Neurosci Bull April 1, 2014, 30(2): 331–345. http://www.neurosci.cn
DOI: 10.1007/s12264-013-1410-3

·Review·

Lipid metabolism in Alzheimer's disease

Qiang Liu[1], Juan Zhang[2]

[1]*CAS Key Laboratory of Brain Function and Disease and School of Life Sciences, University of Science and Technology of China, Hefei 230027, China*

[2]*Department of Genetics, Washington University School of Medicine, St. Louis, MO 63011, USA*

Corresponding author: Qiang Liu. E-mail: liuq2012@ustc.edu.cn

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-1β, 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 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; neurodegeration
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 (Aβ), α2-macroglobulin, and matrix metallopeptidase 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 Aβ 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 Aβ species, including the most abundant 40 amino-acid (Aβ40) and 42 amino-acid (Aβ42) species[70]. Genetic and biochemical evidence suggests that increases in Aβ levels, the Aβ42/Aβ40 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 ubiquinated 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 Aβ and tau is not fully understood. The current view holds that aggregation of Aβ 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 ε2, ε3, and ε4)[71], differing only in a single amino-acid (arginine or cysteine) at residues 112 and 158. The most common allele in humans is ε3, followed by ε4 and ε2[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* ε4 allele is the strongest risk factor for sporadic AD[75]. Compared to individuals without ε4 allele, the increased risk for AD is 2- to 3-fold in people with only one ε4 allele and ~12-fold in those with two ε4 alleles[76, 77]. The ε4 allele is also associated with an early onset of AD[78, 79]. *APOE* ε4 alleles are associated with higher cholesterol levels, whereas *APOE* ε2 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 Aβ 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 Aβ 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 Aβ levels[80, 81].

Cholesterol efflux plays a significant role in Aβ 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 Aβ production[85], whereas deprivation of ABCA1 greatly increases Aβ deposition[86]. Further studies have shown that poor apoE lipidation may promote amyloidogenesis[87].

The conversion from soluble and nontoxic monomeric Aβ to insoluble and toxic oligomeric Aβ is a critical step in AD pathogenesis. Cholesterol facilitates the formation of more neurotoxic aggregates of Aβ[88]. Increased cholesterol levels in the lipid bilayers enhance Aβ 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 Aβ 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 Aβ production, suggesting a delicate balance between cholesterol and Aβ 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

Aβ production: Aβ release increases with cholesteryl ester levels in cultured cells[92]; and Aβ 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 Aβ 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 Aβ production and the formation of amyloid plaques[106]. Similarly, MUFAs, mainly oleic acid, inhibit the production of Aβ and amyloid plaque formation both *in vitro* and *in vivo*[90]. In contrast, arachidonic acid increases Aβ 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×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 cerebrosides, sulfatides, and gangliosides. 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 Aβ activates sphingomyelin hydrolysis and causes ceramide accumulation[110-114], and ceramide in turn influences Aβ 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* ε4 allele carriers, compared to non-ε4 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 Aβ-binding to apoE-associated particles. Moreover, Aβ42 levels correlate with sulfatides in the CSF and sulfatides enhance the uptake of Aβ[109]. Sulfatides may provide a potential link between apoE, Aβ, 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 Aβ, 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 Colombaioni 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 Aβ levels in the AD brain[111], suggesting that ceramide generated by acid sphingomyelinase mediates the toxic effects of hyperphosphorylated tau and Aβ. 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 epoxygenases 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, NAPDH 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 Aβ42-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 Aβ pathway. With the recent failure of clinical trials of drugs solely targeting Aβ, 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 Aβ 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 Aβ 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 $A\beta_{42}$, and reverses contextual memory deficits in amyloid mouse models[158, 159].

ApoE is essential for Aβ deposition in amyloid mouse

models[160]. Thus, disrupting the interaction between apoE and Aβ may reduce Aβ aggregation. Blocking the apoE–Aβ interaction using Aβ-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 Aβ 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 Aβ 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 Aβ 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,

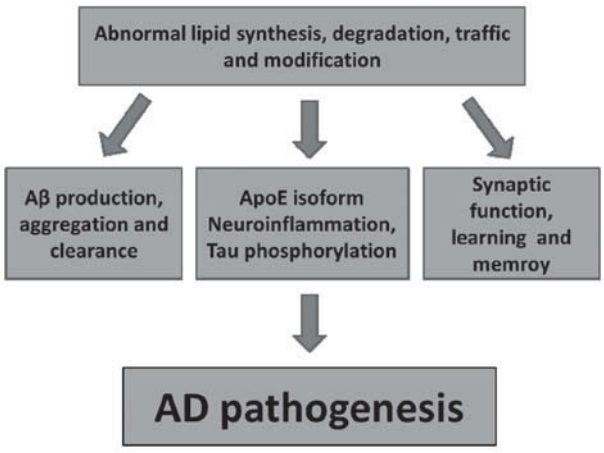

Fig. 1. Potential roles of lipid metabolism in Alzheimer's disease (AD). To understand the role of lipid metabolism in AD pathogenesis, some potential mechanisms have been proposed. Current evidence indicates that lipid metabolism, including synthesis, degradation, trafficking, and modification, may contribute to the process by influencing Aβ 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

REFERENCES

[1] Bjorkhem I, Meaney S. Brain cholesterol: long secret life behind a barrier. Arterioscler Thromb Vasc Biol 2004, 24: 806–815.

