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REVIEW

Novel insights into brain lipid metabolism in Alzheimer's disease: Oligodendrocytes and white matter abnormalities

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Alzheimer's disease (AD) is the most common cause of dementia. A genome-wide association study has shown that several AD risk genes are involved in lipid metabolism. Additionally, epidemiological studies have indicated that the levels of several lipid species are altered in the AD brain. Therefore, lipid metabolism is likely changed in the AD brain, and these alterations might be associated with an exacerbation of AD pathology. Oligodendrocytes are glial cells that produce the myelin sheath, which is a lipid-rich insulator. Dysfunctions of the myelin sheath have been linked to white matter abnormalities observed in the AD brain. Here, we review the lipid composition and metabolism in the brain and myelin and the association between lipidic alterations and AD pathology. We also present the abnormalities in oligodendrocyte lineage cells and white matter observed in AD. Additionally, we discuss metabolic disorders, including obesity, as AD risk factors and the effects of obesity and dietary intake of lipids on the brain.

Alzheimer's disease (AD) is the most common cause of dementia. Depositions of amyloid β peptide (Aβ) and hyperphosphorylated tau protein form senile plaques and neurofibrillary tangles (NFTs), respectively, and induce neurodegeneration in the AD brain. Many risk factors for AD have been identified by

Abbreviations
24-OHC, 24-S-hydroxycholesterol; AA, arachidonic acid; ABCA, ATP-binding cassette subfamily A; AD, Alzheimer's disease; APOE, apolipoprotein E; APOJ, apolipoprotein J; APP, amyloid precursor protein; Aβ, amyloid β; BACE1, beta-secretase 1; BBB, blood–brain barrier; CE, cholesterol ester; CH25H, cholesterol-25 hydroxylase; CLDN, claudin; CNPase, cyclic nucleotide phosphohydrolase; CNS, central nervous system; CSF, cerebrospinal fluid; CYP46A1, cytochrome P450 family 46 subfamily A member 1; DAGs, diacylglycerols; DAM, disease-associated microglia; DAO, disease-associated oligodendrocyte; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FABPs, fatty acid-binding proteins; FAS, fatty acid synthase; FAs, fatty acids; FATPs, fatty acid transport proteins; GM1, glycolipid monosialo-tetrahexosyl-ganglioside; GWAS, genome-wide association study; HFD, high-fat diet; LCPUFAs, long-chain polyunsaturated fatty acids; LDs, lipid droplets; LXR, liver X receptors; MAG, myelin-associated glycoprotein; MAGs, monoacylglycerols; MBP, myelin basic protein; MCI, mild cognitive impairment; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MUFAs, monounsaturated fatty acids; NFTs, neurofibrillary tangles; OPCs, oligodendrocyte precursor cells; PCs, phosphatidylcholines; PEs, phosphatidylethanolamines; PICALM, phosphatidylinositol-binding clathrin assembly protein; PIs, phosphatidylinositols; PLC, phospholipase C; PLTP, phospholipid transfer protein; PPAR, peroxisome proliferator-activated receptor; PS1, presenilin-1; PSs, phosphatidylserines; PUFAs, polyunsaturated fatty acids; RXR, retinoid X receptors; SCAP, SREBP cleavage activating protein; SM, sphingomyelin; SREBF, sterol regulatory element-binding transcription factor; SREBP, sterol regulatory element-binding protein; TAGs, triacylglycerols; TREM2, triggering receptor expressed on myeloid cells 2; VLCFAs, very long-chain fatty acids; WMH, white matter hyperintensities.

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genome-wide association studies (GWAS). Several AD risk genes have a role in lipid metabolism. Additionally, epidemiological studies have shown that the levels of some lipid species are altered in the AD brain, suggesting that altered lipid metabolism exacerbates AD pathology. Thus, several studies have recently focused on lipid metabolism in the brain of patients with AD.

Glial cells, such as microglia, astrocytes, and oligodendrocytes, play important roles in the pathological mechanisms underlying neurodegenerative diseases, including AD. Although the number of glial cells is ten times greater than that of neuronal cells, glial cells have been regarded as supporting cells for neurons for a long time. Microglia are among the most studied glial cells, and their neuroinflammatory functions have been widely assessed in various neurodegenerative diseases. On the contrary, the role of oligodendrocytes in those diseases has not been fully clarified. Oligodendrocytes produce the myelin sheath, a lipid-rich insulator of neuronal axons, and are the main constituents of white matter. Dysfunctions of myelin are related to white matter abnormalities, which have been observed in the brain of patients with AD.

In the present review, we summarize the current knowledge on lipid composition and metabolism in the brain and the myelin. We also review the association between lipid alterations and AD pathology. Additionally, we present the abnormalities in oligodendrocyte lineage cells and white matter found in the AD brain. Because metabolic disorders, including obesity, are known risk factors for AD, we discuss the effects of obesity and dietary intake of lipids on the brain. Lipids and these abbreviations mainly described in this review are summarized in the table (Tables 1–4).

Lipid composition of the brain

The brain is the second most lipid-rich organ after adipose tissue, and at least 50% of the brain dry weight composition is lipids [1]. Lipids in the brain comprise 50% phospholipids, below 40% glycolipids, 10% cholesterol, cholesterol ester (CE), and traces of triacylglycerol [2] (Fig. 1A).

Fatty acids

The synthesis of phospholipids and glycolipids needs fatty acids (FAs) (Table 1). The brain produces mostly saturated FAs (SFAs), but it also synthesizes low amounts of polyunsaturated FAs (PUFAs). Thus, most PUFAs in the brain are supplied from peripheral blood by passive diffusion or by mechanisms mediated by adenosine triphosphate-dependent transporter proteins [1,3,4]. However, the transcriptional machinery for PUFA biosynthesis and long-chain PUFA (LCPUFA)-containing phospholipid

Table 1. Fatty acids (FAs) and these abbreviations described in this review.

Long-chain FAs (LCFAs): C11–20	Very long-chain FAs (VLCFAs): C > 20
Saturated FAs (SFAs)	
Palmitic acid (C16:0)	
Stearic acid (C18:0)	
Monounsaturated FAs (MUFAs)	
Palmitoleic acid (C16:1)	
Oleic acid (C18:1)	
Polyunsaturated FAs (PUFAs)	
ω-6 PUFAs	
Linoleic acid (C18:2)	
Arachidonic acid (AA) (C20:4)	
ω-3 PUFAs	
α-linolenic acid (C18:3)	Docosahexaenoic acid (DHA) (C22:6)
Eicosapentaenoic acid (EPA) (C20:5)	

Table 2. Glycerophospholipids and these abbreviations described in this review.

