inflammatory, so their production is usually accompanied by astrocytic and microglial activation, and inflammatory cytokine release. These cytokines in turn propagate oxidative stress and neuroinflammation^[33–35].

GPs are also precursors for lipid mediators. Arachidonic acid, docosahexaenoic acid, and lysophospholipids, which are produced from GPs by hydrolysis, are important lipid mediators.

Arachidonic acid is metabolized by cyclooxygenases (COX-1 and COX-2), lipoxygenases (LOX), and epoxigenases into prostaglandins, leukotrienes, lipoxins, and thromboxanes, as well as hydroxyeicosatetraenoic, and epoxyeicosatetraenoic, and dihydroxyeicosatrienoic acids^[135, 136]. These metabolites are collectively called eicosanoids; they have a wide range of biological actions including potent effects on inflammation, vasodilation, vasoconstriction, apoptosis, and immune responses. Arachidonic acid plays a role in regulating the activity of many enzymes such as protein kinase A, protein kinase C, NADPH oxidase, choline acetyltransferase, and caspase-3^[137].

COX-1 and COX-2 expression is up-regulated in the cerebral cortex and hippocampal regions of the AD brain compared to age-matched controls^[138, 139]. 5-LOX expression is increased in the hippocampus of the AD brain as well, where it is primarily associated with neurofibrillary structures. Eicosanoid-mediated neuroinflammation may be an essential player in AD pathogenesis^[140]. Although neuroinflammatory mediators promote neurodegeneration in AD, they may stimulate APP processing by enhancing β -site APP cleavage enzyme and therefore are able to establish a vicious cycle^[141].

Docosahexaenoic acid (DHA) is metabolized by 15-LOX into resolvins and neuroprotectins (NPs) and the action of 14-LOX on DHA generates maresins (MaRs)^[142-144]. These metabolites are called docosanoids. The NPD1 pathway promotes neuronal survival *via* not only its anti-inflammatory effects (such as suppression of the pro-inflammatory enzyme COX-2), but also the suppression of A β ₄₂-mediated neurotoxicity^[145-147]. DHA metabolism also decreases the expression of BACE1, activates α -secretase, decreases the neuroprotective sAPPa, and therefore changes the cleavage of APP from the amyloidogenic pathway to the non-amyloidogenic pathway^[148].

Neuronal membrane lysophospholipids include lysophosphatidylcholines, lysophosphatidylethanolamines, lysophosphatidylserines, lysophosphatidylinositols, lysoplasmalogens (lysoplasmenylethanolamine and lysoplasmenylcholine), and lysophosphatidic acid^[149].

Lysophosphatidylcholine/phosphatidylcholine ratio is significantly decreased in the CSF of AD patients compared to controls^[129], indicating that changes in the metabolism of choline-containing phospholipids in the brain are closely associated with the membrane changes in AD^[129].

5-LOX is upregulated in the AD brain and mainly associated with neurofibrillary tangles. Further, hyperphosphorylated tau increases LOX activity in AD^[150]. These events create a vicious cycle and greatly enhance tau pathology and further lead to neuroinflammation and neurodegeneration. Lysophosphatidic acid treatment induces tau phosphorylation and neurite retraction in differentiated neuroblastoma cells mediated by increased GSK3 activity^[151, 152]. In addition, 1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine and 1-O-hexadecyl-sn-glycero-3-phosphocholine are elevated in the AD brain and in AD transgenic mouse models, leading to CDK5-mediated tau hyperphosphorylation^[153].

Therapeutic Progress in Targeting Lipid Metabolism in AD

Most therapeutic approaches to AD target the A β pathway. With the recent failure of clinical trials of drugs solely targeting A β , there is an urgent need for new targets and alternative therapeutic strategies.

ApoE levels in CSF and plasma tend to be lower in patients with AD than in healthy individuals, although such findings remain controversial^[154, 155]. This indicates that increasing apoE expression may prevent or at least slow the progression of AD by accelerating A β metabolism and promoting apoE functions in lipid metabolism and synaptic support. Retinoid X receptors control apoE expression by forming complexes with peroxisome proliferator-activated receptor- γ and liver X receptors^[156, 157]. Therefore, its agonists or antagonists can be used to modulate its levels. Indeed, recent work has demonstrated that oral administration of a retinoid X receptor agonist, bexarotene, in an amyloid mouse model decreases A β plaque deposition and improves cognitive function in an apoE-dependent manner^[156]. The liver X receptor agonist TO901317 also increases apoE levels in the brain, facilitates the clearance of A β ₄₂, and reverses contextual memory deficits in amyloid mouse models^[158, 159].