[2] Korade Z, Kenworthy AK. Lipid rafts, cholesterol, and the brain. Neuropharmacology 2008, 55: 1265–1273.

[3] West XZ, Malinin NL, Merkulova AA, Tischenko M, Kerr BA, Borden EC*, et al.* Oxidative stress induces angiogenesis by activating TLR2 with novel endogenous ligands. Nature 2010, 467: 972–976.

[4] Haughey NJ, Bandaru VV, Bae M, Mattson MP. Roles for dysfunctional sphingolipid metabolism in Alzheimer's disease neuropathogenesis. Biochim Biophys Acta 2010, 1801: 878–886.

[5] Jana A, Pahan K. Fibrillar amyloid-beta-activated human astroglia kill primary human neurons via neutral sphingomyelinase: implications for Alzheimer's disease. J Neurosci 2010, 30: 12676–12689.

[6] Sanchez-Mejia RO, Newman JW, Toh S, Yu GQ, Zhou Y, Halabisky B*, et al.* Phospholipase A2 reduction ameliorates cognitive deficits in a mouse model of Alzheimer's disease. Nat Neurosci 2008, 11: 1311–1318.

[7] Esposito G, Giovacchini G, Liow JS, Bhattacharjee AK, Greenstein D, Schapiro M*, et al.* Imaging neuroinflammation in Alzheimer's disease with radiolabeled arachidonic acid and PET. J Nucl Med 2008, 49: 1414–1421.

[8] Shevchenko A, Simons K. Lipidomics: coming to grips with lipid diversity. Nat Rev Mol Cell Biol 2010, 11: 593–598.

[9] van Meer G. Cellular lipidomics. EMBO J 2005, 24: 3159-3165.

[10] Yetukuri L, Ekroos K, Vidal-Puig A, Oresic M. Informatics and computational strategies for the study of lipids. Mol Biosyst 2008, 4: 121–127.

[11] Wenk MR. The emerging field of lipidomics. Nat Rev Drug Discov 2005, 4: 594–610.

[12] Hussain G, Schmitt F, Loeffler JP, de Aguilar JL. Fatting the brain: a brief of recent research. Front Cell Neurosci 2013, 7: 144.

[13] Fester L, Zhou L, Butow A, Huber C, von Lossow R, Prange-Kiel J*, et al.* Cholesterol-promoted synaptogenesis requires the conversion of cholesterol to estradiol in the hippocampus. Hippocampus 2009, 19: 692–705.

[14] Goritz C, Mauch DH, Pfrieger FW. Multiple mechanisms mediate cholesterol-induced synaptogenesis in a CNS neuron. Mol Cell Neurosci 2005, 29: 190–201.

[15] de Chaves EI, Rusinol AE, Vance DE, Campenot RB, Vance JE. Role of lipoproteins in the delivery of lipids to axons during axonal regeneration. J Biol Chem 1997, 272: 30766–30773.

[16] Goritz C, Mauch DH, Nagler K, Pfrieger FW. Role of glia-derived cholesterol in synaptogenesis: new revelations in the synapse-glia affair. J Physiol Paris 2002, 96: 257–263.

[17] Koudinov AR, Berezov TT. Cholesterol, statins, and Alzheimer disease. PLoS Med 2005, 2: e81; author reply e85.

[18] Mauch DH, Nagler K, Schumacher S, Goritz C, Muller EC, Otto A*, et al.* CNS synaptogenesis promoted by glia-derived cholesterol. Science 2001, 294: 1354–1357.

[19] Klopfenstein DR, Tomishige M, Stuurman N, Vale RD. Role of phosphatidylinositol(4,5)bisphosphate organization in membrane transport by the Unc104 kinesin motor. Cell 2002, 109: 347–358.

[20] Michikawa M. Role of cholesterol in amyloid cascade: cholesterol-dependent modulation of tau phosphorylation and mitochondrial function. Acta Neurol Scand Suppl 2006, 185: 21–26.

[21] Linetti A, Fratangeli A, Taverna E, Valnegri P, Francolini M, Cappello V*, et al.* Cholesterol reduction impairs exocytosis of synaptic vesicles. J Cell Sci 2010, 123: 595–605.

[22] Liu Q, Trotter J, Zhang J, Peters MM, Cheng H, Bao J*, et al.* Neuronal LRP1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration. J Neurosci 2010, 30: 17068–17078.

[23] Liu Q, Zerbinatti CV, Zhang J, Hoe HS, Wang B, Cole SL*, et al.* Amyloid precursor protein regulates brain apolipoprotein E and cholesterol metabolism through lipoprotein receptor LRP1. Neuron 2007, 56: 66–78.

[24] Madra M, Sturley SL. Niemann-Pick type C pathogenesis and treatment: from statins to sugars. Clin Lipidol 2010, 5: 387–395.

[25] Block RC, Dorsey ER, Beck CA, Brenna JT, Shoulson I. Altered cholesterol and fatty acid metabolism in Huntington disease. J Clin Lipidol 2010, 4: 17-23.

[26] Di Paolo G, Kim TW. Linking lipids to Alzheimer's disease:

cholesterol and beyond. Nat Rev Neurosci 2011, 12: 284–296.