Glycerophospholipids and these abbreviations described in this review.	
Diacyl phospholipids	Phosphatidic acids (PAs)
	Phosphatidylcholines (PCs)
	Phosphatidylethanolamines (PEs)
	Phosphatidylserines (PSs)
	Phosphatidylinositols (PIs)
	Phosphatidylglycerols (PGs)
	Cardiolipins (CLs)
Ether lipids	Alkyl-acylphospholipids
	plasmanyl-PE
	Alkenyl-acylphospholipids (plasmalogen)
	plasmenyl-PE

Table 3. Sphingolipids and these abbreviations described in this review.

	Sphingosine		
	↑		
Sphingomyelin (SM)	← Ceramide→	Glucosylceramide	→Gangliosides
	↓		Globosides
	Galactosylceramide		
	↓		
	Sulfatides		

Table 4. Sterols and glycerolipids and these abbreviations described in this review.

Sterols	
Cholesterol	
Cholesterol esters (CEs)	
Oxysterols	24-S-hydroxycholesterol (24-OHC)
	25-hydroxycholesterol (25-OHC)
	27-hydroxycholesterol (27-OHC)
Glycerolipids	
Triacylglycerols (TAGs)	
Diacylglycerols (DAGs)	
Monoacylglycerols (MAGs)	

remodeling is present in the cerebral cortex and is stimulated by dietary intake (low supply of precursors) or hormones (high external demands during pregnancy) [5]. LCPUFAs are the source of eicosanoids and docosanoids, which mediate neuroprotective and anti-inflammatory functions [6]. PUFAs, including docosahexaenoic acid (DHA), modulate synaptic plasticity and neurotransmission [1,7]. Moreover, FAs have important roles as energy substrates and bioactive molecules. FA oxidation (β-oxidation) accounts for approximately 20% of the total energy requirements in the brain [8].

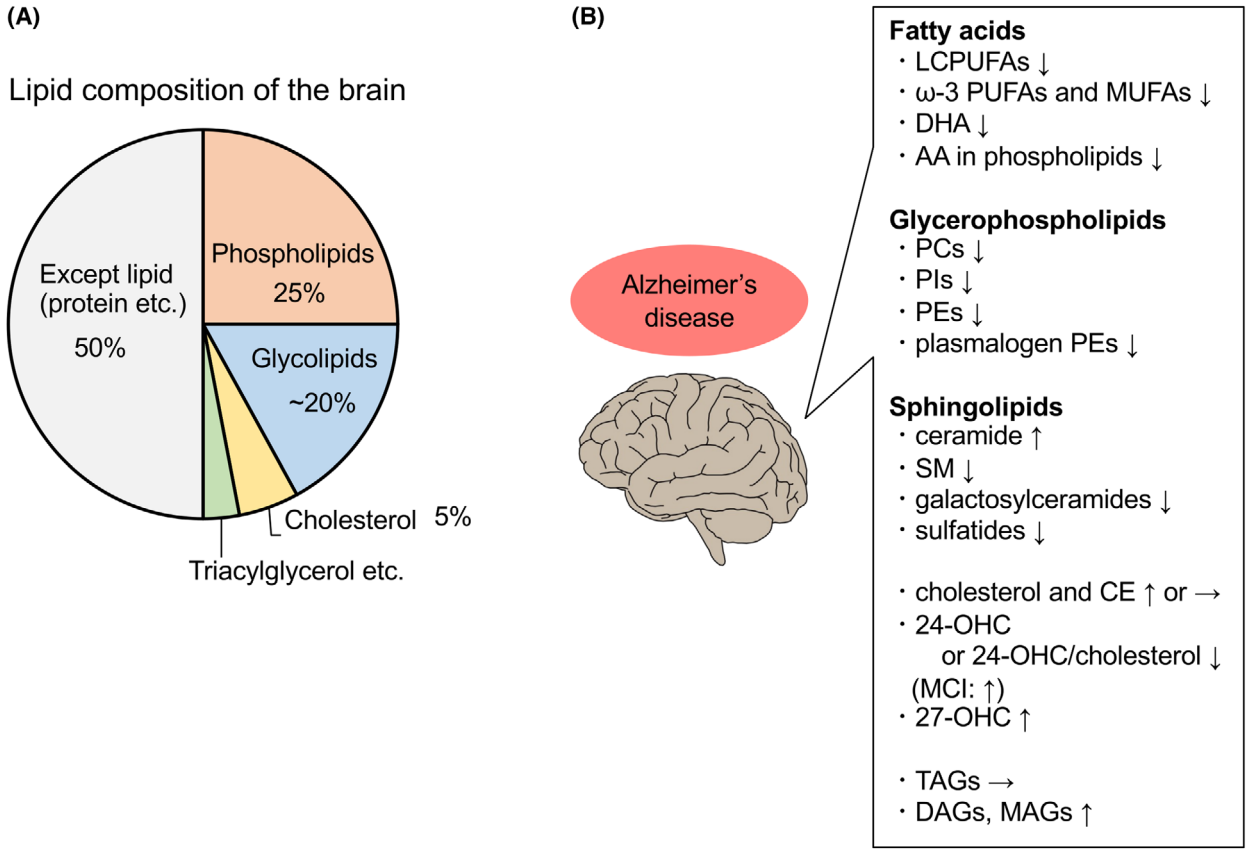

Fig. 1. Lipid composition of the brain and alterations in lipid levels in the AD brain. (A) Lipid composition of the brain. The brain is a lipid-rich organ, and at least 50% of the brain dry weight is lipids. In the brain, lipids comprise 50% phospholipids, below 40% glycolipids, 10% cholesterol and CEs, and traces of triacylglycerol. The figure was created based on reference [2]. (B) Levels of several lipid species are altered in the brain of patients with AD.

Glycerophospholipids

Glycerophospholipids are the main species of phospholipids (Table 2). As in other tissues, phosphatidylcholines (PCs) and phosphatidylethanolamines (PEs) are the main components of cellular membranes, and anchor membrane proteins in the brain [1,9,10]. PCs and PEs participate in determining the stability, permeability, and fluidity of neural membranes, and alterations of PC and PE compositions lead to neurological diseases [11]. Additionally, the degradation of glycerophospholipids produces second messengers such as LCPUFAs [11,12].