ApoE is essential for A β deposition in amyloid mouse

models^[160]. Thus, disrupting the interaction between apoE and A β may reduce A β aggregation. Blocking the apoE–A β interaction using A β -mimicking peptides could, therefore, be an effective approach to the treatment of AD.

ApoE4 is structurally different from apoE2 and apoE3 due to different domain interactions^[161], and this difference probably contributes to its harmful effects. Modifying apoE4 structure towards apoE3 might, therefore, be a potential approach to alleviating these effects. CB9032258 (a phthalazinone analog) and its derivatives disrupt apoE4 domain interaction and restore the functional activity of apoE4 in neurons^[162].

ApoE receptors are also potential targets for AD therapy. For example, LRP1 and LDLR play crucial roles in brain lipid metabolism and A β clearance^[22, 23, 50].

The cholesterol hypothesis has drawn increasing attention over the past decade, and statin-mediated neuroprotection has received increasing attention^[163–165]. Lipid-lowering therapy such as statins has been shown to lower the prevalence of AD-like dementia, both in case-control retrospective cohorts^[166–168] and in observational studies^[169, 170]. Furthermore, the Rotterdam study showed that AD patients undergoing statin therapy have lower levels of biomarkers of the disease in the CSF and slightly increased cognitive performance^[171]. Also, this study concluded that it reduced the risk of LOAD by almost 50%.

Conclusions and Perspectives

Prevailing data suggest that abnormal lipid metabolism influences A β metabolism and deposition in both brain parenchyma and vasculature as well as tau hyperphosphorylation and aggregation, which is then likely to trigger a series of downstream catalytic events that eventually affect the progression of the pathogenesis of AD (Fig. 1). It is critical to keep track of lipid metabolism and develop biomarkers for diagnosis based on the lipid changes. Given the huge number of lipids and the complex molecular composition of the cellular lipidome, it is very difficult to decipher the detailed molecular and cellular mechanisms in both cellular systems and animal models. A recent technological advance in lipid analysis is the development of lipidomics^[11, 172, 173], which provides a system-level method to analyze the diversity of lipid species. Using quantitative lipidomics, we can identify a

wide variety of lipid changes in given cellular or animal or human samples, which will allow us to identify the biochemical pathways and study the mechanistic basis of the disease. One of the outstanding questions in the AD field is whether lipids are the molecular links between familial and sporadic AD. One way to answer this is through clinical screening of blood, CSF, and brain samples from different AD patients using the quantitative lipidomics method. This will allow us not only to identify the specific lipid changes but also to reveal the specific effects of particular lipids in the pathogenesis of the disease.

ApoE-mediated lipid metabolism is increasingly recognized as an important player in AD pathogenesis, but the molecular and cellular mechanisms by which it influences A β metabolism, tau phosphorylation, and pathogenesis are not well understood. An understanding of the glia-derived lipid production, trafficking, targeting, and metabolism may provide clues. The rapid advances in sequencing and annotating genomes have led to a rapid growth of knowledge and large datasets focused on protein, RNA, and DNA. Combining proteomics, transcriptomics,

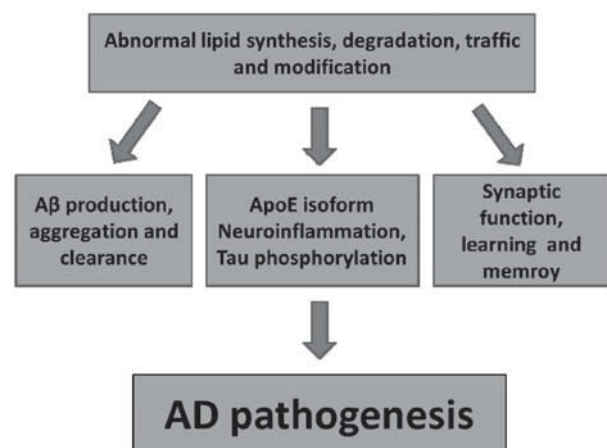


Fig. 1. Potential roles of lipid metabolism in Alzheimer's disease (AD). To understand the role of lipid metabolism in AD pathogenesis, some potential mechanisms have been proposed. Current evidence indicates that lipid metabolism, including synthesis, degradation, trafficking, and modification, may contribute to the process by influencing A β production, aggregation, and clearance. Lipid metabolism may also mediate pathogenesis through its effects on neuroinflammation, tau phosphorylation, and synaptic activity.

and genomics data with lipidomics data may provide a more complete picture and further direct the understanding of lipid biology.

ACKNOWLEDGEMENTS

This review was supported by grants from the National Natural Science Foundation of China (91332111 and 31371087), the National Basic Research Development Program of China (2014CB548100), the Thousand Young Talents Program (Q. Liu) and start-up funds (Q. Liu) from the University of Science and Technology of China.

Received date: 2013-12-22; Accepted date: 2014-02-25

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