[27] Wang Q, Yan J, Chen X, Li J, Yang Y, Weng J*, et al.* Statins: multiple neuroprotective mechanisms in neurodegenerative diseases. Exp Neurol 2011, 230: 27–34.

[28] Frisardi V, Panza F, Seripa D, Farooqui T, Farooqui AA. Glycerophospholipids and glycerophospholipid-derived lipid mediators: a complex meshwork in Alzheimer's disease pathology. Prog Lipid Res 2011, 50: 313–330.

[29] Palsdottir H, Hunte C. Lipids in membrane protein structures. Biochim Biophys Acta 2004, 1666: 2–18.

[30] Bazan NG. Lipid signaling in neural plasticity, brain repair, and neuroprotection. Mol Neurobiol 2005, 32: 89–103.

[31] Han X, Holtzman DM, McKeel DW, Jr. Plasmalogen deficiency in early Alzheimer's disease subjects and in animal models: molecular characterization using electrospray ionization mass spectrometry. J Neurochem 2001, 77: 1168–1180.

[32] Pettegrew JW, Panchalingam K, Hamilton RL, McClure RJ. Brain membrane phospholipid alterations in Alzheimer's disease. Neurochem Res 2001, 26: 771–782.

[33] Farooqui AA, Rapoport SI, Horrocks LA. Membrane phospholipid alterations in Alzheimer's disease: deficiency of ethanolamine plasmalogens. Neurochem Res 1997, 22: 523–527.

[34] Stephenson D, Rash K, Smalstig B, Roberts E, Johnstone E, Sharp J*, et al.* Cytosolic phospholipase A2 is induced in reactive glia following different forms of neurodegeneration. Glia 1999, 27: 110–128.

[35] Farooqui AA, Ong WY, Horrocks LA. Plasmalogens, docosahexaenoic acid and neurological disorders. Adv Exp Med Biol 2003, 544: 335–354.

[36] Kanfer JN, Sorrentino G, Sitar DS. Phospholipases as mediators of amyloid beta peptide neurotoxicity: an early event contributing to neurodegeneration characteristic of Alzheimer's disease. Neurosci Lett 1998, 257: 93–96.

[37] Malaplate-Armand C, Florent-Bechard S, Youssef I, Koziel V, Sponne I, Kriem B*, et al.* Soluble oligomers of amyloid-beta peptide induce neuronal apoptosis by activating a cPLA2-dependent sphingomyelinase-ceramide pathway. Neurobiol Dis 2006, 23: 178–189.

[38] Kriem B, Sponne I, Fifre A, Malaplate-Armand C, Lozac'h-Pillot K, Koziel V*, et al.* Cytosolic phospholipase A2 mediates neuronal apoptosis induced by soluble oligomers of the amyloid-beta peptide. FASEB J 2005, 19: 85–87.

[39] Yu H, Bi Y, Ma W, He L, Yuan L, Feng J*, et al.* Long-term effects of high lipid and high energy diet on serum lipid, brain fatty acid composition, and memory and learning ability in mice. Int J Dev Neurosci 2010, 28: 271–276.

[40] Ochoa JJ, Pamplona R, Ramirez-Tortosa MC, Granados-Principal S, Perez-Lopez P, Naudi A*, et al.* Age-related changes in brain mitochondrial DNA deletion and oxidative stress are differentially modulated by dietary fat type and coenzyme Q(1)(0). Free Radic Biol Med 2011, 50: 1053–1064.

[41] Pfrieger FW. Cholesterol homeostasis and function in neurons of the central nervous system. Cell Mol Life Sci 2003, 60: 1158–1171.

[42] Papassotiropoulos A, Lutjohann D, Bagli M, Locatelli S, Jessen F, Rao ML*, et al.* Plasma 24S-hydroxycholesterol: a peripheral indicator of neuronal degeneration and potential state marker for Alzheimer's disease. Neuroreport 2000, 11: 1959–1962.

[43] Poirier J, Baccichet A, Dea D, Gauthier S. Cholesterol synthesis and lipoprotein reuptake during synaptic remodelling in hippocampus in adult rats. Neuroscience 1993, 55: 81–90.

[44] Herz J, Bock HH. Lipoprotein receptors in the nervous system. Annu Rev Biochem 2002, 71: 405–434.

[45] Cam JA, Bu G. Modulation of beta-amyloid precursor protein trafficking and processing by the low density lipoprotein receptor family. Mol Neurodegener 2006, 1: 8.

[46] Fryer JD, Demattos RB, McCormick LM, O'Dell MA, Spinner ML, Bales KR*, et al.* The low density lipoprotein receptor regulates the level of central nervous system human and murine apolipoprotein E but does not modify amyloid plaque pathology in PDAPP mice. J Biol Chem 2005, 280: 25754–25759.

[47] Lamsa R, Helisalmi S, Herukka SK, Tapiola T, Pirttila T, Vepsalainen S*, et al.* Genetic study evaluating LDLR polymorphisms and Alzheimer's disease. Neurobiol Aging 2008, 29: 848–855.

[48] Zou F, Gopalraj RK, Lok J, Zhu H, Ling IF, Simpson JF*, et al.* Sex-dependent association of a common low-density lipoprotein receptor polymorphism with RNA splicing efficiency in the brain and Alzheimer's disease. Hum Mol Genet 2008, 17: 929–935.