Sphingolipids

Sphingolipids (sphingophospholipid and sphingoglycolipid) are also components of cellular membranes, and are involved in neurogenesis and synaptogenesis [13,14] (Table 3). Sphingolipids in synaptic membranes regulate the activity of neurotransmitter receptors [15]. Sphingomyelin (SM), galactosylceramides, and sulfatides are important components of myelin (mentioned in a later chapter). Gangliosides exist in the central nervous system (CNS) at high levels and are associated with cell signaling and neuroprotection [14].

Cholesterol

The brain also contains high levels of cholesterol compared with those in other tissues, and 25% of the whole-body cholesterol is in the brain [10,16] (Table 4). Most sterols in peripheral blood cannot cross the blood–brain barrier (BBB); therefore, they are synthesized in the CNS. The rate of sterol exchange between the brain and peripheral tissues per day is estimated to be lower than 1% [1,4]. Cholesterol is synthesized predominantly in astrocytes and transferred to neurons through lipoproteins containing apolipoprotein E (APOE). In the brain, cholesterol mainly exists in

myelin sheaths, and most of the cholesterol is in an unesterified form, whereas CE accounts for only 1% of the cholesterol stored in lipid droplets (LDs) [17].

Cholesterol is converted into the oxysterol 24-S-hydroxycholesterol (24-OHC), the main free cholesterol species in the brain, by cytochrome P450 family 46 subfamily A member 1 (CYP46A1). CYP46A1 is highly expressed in neurons including pyramidal cells of the cerebral cortex and Purkinje cells of the cerebellum [18–20]. Around 80% of the whole-body 24-OHC is distributed and produced in the brain [21,22]. 24-OHC can cross the BBB and is released into the bloodstream, thus preserving cholesterol homeostasis in the CNS [16]. Cholesterol in the brain also converted into 27-OHC by CYP27A1, and then into 7α-hydroxy-3-oxo-4-cholestenoic acid by CYP7B1. CYP27A1 is ubiquitously expressed, but is expressed in neurons, astrocytes, and oligodendrocytes at the low level [19–21,23]. 27-OHC is a major cholesterol metabolite in periphery. Therefore, 24-OHC is exported from the brain into the periphery, while 27-OHC enters into the brain [24]. The 27-OHC:24-OHC ratio is 1 : 8 in the frontal cortex, 1 : 5 in the occipital cortex, and 1 : 10 in the basal ganglia [25]. 25-OHC, another oxysterol produced by cholesterol-25 hydroxylase (CH25H) [26], is enriched in macrophages, dendritic cells, and microglia [27–29]. The expression of CH25H is induced by inflammatory response [28,30].

Alterations of lipid levels in the brain of patients with AD

In the brain of patients with AD, the levels of lipid species are altered. Most of these changes were observed at early disease stages and/or in brain regions initially affected by AD pathology [9] (Fig. 1B).

Fatty acids

The levels of LCPUFAs, particularly in lipid rafts, were decreased in the brain of patients with AD and mouse models of AD, which leading to abnormalities in nerve cell membranes and pro-amyloidogenic processing. Such reduction in LCPUFAs is also caused by aging, but is exacerbated in AD pathology [1,31]. Levels of unsaturated FAs, including those of ω-3 PUFAs and monounsaturated FAs (MUFAs; primarily oleic acid), are decreased in the brain of patients with AD [32,33]. The composition in FAs of lipid rafts is characterized by low levels of ω-3 PUFAs and MUFAs in the cerebral cortex of patients with AD [9,34] and in the entorhinal and frontal cortices of patients with early-stage AD [35]. DHA, a ω-3 PUFA, is the most abundant PUFA in the brain. The levels of DHA are lower in the AD brain, particularly in vulnerable regions such as the hippocampus [36–38]. Moreover, DHA content in the cerebrospinal fluid (CSF) has been positively correlated with cognitive performance [39]. The level of arachidonic acid (AA), a ω-6 PUFA, in phospholipids is decreased in the hippocampus of patients with AD [36].

Glycerophospholipids

Levels of glycerophospholipids including PCs [40,41], phosphatidylinositols (PIs) [42,43], and PEs [40,41], are decreased in the brain of patients with mild cognitive impairment (MCI) and AD, particularly in vulnerable regions such as the hippocampus and cerebral cortex. The levels of plasmalogen PEs are lower in the white and gray matters of the AD brain [44].

Sphingolipids

Ceramide is a key molecule for the synthesis, recycling, and degradation of other sphingolipids. Ceramide levels are increased in early-stage AD brains, particularly in the frontal and temporal cortices [45–47]. SM, galactosylceramides, and sulfatides are important components of myelin (mentioned in a later chapter). SM levels are lower in the AD brain, but this decrease has been observed at a specific disease stage and in a specific brain region [48–50]. Galactosylceramide levels are also decreased in the hippocampus at early AD stages, before the apparition of tau pathology [51]. Sulfatides are also derived from ceramide. Sulfatide levels are lower in both gray and white matters of the cerebral cortex at the prodromal and early AD stages [47,52]. These decreases in sphingolipid levels have been involved in myelin degeneration and loss of white matter integrity in the AD brain.

Cholesterol

Most studies have suggested that cholesterol levels are increased in the brain and blood of patients with AD [25,45,53,54]. Brain cholesterol levels have been positively correlated with the severity of AD [45], and higher cholesterol levels were observed in the cores of senile plaques in the human brain [55]. Moreover, the levels of total CE are increased by more than 1.8-fold in the entorhinal cortex of patients with AD and in AD mouse models [56,57]. However, some studies reported no change in cholesterol levels in the human AD brain [58,59]. It was also reported that the levels

of 24-OHC or 24-OHC/cholesterol were decreased in the AD brain [20,25,58,60]. In addition, one of these studies showed an increase in 27-OHC in the AD brain [25]. On the contrary, the level of 24-OHC was increased in the postmortem brain of patients with MCI [58]. The gene expression of CH25H, an enzyme producing 25-OHC, was increased in the brains of patients with AD [61] and AD mouse models [62–64].

Triacylglycerols, diacylglycerols, and monoacylglycerols

The levels of triacylglycerols (TAGs), diacylglycerols (DAGs), and monoacylglycerols (MAGs) in the brain of patients with AD have also been investigated (Table 4). Although TAG levels are not altered in AD brains, MAG and DAG levels are increased in the frontal cortex of patients with MCI and AD [56,65,66].

Lipidome analysis in Alzheimer's disease mouse models

Recently, lipidome analyses have been conducted using human and mouse brains. Lipidome analyses can comprehensively identify the alterations in the levels of tens of thousands of lipids. Several lipidome analyses revealed that levels of some lipid species are altered in the brain of AD mouse models. However, these alterations are inconsistent among models and/or disease stages. In lipidome studies using amyloid precursor protein (APP)/presenilin-1 (PS1) [67,68], Tg2576 x JNPL3 [57], and App$^{NL\text{-}G\text{-}F}$ mice [69], levels of some FAs, eicosanoids, glycerophospholipids, sphingolipids, DAGs, and TAGs were altered in the brain. In the future, and despite their complexity, the results of these lipidome analyses will provide important information to identify new lipid-linked pathological mechanisms involved in AD.

Association between lipid metabolism in the brain and Alzheimer's disease pathology

Alzheimer's disease risk factors mediating lipid metabolism

Alzheimer's disease risk genes have been identified by GWAS, and some of these genes are involved in lipid metabolism. The genetic variant of *APOE* encoded by the *APOE ε4* allele is a well-known risk factor for AD and is associated with changes in cholesterol and sphingolipid metabolisms [70,71]. APOE is the main cholesterol carrier and binds to Aβ peptides in the brain to promote Aβ clearance [72]. In *Apoe* knockout mice, cholesterol biosynthesis is reduced, leading to low levels of brain cholesterol [73]. Moreover, aging results in impaired cognitive functions of *Apoe* knockout mice [74]. Triggering receptor expressed on myeloid cells 2 (*TREM2*), apolipoprotein J (*APOJ*) (*CLU*), phosphatidylinositol-binding clathrin assembly protein (*PICALM*), ATP-binding cassette subfamily A member 1 (*ABCA1*), and *ABCA7* are risk genes for sporadic AD [9]. APOJ (CLU), PICALM, ABCA1, and ABCA7 mediate lipid transport. TREM2 is expressed on the surface of microglia and can bind to Aβ, lipids, and lipoproteins. TREM2 has been associated with the clearance of myelin debris and remyelination by regulating cholesterol esterification and metabolism of LDs in microglia [75,76]. Sterol regulatory element-binding transcription factor 2 (*SREBF2*) is also considered a genetic risk factor for AD [9] and encodes sterol regulatory element-binding protein 2 (SREBP2), a key regulator of cholesterol metabolism. Overexpression of SREBP2 in APP/PS1 mice stimulates cholesterol synthesis and induces oxidative damage, amyloid accumulation, neuroinflammation, cognitive decline, tau hyperphosphorylation, and NFT formation [77]. Conversely, the genetic ablation of SREBP2 in astrocytes reduces Aβ and tau pathologies [78].

Fatty acid metabolism in Alzheimer's disease brain

Fatty acid metabolism is also altered in the AD brain. The levels of palmitic acid (C16) are increased and FA synthase (FAS) protein expression is upregulated in the brain of APP/PS1 mice [79]. FAS protein levels are also increased in the cerebral cortex of patients with AD, especially in regions surrounding amyloid plaques [79,80]. Additionally, acetyl CoA carboxylase, another key enzyme of FA synthesis, is activated in the brain of mouse models of familial AD [81]. Peroxisome proliferator-activated receptor α (PPARα) is a nuclear receptor positively related to β-oxidation. The mRNA levels of PPARα are significantly lower in AD brains [82]. Although β-oxidation occurs primarily in mitochondria, it also takes place in the peroxisomes, specifically for very long-chain fatty acids (VLCFAs, ≧ C20) [83]. In the brain of patients with advanced AD, VLCFAs accumulate and the volume of peroxisomes in the soma of neurons is increased, and a loss of peroxisomes in neuronal processes occurs with tau hyperphosphorylation [84]. In 3 x Tg mice, LD accumulation has been observed in ependymal cells in

the subventricular region, and the proliferation of neural stem cells is suppressed [85]. Several lipid-sensitive nuclear receptors such as liver X receptors/retinoid X receptors (LXR/RXR), PPARγ, and PPARα have been associated with AD pathology and are potential therapeutic targets [9].

Lipids and amyloid pathology

Several types of lipids have been involved in the formation of Aβ depositions. Phospholipid transfer protein (PLTP) is associated with lipid and lipoprotein metabolism. PLTP deficiency results in lower levels of PEs and phosphatidylserines (PSs) in the brain, increased intracellular accumulation of Aβ, and memory dysfunction in AD [86]. Phospholipase C (PLC) is an enzyme associated with phospholipid metabolism, especially hydrolysis of phosphatidylinositol-4,5-bisphosphate. PLC inhibition decreases the turnover of phosphatidylinositol-4, 5-bisphosphate, thus reducing the secretion of Aβ42 [87]. Sphingolipid metabolism has also been associated with the formation of Aβ42 oligomers. Accumulation of SM inhibits γ-secretase activity and, consequently, a reduction in Aβ secretion [88,89]. Glycosphingolipids have been linked with the formation of amyloid fibrils [90]. Glycolipid monosialo-tetrahexosyl-ganglioside (GM1) binds to released Aβ to form a GM1–Aβ complex in the brain of patients with AD, and the level of GM1–Aβ complexes in the CSF is correlated with the levels of Aβ oligomers [91]. Additionally, cholesterol in lipid rafts contributes to reducing the distance between APP and beta-secretase 1 (BACE1) before rapid endocytosis [92,93]. It has also been reported that cholesterol is involved in the activation of BACE1 and γ-secretase [94]. In addition, brain cholesterol affects tau pathology. The increase in tau phosphorylation and aggregation has been linked with high cholesterol levels in the brain and with a high dietary intake of cholesterol [95,96]. 24-OHC is also related to Aβ pathology, but both positive and negative effects were reported. 24-OHC promotes or suppresses Aβ production, which was presumably dependent on its concentration in the cells [20]. 27-OHC increases the Aβ deposition in the brain by regulating the production, transportation, and elimination of Aβ [97].

Lipid composition and metabolism of myelin and oligodendrocytes

Oligodendrocytes are kind of glial cells in the CNS and play an important role in producing the myelin sheath. Although most biological membranes contain the same amounts of proteins and lipids, myelin sheaths contain high levels of lipids (70–85%) and low protein levels of proteins (15–30%). The lipid composition in myeline sheaths is 40% cholesterol, 40% phospholipids, and 20% glycolipids (Fig. 2A). In contrast, most biological membranes comprise 25% cholesterol, 65% phospholipids, and 10% glycolipids. Cholesterol, galactosylceramides, and plasmalogens are the major lipid components of myelin and represent 65% of the total lipids in myelin [98–101] (Fig. 2B).