[49] Cao D, Fukuchi K, Wan H, Kim H, Li L. Lack of LDL receptor aggravates learning deficits and amyloid deposits in Alzheimer transgenic mice. Neurobiol Aging 2006, 27: 1632–1643.

[50] Kim J, Castellano JM, Jiang H, Basak JM, Parsadanian M, Pham V*, et al.* Overexpression of low-density lipoprotein receptor in the brain markedly inhibits amyloid deposition and increases extracellular A beta clearance. Neuron 2009, 64: 632–644.

[51] Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. Nat Rev Neurosci 2009, 10: 333–344.

[52] Zerbinatti CV, Wozniak DF, Cirrito J, Cam JA, Osaka H,

Bales KR*, et al.* Increased soluble amyloid-beta peptide and memory deficits in amyloid model mice overexpressing the low-density lipoprotein receptor-related protein. Proc Natl Acad Sci U S A 2004, 101: 1075–1080.

[53] Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. Neuron 1993, 11: 575–580.

[54] Rapp A, Gmeiner B, Huttinger M. Implication of apoE isoforms in cholesterol metabolism by primary rat hippocampal neurons and astrocytes. Biochimie 2006, 88: 473–483.

[55] Fagan AM, Bu G, Sun Y, Daugherty A, Holtzman DM. Apolipoprotein E-containing high density lipoprotein promotes neurite outgrowth and is a ligand for the low density lipoprotein receptor-related protein. J Biol Chem 1996, 271: 30121–30125.

[56] Dean M, Allikmets R. Complete characterization of the human ABC gene family. J Bioenerg Biomembr 2001, 33: 475–479.

[57] Schmitz G, Langmann T, Heimerl S. Role of ABCG1 and other ABCG family members in lipid metabolism. J Lipid Res 2001, 42: 1513–1520.

[58] Dean M, Hamon Y, Chimini G. The human ATP-binding cassette (ABC) transporter superfamily. J Lipid Res 2001, 42: 1007–1017.

[59] Schmitz G, Kaminski WE, Orso E. ABC transporters in cellular lipid trafficking. Curr Opin Lipidol 2000, 11: 493–501.

[60] Puglielli L, Tanzi RE, Kovacs DM. Alzheimer's disease: the cholesterol connection. Nat Neurosci 2003, 6: 345–351.

[61] Hirsch-Reinshagen V, Zhou S, Burgess BL, Bernier L, McIsaac SA, Chan JY*, et al.* Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain. J Biol Chem 2004, 279: 41197–41207.

[62] Wahrle SE, Jiang H, Parsadanian M, Legleiter J, Han X, Fryer JD*, et al.* ABCA1 is required for normal central nervous system ApoE levels and for lipidation of astrocyte-secreted apoE. J Biol Chem 2004, 279: 40987–40993.

[63] Gelissen IC, Harris M, Rye KA, Quinn C, Brown AJ, Kockx M*, et al.* ABCA1 and ABCG1 synergize to mediate cholesterol export to apoA-I. Arterioscler Thromb Vasc Biol 2006, 26: 534–540.

[64] Vaughan AM, Oram JF. ABCA1 and ABCG1 or ABCG4 act sequentially to remove cellular cholesterol and generate cholesterol-rich HDL. J Lipid Res 2006, 47: 2433–2443.

[65] Kennedy MA, Barrera GC, Nakamura K, Baldan A, Tarr P, Fishbein MC*, et al.* ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation. Cell Metab 2005, 1: 121–131.

[66] Baldan A, Tarr P, Vales CS, Frank J, Shimotake TK, Hawgood S*, et al.* Deletion of the transmembrane transporter ABCG1 results in progressive pulmonary lipidosis. J Biol Chem 2006, 281: 29401–29410.

[67] Karten B, Campenot RB, Vance DE, Vance JE. Expression of ABCG1, but not ABCA1, correlates with cholesterol release by cerebellar astroglia. J Biol Chem 2006, 281: 4049–4057.

[68] Holtzman DM, Mandelkow E, Selkoe DJ. Alzheimer disease in 2020. Cold Spring Harb Perspect Med 2012, 2.

[69] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002, 297: 353-356.

[70] Steiner H, Haass C. Intramembrane proteolysis by presenilins. Nat Rev Mol Cell Biol 2000, 1: 217–224.

[71] Rall SC, Jr., Weisgraber KH, Mahley RW. Human apolipoprotein E. The complete amino acid sequence. J Biol Chem 1982, 257: 4171–4178.

[72] Zannis VI, Breslow JL, Utermann G, Mahley RW, Weisgraber KH, Havel RJ*, et al.* Proposed nomenclature of apoE isoproteins, apoE genotypes, and phenotypes. J Lipid Res 1982, 23: 911–914.

[73] Grehan S, Tse E, Taylor JM. Two distal downstream enhancers direct expression of the human apolipoprotein E gene to astrocytes in the brain. J Neurosci 2001, 21: 812–822.

[74] Xu PT, Schmechel D, Qiu HL, Herbstreith M, Rothrock-Christian T, Eyster M*, et al.* Sialylated human apolipoprotein E (apoEs) is preferentially associated with neuron-enriched cultures from APOE transgenic mice. Neurobiol Dis 1999, 6: 63–75.

[75] Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, Jr.*, et al.* Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994, 7: 180–184.

[76] Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet 2007, 39: 17–23.

[77] Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu Rev Med 1996, 47: 387–400.

[78] Gomez-Isla T, West HL, Rebeck GW, Harr SD, Growdon JH, Locascio JJ*, et al.* Clinical and pathological correlates of apolipoprotein E epsilon 4 in Alzheimer's disease. Ann Neurol 1996, 39: 62–70.

[79] Strittmatter WJ, Saunders AM, Goedert M, Weisgraber KH, Dong LM, Jakes R*, et al.* Isoform-specific interactions of apolipoprotein E with microtubule-associated protein tau: implications for Alzheimer disease. Proc Natl Acad Sci U S A 1994, 91: 11183–11186.

[80] Fassbender K, Simons M, Bergmann C, Stroick M, Lutjohann D, Keller P*, et al.* Simvastatin strongly reduces levels of

Alzheimer's disease beta -amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. Proc Natl Acad Sci U S A 2001, 98: 5856–5861.

[81] Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG, Simons K. Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc Natl Acad Sci U S A 1998, 95: 6460–6464.

[82] Wahrle S, Das P, Nyborg AC, McLendon C, Shoji M, Kawarabayashi T*, et al.* Cholesterol-dependent gamma-secretase activity in buoyant cholesterol-rich membrane microdomains. Neurobiol Dis 2002, 9: 11–23.

[83] Zha Q, Ruan Y, Hartmann T, Beyreuther K, Zhang D. GM1 ganglioside regulates the proteolysis of amyloid precursor protein. Mol Psychiatry 2004, 9: 946–952.

[84] Refolo LM, Pappolla MA, LaFrancois J, Malester B, Schmidt SD, Thomas-Bryant T*, et al.* A cholesterol-lowering drug reduces beta-amyloid pathology in a transgenic mouse model of Alzheimer's disease. Neurobiol Dis 2001, 8: 890–899.

[85] Sun Y, Yao J, Kim TW, Tall AR. Expression of liver X receptor target genes decreases cellular amyloid beta peptide secretion. J Biol Chem 2003, 278: 27688–27694.

[86] Hirsch-Reinshagen V, Maia LF, Burgess BL, Blain JF, Naus KE, McIsaac SA*, et al.* The absence of ABCA1 decreases soluble ApoE levels but does not diminish amyloid deposition in two murine models of Alzheimer disease. J Biol Chem 2005, 280: 43243–43256.

[87] Hirsch-Reinshagen V, Donkin J, Stukas S, Chan J, Wilkinson A, Fan J*, et al.* LCAT synthesized by primary astrocytes esterifies cholesterol on glia-derived lipoproteins. J Lipid Res 2009, 50: 885–893.

[88] Yanagisawa K. Cholesterol and amyloid beta fibrillogenesis. Subcell Biochem 2005, 38: 179–202.

[89] Kakio A, Nishimoto SI, Yanagisawa K, Kozutsumi Y, Matsuzaki K. Cholesterol-dependent formation of GM1 ganglioside-bound amyloid beta-protein, an endogenous seed for Alzheimer amyloid. J Biol Chem 2001, 276: 24985–24990.

[90] Amtul Z, Westaway D, Cechetto DF, Rozmahel RF. Oleic acid ameliorates amyloidosis in cellular and mouse models of Alzheimer's disease. Brain Pathol 2011, 21: 321–329.

[91] Amtul Z, Uhrig M, Wang L, Rozmahel RF, Beyreuther K. Detrimental effects of arachidonic acid and its metabolites in cellular and mouse models of Alzheimer's disease: structural insight. Neurobiol Aging 2012, 33: 831 e821–831.

[92] Puglielli L, Konopka G, Pack-Chung E, Ingano LA, Berezovska O, Hyman BT*, et al*. Acyl-coenzyme A: cholesterol acyltransferase modulates the generation of the amyloid beta-peptide. Nat Cell Biol 2001, 3: 905–912.

[93] Hutter-Paier B, Huttunen HJ, Puglielli L, Eckman CB, Kim DY, Hofmeister A*, et al.* The ACAT inhibitor CP-113,818 markedly reduces amyloid pathology in a mouse model of Alzheimer's disease. Neuron 2004, 44: 227–238.

[94] Shobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. Lancet Neurol 2005, 4: 841–852.

[95] Bjorkhem I, Cedazo-Minguez A, Leoni V, Meaney S. Oxysterols and neurodegenerative diseases. Mol Aspects Med 2009, 30: 171–179.

[96] Bjorkhem I. Crossing the barrier: oxysterols as cholesterol transporters and metabolic modulators in the brain. J Intern Med 2006, 260: 493–508.

[97] Lutjohann D, Papassotiropoulos A, Bjorkhem I, Locatelli S, Bagli M, Oehring RD*, et al.* Plasma 24S-hydroxycholesterol (cerebrosterol) is increased in Alzheimer and vascular demented patients. J Lipid Res 2000, 41: 195–198.

[98] Kolsch H, Heun R, Kerksiek A, Bergmann KV, Maier W, Lutjohann D. Altered levels of plasma 24S- and 27-hydroxycholesterol in demented patients. Neurosci Lett 2004, 368: 303–308.

[99] Khandelwal PJ, Herman AM, Moussa CE. Inflammation in the early stages of neurodegenerative pathology. J Neuroimmunol 2011, 238: 1–11.