Cholesterol

Cholesterol in myelin would be mainly provided by oligodendrocytes and astrocytes [102–105]. Cholesterol in membrane bilayers increases myelin viscosity and stabilizes lipids and proteins [98,106]. Moreover, cholesterol is needed for synthesizing myelin during maturation of the CNS, and its availability is a limiting factor for the growth of myelin membranes [105].

Galactosylceramide

Galactosylceramides and sulfatides, which are sulfated forms of galactosylceramides, represent 20% of total myelin lipids in oligodendrocytes [107]. Galactosylceramides exist preferentially in compact myelin, whereas sulfatides are mainly found in noncompact myelin [108]. In myelin membranes, galactosylceramides and highly hydrophobic proteins form hydrophobic forces, which are important for myelin formation and stability [109,110]. However, galactosylceramides are not essential for myelin formation, and other glycolipids, such as glucosylceramides, can be produced as partial substitution [109,111].

Plasmalogen

Ethanolamine plasmalogens are the main phospholipids in myelin [98]. Although their functions have not been clarified, plasmalogens have been associated with the compact and stable formation of myelin through the strengthening of lipid bonds [44,109]. Moreover, it has also been suggested that plasmalogens protect myelin against oxidative stress associated with aging [112].

Fatty acids and myelin

Fatty acids are among the lipids, which, besides cholesterol, are abundantly required to assemble and maintain the formation of myelin. Thus, myelinating cells are vulnerable to the depletion and dysregulation of FAs and

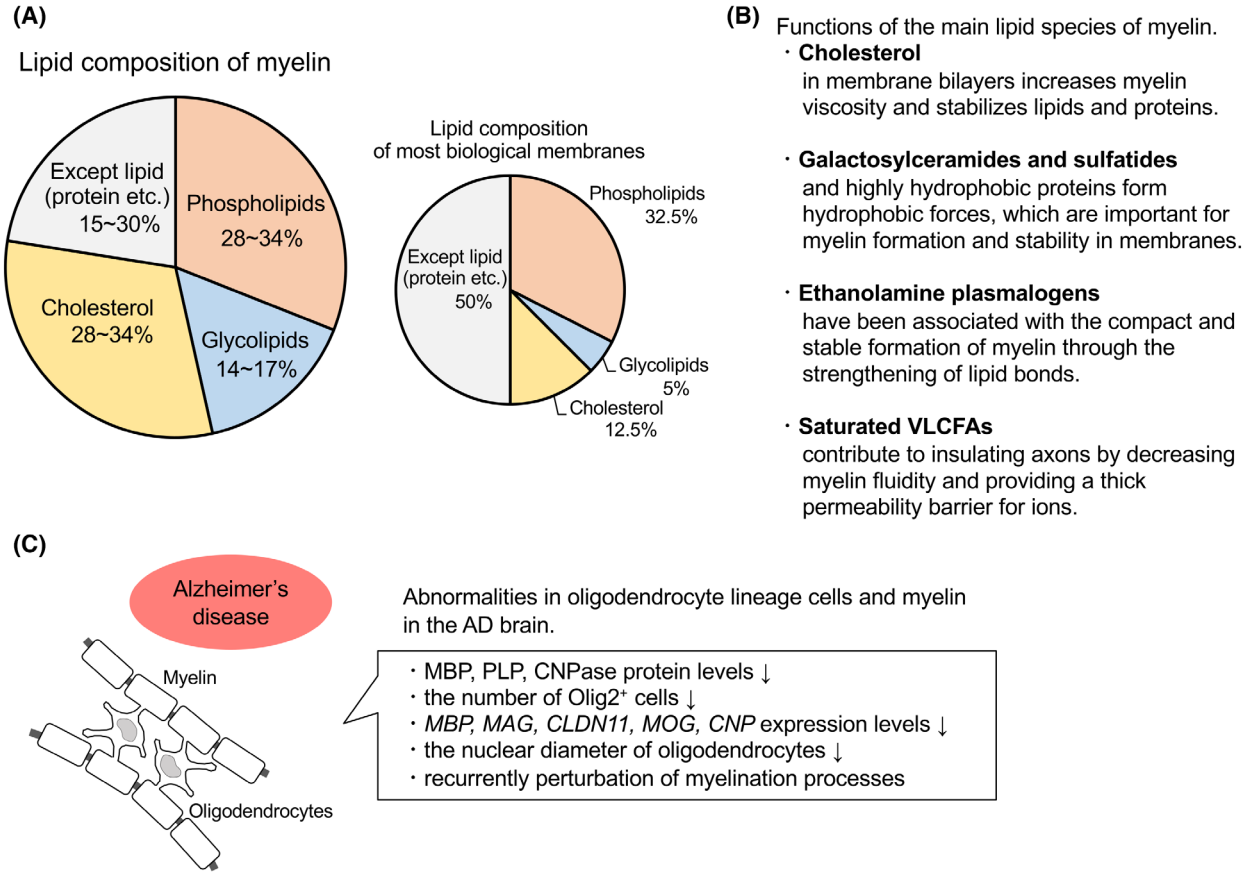

Fig. 2. Lipid composition and functions of myelin and alterations in oligodendrocytes and myelin in the AD brain. (A) Lipid composition of myelin. The myelin sheath contains high levels of lipids (70–85%) and low protein levels (15–30%). Lipids in the myeline sheath comprise 40% cholesterol, 40% phospholipids, and 20% glycolipids. In contrast, most biological membranes contain the same levels of proteins and lipids, and the lipid composition is 25% cholesterol, 65% phospholipids, and 10% glycolipids. The figure was created based on reference [98]. (B) Functions of the main lipid species of myelin. (C) Oligodendrocyte lineage cells and myelin are negatively affected in patients with AD.

lipids [113,114]. The most abundant FAs in myelin are saturated VLCFAs. Myelin comprises a higher percentage of VLCFAs than that in other plasma membranes [113,115]. VLCFAs have over 20 carbons and are synthesized in the endoplasmic reticulum from long-chain FAs, which have over 16 carbons [115]. Saturated VLCFAs contribute to insulating axons by decreasing myelin fluidity and providing a thick permeability barrier for ions. Saturated VLCFAs interact with each other through their tails (straight structure with no double bonds), thus leading to the rigidity of membranes [113]. It has been reported that a reduction in the levels of ceramide species with VLCFA residues induces myelin defects in mice [116]. Additionally, the accumulation of VLCFAs decreases myelin stability and/or synthesis of plasmalogens, which can also cause demyelination [117–119]. Another study has shown that the accumulation of VLCFAs in oligodendrocytes contributes to the loss of peroxisome function, causing demyelination, axonal degeneration, neuroinflammation, and neurodegenerative phenotypes in mice [118].

Fatty acid synthesis

De novo FA synthesis is important for the formation and growth of myelin [102,120]. SREBP1 and SREBP cleavage activating protein (SCAP) regulate the expression of genes related to FA synthesis. SREBP1 is activated by the depletion of intracellular cholesterol; therefore, FA synthesis is associated with cholesterol synthesis [121]. The expression of FAS, induced by SREBP1, correlates with myelination in peripheral nerves during development [122]. It has also been reported that deficiency of SCAP in Schwann cells decreases the levels of saturated VLCFAs in mice [123].

Fatty acid transport

Fatty acids in myelinating cells are provided by endothelial cells and astrocytes by passive diffusion or by active transport through FA translocase (CD36) and FA transport proteins (FATPs) [98,124,125]. However, the roles of CD36 and FATPs in oligodendrocyte lineage cells and myelin have not been clarified. FATP1 is a predominant isoform expressed in the CNS, and FATP4 is also highly expressed in the brain [126]. FA-binding proteins (FABPs) are molecular chaperones for FAs and are involved in FA transport. FABP7 and FABP5 are expressed in oligodendrocytes at different developmental stages. In mice, FABP7 has been related to the proliferation in oligodendrocytes and differentiation of immature oligodendrocytes, whereas FABP5 has been linked to differentiation of oligodendrocytes into mature myelinating oligodendrocytes. However, neither FABP7 nor FABP5 plays important roles in myelin formation [127].

Fatty acid oxidation

For a long time, it was considered that FA oxidation for energy requirement does not occur in oligodendrocytes because of their high demand in FAs for myelination but that it is conducted exclusively in astrocytes [128,129]. However, some reports have suggested that the energetic profiles of myelinating cells and astrocytes are similar [98,130,131]. Although FA oxidation might occur in oligodendrocyte lineage cells, further analyses are needed to clarify this hypothesis.

Abnormalities in oligodendrocytes and myelin in Alzheimer's disease brain

Patients with Alzheimer's disease

Several studies have suggested that abnormalities of oligodendrocyte lineage cells or myelin occur in the brain of patients with AD (Fig. 2C). It has been reported that levels of several proteins linked to the oligodendrocyte lineage [myelin basic protein (MBP), myelin proteolipid protein, and cyclic nucleotide phosphohydrolase (CNPase)] are significantly lower in the white matter of postmortem AD brains. In the same study, total protein and cholesterol levels were also significantly decreased, and the composition in FAs was altered in the white matter of postmortem AD brains. These results indicate that a loss of myelin occurs in the white matter of the AD brain [132]. Olig2 is an oligodendrocyte lineage marker, and the number of Olig2-positive cells is decreased in the brain of patients with AD [133]. Our group reported that the expression of oligodendrocyte lineage genes [*MBP*, myelin-associated glycoprotein (*MAG*), claudin 11 (*CLDN11*), myelin oligodendrocyte glycoprotein (*MOG*), *CNP*] is decreased in the precuneus of postmortem AD brains [134]. In addition, it has been reported that the nuclear diameter of oligodendrocytes is shorter, whereas that of neurons is unchanged in the parahippocampal white matter of patients with AD [135]. A recent study using single-cell transcriptomic analysis showed that myelination processes were recurrently perturbed in oligodendrocytes, oligodendrocyte precursor cells (OPCs), and other cell types in the prefrontal cortex of patients with AD [136].

Alzheimer's disease animal models

Anomalies in oligodendrocyte lineage cells have also been reported in AD animal models. Mutations of PS1, a subunit of γ-secretase, lead to a vulnerability of oligodendrocytes against toxicities induced by glutamate and Aβ peptides and are accompanied by a deficit in calcium regulation [137]. A report indicated that MBP levels and the number of myelinating oligodendrocytes are decreased in 3 x Tg AD mice. Additionally, the number of mature nonmyelinating cells was increased, whereas the number of immature oligodendrocytes remained unchanged [138]. It has also been reported that the number of OPCs was increased in APP/PS1 mice [133]. Another report showed that the proliferative rate of OPCs is increased in APP/PS1 mice. These OPCs differentiate into mature oligodendrocytes and form myelin sheaths, despite of decrease in the level of whole myelination [139,140].

A recent study showed that myelin dysfunction in AD mice caused the accumulation of Aβ-producing machinery within axonal swellings, and increased cleavage of APP in the cerebral cortex. Moreover, AD mice lacked microglia around plaques under the dysfunction of myelin, and similar but distinct disease-associated microglia (DAM) signatures were induced concomitantly with myelin damage and amyloid plaques. DAM were apparently distracted by adjacent myelin damage, despite that DAM usually clear amyloid plaques [141].

These studies from patients with AD or animal models of AD suggest that, although detailed responses to AD pathology remain unclear, oligodendrocyte lineage cells and myelin are negatively affected in AD.

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Disease-associated oligodendrocytes in Alzheimer's disease

Disease-associated oligodendrocytes (DAOs) have been described in neurodegenerative diseases including AD. In 5xFAD mice, oligodendrocytes increased with brain pathology were termed DAOs, and expressed SERPIN3A/SERPINA3 in the diseased cortical regions and near Aβ plaques. Moreover, SERPIN3A/SERPINA3 was also expressed in the human AD brain, and this level was correlated with cognitive decline [142]. Another study indicated that three distinct DAOs were identified in mouse models of AD from single-cell RNA sequencing: DA1 (associated with immunogenic genes), DA2 (associated with genes influencing survival), and IFN (associated with interferon response genes). DA1 and DA2 are established in the regions outside the demyelinating lesion, and DA1 repopulated in the regions with remyelination. However, the signature of oligodendrocyte activation observed in patients with AD was distinct from those observed in AD mice [143]. In $App^{NL\text{-}G\text{-}F}$ mice, the activation of DAOs ($Mbp^{+}Cd74^{+}$ oligodendrocytes) was associated with the abnormality of Erk1/2 signaling. Inhibition of Erk1/2 signaling in DAOs rescued impairment of axonal myelination, and decreased Aβ pathologies and cognitive decline [144].