[100] Fan QW, Yu W, Senda T, Yanagisawa K, Michikawa M. Cholesterol-dependent modulation of tau phosphorylation in cultured neurons. J Neurochem 2001, 76: 391–400.

[101] Glockner F, Meske V, Lutjohann D, Ohm TG. Dietary cholesterol and its effect on tau protein: a study in apolipoprotein E-deficient and P301L human tau mice. J Neuropathol Exp Neurol 2011, 70: 292–301.

[102] Love S, Bridges LR, Case CP. Neurofibrillary tangles in Niemann-Pick disease type C. Brain 1995, 118 (Pt 1): 119–129.

[103] Sawamura N, Gong JS, Chang TY, Yanagisawa K, Michikawa M. Promotion of tau phosphorylation by MAP kinase Erk1/2 is accompanied by reduced cholesterol level in detergent-insoluble membrane fraction in Niemann-Pick C1-deficient cells. J Neurochem 2003, 84: 1086–1096.

[104] Bu B, Li J, Davies P, Vincent I. Deregulation of cdk5, hyperphosphorylation, and cytoskeletal pathology in the Niemann-Pick type C murine model. J Neurosci 2002, 22: 6515–6525.

[105] Amtul Z, Uhrig M, Rozmahel RF, Beyreuther K. Structural insight into the differential effects of omega-3 and omega-6 fatty acids on the production of Abeta peptides and amyloid plaques. J Biol Chem 2011, 286: 6100–6107.

[106] Lebbadi M, Julien C, Phivilay A, Tremblay C, Emond V, Kang JX*, et al.* Endogenous conversion of omega-6 into omega-3 fatty acids improves neuropathology in an animal model of Alzheimer's disease. J Alzheimers Dis 2011, 27: 853–869.

[107] Martin V, Fabelo N, Santpere G, Puig B, Marin R, Ferrer I*, et al.* Lipid alterations in lipid rafts from Alzheimer's disease

human brain cortex. J Alzheimers Dis 2010, 19: 489–502.

[108] Fraser T, Tayler H, Love S. Fatty acid composition of frontal, temporal and parietal neocortex in the normal human brain and in Alzheimer's disease. Neurochem Res 2010, 35: 503–513.

[109] Han X, D MH, McKeel DW, Jr., Kelley J, Morris JC. Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis. J Neurochem 2002, 82: 809–818.

[110] Cutler RG, Kelly J, Storie K, Pedersen WA, Tammara A, Hatanpaa K*, et al.* Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. Proc Natl Acad Sci U S A 2004, 101: 2070–2075.

[111] He X, Huang Y, Li B, Gong CX, Schuchman EH. Deregulation of sphingolipid metabolism in Alzheimer's disease. Neurobiol Aging 2010, 31: 398–408.

[112] Satoi H, Tomimoto H, Ohtani R, Kitano T, Kondo T, Watanabe M*, et al.* Astroglial expression of ceramide in Alzheimer's disease brains: a role during neuronal apoptosis. Neuroscience 2005, 130: 657–666.

[113] Hejazi L, Wong JW, Cheng D, Proschogo N, Ebrahimi D, Garner B*, et al.* Mass and relative elution time profiling: two-dimensional analysis of sphingolipids in Alzheimer's disease brains. Biochem J 2011, 438: 165–175.

[114] Lee JT, Xu J, Lee JM, Ku G, Han X, Yang DI*, et al.* Amyloid-beta peptide induces oligodendrocyte death by activating the neutral sphingomyelinase-ceramide pathway. J Cell Biol 2004, 164: 123–131.

[115] Patil S, Melrose J, Chan C. Involvement of astroglial ceramide in palmitic acid-induced Alzheimer-like changes in primary neurons. Eur J Neurosci 2007, 26: 2131–2141.

[116] Puglielli L, Ellis BC, Saunders AJ, Kovacs DM. Ceramide stabilizes beta-site amyloid precursor protein-cleaving enzyme 1 and promotes amyloid beta-peptide biogenesis. J Biol Chem 2003, 278: 19777–19783.

[117] Kracun I, Kalanj S, Talan-Hranilovic J, Cosovic C. Cortical distribution of gangliosides in Alzheimer's disease. Neurochem Int 1992, 20: 433–438.

[118] Svennerholm L, Gottfries CG. Membrane lipids, selectively diminished in Alzheimer brains, suggest synapse loss as a primary event in early-onset form (type I) and demyelination in late-onset form (type II). J Neurochem 1994, 62: 1039–1047.

[119] Svennerholm L, Bostrom K, Jungbjer B, Olsson L. Membrane lipids of adult human brain: lipid composition of frontal and temporal lobe in subjects of age 20 to 100 years. J Neurochem 1994, 63: 1802–1811.

[120] Crino PB, Ullman MD, Vogt BA, Bird ED, Volicer L. Brain gangliosides in dementia of the Alzheimer type. Arch Neurol 1989, 46: 398–401.

[121] Han X, Cheng H, Fryer JD, Fagan AM, Holtzman DM. Novel role for apolipoprotein E in the central nervous system. Modulation of sulfatide content. J Biol Chem 2003, 278: 8043–8051.

[122] Yuki D, Sugiura Y, Zaima N, Akatsu H, Hashizume Y, Yamamoto T*, et al.* Hydroxylated and non-hydroxylated sulfatide are distinctly distributed in the human cerebral cortex. Neuroscience 2011, 193: 44–53.