Brain atrophy and white matter abnormalities in Alzheimer's disease: Human studies

Hippocampal atrophy

Hippocampal atrophy is one of the best-known biomarkers used in clinics for magnetic resonance imaging (MRI). Several MRI studies have indicated that hippocampal volume is reduced by 10–15% in patients with an amnestic variant of MCI and by 20–25% in the patients at the clinical AD stage [145]. Progressive rates of hippocampal atrophy are 4.66% per year for patients with AD and 1.41% per year for healthy controls [146]. A reduction in hippocampal volume for a long time correlates with cognitive decline [147,148]. Moreover, the reduction in hippocampal volume is correlated with the severity of cognitive impairments and episodic memory deficits in patients with MCI and AD [149]. On the contrary, hippocampal atrophy is also observed in patients with vascular dementia [150,151], semantic dementia [152], Parkinson's disease dementia [151,153], and frontotemporal lobar degeneration [154]. Moreover, hippocampal volume correlates with Braak staging and the remaining number of neurons in dementia and aging [153,155–157].

White matter abnormalities

White matter abnormalities are observed in cerebrovascular diseases. However, recently, it has been considered a hallmark of AD. White matter hyperintensities (WMH) are signal anomalies visualized by T2-weighted MRI. WMH are especially observed in deep periventricular white matter, where the blood perfusion rate is low. The blood flow in the white matter is reduced by aging and AD, resulting in hypoxic and ischemic damage and lower vessel densities [158,159]. Nasrabady and colleagues reported that WMH predicted the incidence of AD [160–162] and the degree of cognitive impairment in patients with AD [163]. They also indicated that WMH were associated with the *APOE4* risk genes in late-onset AD [164]. Recently, a study from Dominantly Inherited Alzheimer's Network (DIAN) showed that WMH volume is increased in patients with autosomal dominant and fully penetrant AD mutations, as early as 20 years before the expected onset of symptoms. In these preclinical patients, WMH severity correlates with Aβ1–42 levels in CSF [165]. Notably, the association between WMH severity and amyloid levels in CSF was independent of vascular risk factors [166]. Additionally, an increase in tau levels in CSF is predicted by WMH severity in patients with MCI [167,168]. On the contrary, vascular and BBB impairments, small hemorrhagic lesions, and iron accumulation have been observed in the brain of patients with preclinical AD [169]. However, neuroimaging studies have shown that white matter networks are already defective at the preclinical AD stage in the absence of neurodegenerative changes, cortical atrophy, or cortical glucose reduction [170]. Studies in AD animal models also suggest that white matter defects are observed before the appearance of cortical amyloid plaques and tangles [138,171]. McAleese and colleagues evaluated the effect of neurodegeneration on white matter abnormalities in the parietal and frontal cortex of AD brains. In the parietal cortex, WMH pathogenesis associated with AD was linked to Wallerian-like degeneration caused by AD pathology, whereas WMH occurring without AD were related to vasculopathy and ischemia. In contrast, in the frontal cortex, WMH pathogenesis associated with AD was related to both degenerative and vasculopathy mechanisms [172,173]. It has been speculated that neurodegeneration in AD induces white matter abnormalities in specific regions of the brain.

White matter abnormalities and myelin

Myeline sheaths are abundant in the white matter. WMH have been histopathologically associated with myelin pallor, loss of myelin, and loss of myelinated axons, which are accompanied by changes in the arterial adventitia in deep white matter [174–176]. A loss of myelin was observed in the AD brains, particularly in the forebrain, entorhinal cortex, hippocampus, and amygdala (regions myelinated later during normal development of the CNS). The loss of myelin in these regions was significantly greater than that in the spinal cord and brain stem (regions myelinated earlier during normal development of the CNS) [177–181]. It is suggested that a loss of myelin participates in white matter abnormalities, which may exacerbate brain atrophy in AD.

Association between obesity and Alzheimer's disease

Obesity is a known risk factor for AD. Several epidemiological studies have indicated that the risk of developing dementia is increased by obesity in midlife (age in 50s and 60s). Some of these reports showed an increased risk of AD in obese humans, particularly in women [182–186]. A study focusing on the alteration of lipid compositions in the brain of obese APP23 mice fed a high-fat diet (HFD) was conducted using lipidome analysis. Although the total amount of phospholipids was not changed, the levels of 24 lipid species were significantly altered by the HFD. Particularly, the analysis of network visualization of correlated lipids revealed that HFD induced an overall imbalance, with the most remarkable effect being on cardiolipin molecular subspecies [187]. On the contrary, epidemiological studies indicated that obesity in late life (≧ 60 years old) was not associated with a higher risk for earlier onset of AD [182,188]. In addition, obese humans often have other metabolic disorders, such as type 2 diabetes, hypercholesterolemia, and hypertension, which can induce cardiovascular diseases and have been associated with dementia and AD [9].

Impacts of obesity on brain functions in rodents fed a high-fat diet

The impacts of obesity on brain functions are widely studied using rodents fed an HFD [189]. In mice, HFD increases the levels of Aβ in the hippocampus and induces amyloid depositions in the brain [190,191]. Furthermore, several studies using mice and rats showed that neuroinflammation was induced by HFD. HFD increases the expression levels of nuclear factor-κB, interleukin-1β, and toll-like receptor 4, and densities of astrocytes and microglia in the brain [191–193]. Neuroinflammation induced by HFD has been related to BBB leakage [189,194,195]. In addition, several studies have indicated that rodents fed HFD exhibited impaired working [196], spatial [197], sustained recognition [193], long-term [198], and episodic [199] memories. These memory impairments induced by HFD have been associated with synaptic dysfunctions and neuronal death, synaptic degeneration in the hippocampus and cerebral cortex [200], an increase in apoptotic signals in the hippocampus [191], and a decrease in acetylcholinesterase activity in various regions including the prefrontal cortex [201]. On the contrary, in APP23-ob/ob mice, the AD mouse model crossed with the obese mice by overeating of a normal diet, Aβ burden was not increased, and the expression of microglial markers were down-regulated in the brain. However, learning and memory deficit were exacerbated in these mice [202,203]. Further analyses are needed to clarify the association between obesity and the AD pathologies.

Obesity and brain atrophy in humans

Obesity has been associated with brain atrophy [204]. Studies using diffusion-weighted imaging (diffusion MRI) have indicated that obesity measures are negatively correlated with fiber connectivity [205–210]. White matter structure in the corpus callosum (genu, trunk, and splenium), cerebellar peduncle, corona radiata [209,210], fornix [210], and uncinate fasciculus [206] is altered in obese older adults. White matter volume in obese humans has also been related to a greater degree of atrophy, which is maximal in middle age (approximately 40 years old) and corresponds to an estimated increase in brain age by 10 years [211]. On the contrary, other studies have not found any association between obesity and white matter integrity or positive interaction between body mass index and white matter integrity and volume [212–214]. In addition, the reduction in lean body mass in patients with early-stage AD has been related to brain atrophy and lower cognitive performance, when controlling for age and sex [215]. Thus, although obesity seems to be associated with brain atrophy and white matter integrity, more analyses are required.

Effects of dietary intake of specific lipid species on Alzheimer's disease

Regardless of obesity, dietary intake of several lipid species and internal lipid conditions may affect AD

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pathology. Epidemiological studies have indicated that AD risk is decreased by high dietary intake of ω-3 PUFAs [especially DHA and eicosapentaenoic acid (EPA)] and is increased by low intake of these ω-3 PUFAs [216,217]. Omega-3 PUFAs are involved in inflammation response against Aβ [218] and activate RXR and PPARs, which directly affect Aβ metabolism [219–221]. DHA and EPA contribute to reducing Aβ levels by lowering the activity of β- and γ-secretases and by stimulating insulin-degrading enzyme, which degrades Aβ [222,223]. On the contrary, randomized clinical trials showed that dietary supplementation with DHA did not delay cognitive decline in patients with mild-to-moderate AD. Subgroup analysis in these trials showed a positive effect of DHA in ApoE4 noncarrier patients with very mild AD [224]. The effect of a ketogenic diet (comprising high levels of saturated fats and low amounts of carbohydrates) has also been assessed in patients with AD and animal models of AD. Ketogenic diet reduces Aβ pathology and improves metabolic and cognitive functions in both aging and AD animal models [225,226]. Although ketogenic interventions were effective in early-phase clinical trials, further studies showing long-term effects on AD are required [9,227–230].

Diets with specific FA composition have been linked to the development or maintenance of myelin. Diets excluding essential FAs lead to alterations in FA composition of myelin and cause myelin splitting, but do not significantly affect myelination [231]. A ketogenic diet has been reported to reduce axonal degeneration and improve motor functions in a mouse model of Pelizaeus–Merzbacher disease [232].

Conclusions and perspectives

The lipid composition of the brain is altered in AD, and several lipid species may affect the functions of oligodendrocytes and myelin. Therefore, lipid metabolism is likely altered in the AD brain, particularly in myelin or oligodendrocyte lineage cells, which are vulnerable to lipidic changes. In addition, several studies have shown white matter abnormalities and oligodendrocyte dysfunctions in AD brains. Further analyses are required to define the association between the alteration of brain lipid metabolism and dysfunction of oligodendrocytes and white matter abnormalities in the AD brain. Moreover, obesity is a risk factor for AD, and several studies have shown a link between obesity and brain

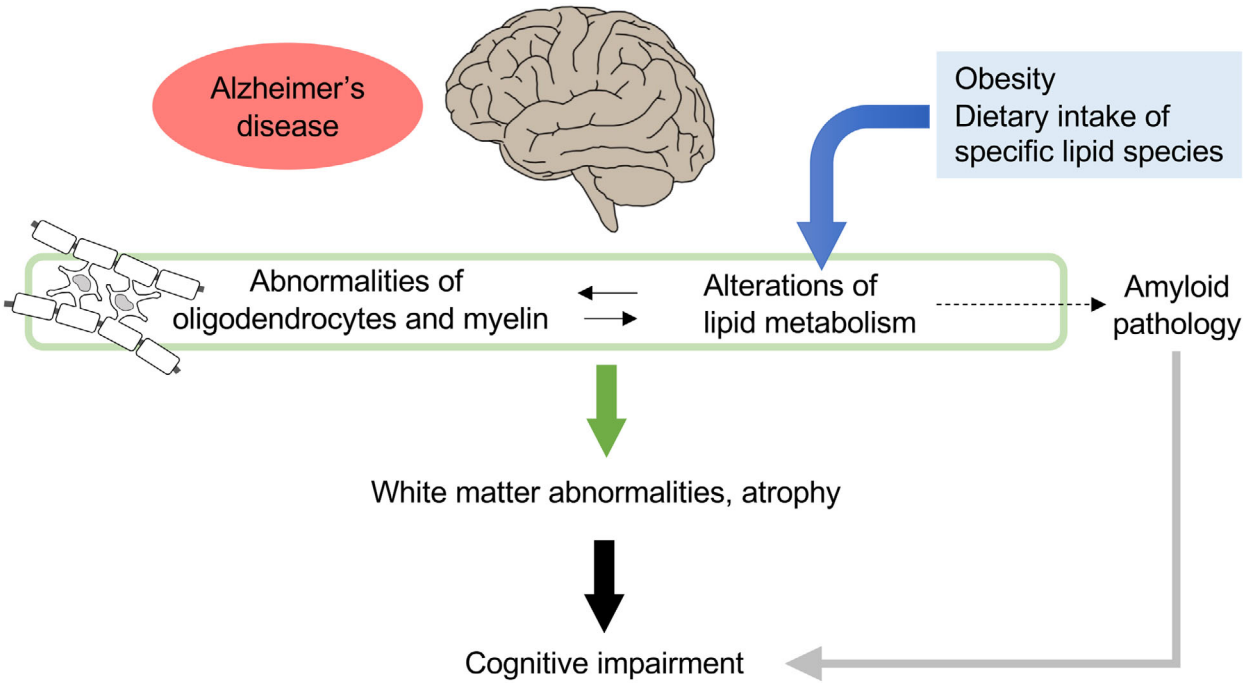

Fig. 3. Hypothetical mechanism showing that alterations in lipid metabolism in the brain exacerbate AD pathology by inducing oligodendrocyte abnormalities. Lipid metabolism may be altered in the AD brain, particularly in myelin or oligodendrocyte lineage cells, which may cause white matter abnormalities and/or atrophy leading to cognitive impairment. Moreover, obesity and diets containing specific lipids might exacerbate or improve AD pathology.

atrophy. Dietary intake of specific lipids may improve AD pathology. In the future, the contribution of peripheral dietary intake to AD pathology needs to be clarified (Fig. 3).

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Author contribution

N. K. and K. Y. wrote the manuscript, and prepared the figures.

Conflict of interest

The authors declare no conflict of interest.

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