[123] Cheng H, Xu J, McKeel DW, Jr., Han X. Specificity and potential mechanism of sulfatide deficiency in Alzheimer's disease: an electrospray ionization mass spectrometric study. Cell Mol Biol (Noisy-le-grand) 2003, 49: 809–818.

[124] Li H, Evin G, Hill AF, Hung YH, Bush AI, Garner B. Dissociation of ERK signalling inhibition from the anti-amyloidogenic action of synthetic ceramide analogues. Clin Sci (Lond) 2012, 122: 409–419.

[125] Colombaioni L, Garcia-Gil M. Sphingolipid metabolites in neural signalling and function. Brain Res Brain Res Rev 2004, 46: 328–355.

[126] Hagen N, Hans M, Hartmann D, Swandulla D, van Echten-Deckert G. Sphingosine-1-phosphate links glycosphingolipid metabolism to neurodegeneration via a calpain-mediated mechanism. Cell Death Differ 2011, 18: 1356–1365.

[127] Geekiyanage H, Upadhye A, Chan C. Inhibition of serine palmitoyltransferase reduces Abeta and tau hyperphosphorylation in a murine model: a safe therapeutic strategy for Alzheimer's disease. Neurobiol Aging 2013, 34: 2037–2051.

[128] Nitsch R, Pittas A, Blusztajn JK, Slack BE, Growdon JH, Wurtman RJ. Alterations of phospholipid metabolites in postmortem brain from patients with Alzheimer's disease. Ann N Y Acad Sci 1991, 640: 110–113.

[129] Mulder C, Wahlund LO, Teerlink T, Blomberg M, Veerhuis R, van Kamp GJ*, et al.* Decreased lysophosphatidylcholine/phosphatidylcholine ratio in cerebrospinal fluid in Alzheimer's disease. J Neural Transm 2003, 110: 949–955.

[130] Stokes CE, Hawthorne JN. Reduced phosphoinositide concentrations in anterior temporal cortex of Alzheimer-diseased brains. J Neurochem 1987, 48: 1018–1021.

[131] Soderberg M, Edlund C, Kristensson K, Dallner G. Fatty acid composition of brain phospholipids in aging and in Alzheimer's disease. Lipids 1991, 26: 421–425.

[132] Wells K, Farooqui AA, Liss L, Horrocks LA. Neural membrane phospholipids in Alzheimer disease. Neurochem Res 1995, 20: 1329–1333.

[133] Guan Z, Wang Y, Cairns NJ, Lantos PL, Dallner G, Sindelar PJ. Decrease and structural modifications of phosphatidylethanolamine plasmalogen in the brain with Alzheimer disease. J Neuropathol Exp Neurol 1999, 58:

740–747.

[134] Igarashi M, Ma K, Gao F, Kim HW, Rapoport SI, Rao JS. Disturbed choline plasmalogen and phospholipid fatty acid concentrations in Alzheimer's disease prefrontal cortex. J Alzheimers Dis 2011, 24: 507–517.

[135] Farooqui AA. Studies on plasmalogen-selective phospholipase A2 in brain. Mol Neurobiol 2010, 41: 267–273.

[136] Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol 1998, 38: 97–120.

[137] Farooqui AA, Horrocks LA, Farooqui T. Interactions between neural membrane glycerophospholipid and sphingolipid mediators: a recipe for neural cell survival or suicide. J Neurosci Res 2007, 85: 1834–1850.

[138] Pasinetti GM, Aisen PS. Cyclooxygenase-2 expression is increased in frontal cortex of Alzheimer's disease brain. Neuroscience 1998, 87: 319–324.

[139] Qin W, Ho L, Pompl PN, Peng Y, Zhao Z, Xiang Z*, et al.* Cyclooxygenase (COX)-2 and COX-1 potentiate beta-amyloid peptide generation through mechanisms that involve gamma-secretase activity. J Biol Chem 2003, 278: 50970–50977.

[140] Halliday G, Robinson SR, Shepherd C, Kril J. Alzheimer's disease and inflammation: a review of cellular and therapeutic mechanisms. Clin Exp Pharmacol Physiol 2000, 27: 1–8.

[141] Heneka MT, O'Banion MK. Inflammatory processes in Alzheimer's disease. J Neuroimmunol 2007, 184: 69–91.

[142] Hong S, Gronert K, Devchand PR, Moussignac RL, Serhan CN. Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. J Biol Chem 2003, 278: 14677–14687.

[143] Marcheselli VL, Hong S, Lukiw WJ, Tian XH, Gronert K, Musto A*, et al.* Novel docosanoids inhibit brain ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. J Biol Chem 2003, 278: 43807–43817.

[144] Serhan CN, Yang R, Martinod K, Kasuga K, Pillai PS, Porter TF*, et al.* Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. J Exp Med 2009, 206: 15–23.

[145] Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K*, et al.* A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. J Clin Invest 2005, 115: 2774–2783.

[146] Bazan NG. Neuroprotectin D1-mediated anti-inflammatory and survival signaling in stroke, retinal degenerations, and Alzheimer's disease. J Lipid Res 2009, 50 Suppl: S400–405.

[147] Bazan NG. Cellular and molecular events mediated by docosahexaenoic acid-derived neuroprotectin D1 signaling in photoreceptor cell survival and brain protection. Prostaglandins Leukot Essent Fatty Acids 2009, 81: 205–211.

[148] Zhao Y, Calon F, Julien C, Winkler JW, Petasis NA, Lukiw WJ*, et al.* Docosahexaenoic acid-derived neuroprotectin D1 induces neuronal survival via secretase- and PPARgamma-mediated mechanisms in Alzheimer's disease models. PLoS One 2011, 6: e15816.

[149] Farooqui A, Horrocks L. Glycerophospholipids in the Brain: Phospholipases A2 in Neurological Disorders. New York: Springer. 2007: 1–394.

[150] Ikonomovic MD, Abrahamson EE, Uz T, Manev H, Dekosky ST. Increased 5-lipoxygenase immunoreactivity in the hippocampus of patients with Alzheimer's disease. J Histochem Cytochem 2008, 56: 1065–1073.

[151] Sayas CL, Moreno-Flores MT, Avila J, Wandosell F. The neurite retraction induced by lysophosphatidic acid increases Alzheimer's disease-like Tau phosphorylation. J Biol Chem 1999, 274: 37046–37052.

[152] Sayas CL, Avila J, Wandosell F. Regulation of neuronal cytoskeleton by lysophosphatidic acid: role of GSK-3. Biochim Biophys Acta 2002, 1582: 144–153.

[153] Ryan SD, Whitehead SN, Swayne LA, Moffat TC, Hou W, Ethier M*, et al*. Amyloid-beta42 signals tau hyperphosphorylation and compromises neuronal viability by disrupting alkylacylglycerophosphocholine metabolism. Proc Natl Acad Sci U S A 2009, 106: 20936–20941.

[154] Hesse C, Larsson H, Fredman P, Minthon L, Andreasen N, Davidsson P*, et al.* Measurement of apolipoprotein E (apoE) in cerebrospinal fluid. Neurochem Res 2000, 25: 511–517.

[155] Gupta VB, Laws SM, Villemagne VL, Ames D, Bush AI, Ellis KA*, et al.* Plasma apolipoprotein E and Alzheimer disease risk: the AIBL study of aging. Neurology 2011, 76: 1091–1098.

[156] Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo JC, Zinn AE*, et al*. ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. Science 2012, 335: 1503–1506.

[157] Chawla A, Boisvert WA, Lee CH, Laffitte BA, Barak Y, Joseph SB*, et al*. A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. Mol Cell 2001, 7: 161–171.

[158] Riddell DR, Zhou H, Comery TA, Kouranova E, Lo CF, Warwick HK*, et al.* The LXR agonist TO901317 selectively lowers hippocampal Abeta42 and improves memory in the Tg2576 mouse model of Alzheimer's disease. Mol Cell Neurosci 2007, 34: 621–628.

[159] Vanmierlo T, Rutten K, Dederen J, Bloks VW, van Vark-van der Zee LC, Kuipers F*, et al.* Liver X receptor activation restores memory in aged AD mice without reducing amyloid. Neurobiol Aging 2011, 32: 1262–1272.

[160] Bales KR, Verina T, Dodel RC, Du Y, Altstiel L, Bender M,

et al. Lack of apolipoprotein E dramatically reduces amyloid beta-peptide deposition. Nat Genet 1997, 17: 263–264.

[161] Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A 2006, 103: 5644–5651.

[162] Chen HK, Liu Z, Meyer-Franke A, Brodbeck J, Miranda RD, McGuire JG*, et al.* Small molecule structure correctors abolish detrimental effects of apolipoprotein E4 in cultured neurons. J Biol Chem 2012, 287: 5253–5266.

[163] Fonseca AC, Resende R, Oliveira CR, Pereira CM. Cholesterol and statins in Alzheimer's disease: current controversies. Exp Neurol 2010, 223: 282–293.

[164] Kandiah N, Feldman HH. Therapeutic potential of statins in Alzheimer's disease. J Neurol Sci 2009, 283: 230–234.

[165] Menge T, Hartung HP, Stuve O. Statins--a cure-all for the brain? Nat Rev Neurosci 2005, 6: 325–331.

[166] Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet 2000, 356: 1627–1631.

[167] Hajjar I, Schumpert J, Hirth V, Wieland D, Eleazer GP. The impact of the use of statins on the prevalence of dementia and the progression of cognitive impairment. J Gerontol A Biol Sci Med Sci 2002, 57: M414–418.

[168] Rockwood K, Kirkland S, Hogan DB, MacKnight C, Merry H, Verreault R*, et al.* Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002, 59: 223–227.

[169] Rodriguez EG, Dodge HH, Birzescu MA, Stoehr GP, Ganguli M. Use of lipid-lowering drugs in older adults with and without dementia: a community-based epidemiological study. J Am Geriatr Soc 2002, 50: 1852–1856.

[170] Dufouil C, Richard F, Fievet N, Dartigues JF, Ritchie K, Tzourio C*, et al.* APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. Neurology 2005, 64: 1531–1538.

[171] Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry 2009, 80: 13–17.

[172] Piomelli D, Astarita G, Rapaka R. A neuroscientist's guide to lipidomics. Nat Rev Neurosci 2007, 8: 743–754.

[173] Klose C, Surma MA, Simons K. Organellar lipidomics--background and perspectives. Curr Opin Cell Biol 2013, 25: 406–413.