

Perspective: The Potential Role of Circulating Lysophosphatidylcholine in Neuroprotection against Alzheimer Disease

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ABSTRACT

Alzheimer disease (AD), the most common cause of dementia, is a progressive disorder involving cognitive impairment, loss of learning and memory, and neurodegeneration affecting wide areas of the cerebral cortex and hippocampus. AD is characterized by altered lipid metabolism in the brain. Lower concentrations of long-chain PUFAs have been described in the frontal cortex, entorhinal cortex, and hippocampus in the brain in AD. The brain can synthesize only a few fatty acids; thus, most fatty acids must enter the brain from the blood. Recent studies show that PUFAs such as DHA (22:6) are transported across the blood–brain barrier (BBB) in the form of lysophosphatidylcholine (LPC) via a specific LPC receptor at the BBB known as the sodium-dependent LPC symporter 1 (MFSD2A). Higher dietary PUFA intake is associated with decreased risk of cognitive decline and dementia in observational studies; however, PUFA supplementation, with fatty acids esterified in triacylglycerols did not prevent cognitive decline in clinical trials. Recent studies show that LPC is the preferred carrier of PUFAs across the BBB into the brain. An insufficient pool of circulating LPC containing long-chain fatty acids could potentially limit the supply of long-chain fatty acids to the brain, including PUFAs such as DHA, and play a role in the pathobiology of AD. Whether adults with low serum LPC concentrations are at greater risk of developing cognitive decline and AD remains a major gap in knowledge. Preventing and treating cognitive decline and the development of AD remain a major challenge. The LPC pathway is a promising area for future investigators to identify modifiable risk factors for AD. *Adv Nutr* 2020;11:760–772.

Keywords: Alzheimer disease, blood–brain barrier, cognition, dementia, docosahexaenoic acid, lysophosphatidylcholine, polyunsaturated fatty acid

Introduction

Alzheimer disease (AD) is a progressive degenerative brain disease and the most common cause of dementia, accounting for approximately two-thirds of the estimated 40–50 million people living with dementia worldwide (1, 2). The characteristic symptoms of dementia are difficulties with memory, language, problem-solving, and other cognitive skills (3). The average duration of AD is 8–10 y, but the

clinical phase of AD is preceded by a long preclinical phase, which may extend over 2 decades (4). The pathology of AD is characterized by accumulation of amyloid β peptide and microtubule-associated protein τ , brain region-specific decline in glucose metabolism, and altered mitochondrial dynamics and function (4, 5). There is increasing evidence that AD is a multifactorial and heterogeneous disease with multiple contributors, including cerebrovascular disease (6–10). There is currently no therapeutic intervention to prevent cognitive decline and the development of AD.

Altered lipid metabolism in the brain is characteristic of AD (11–15). The brain is the second most lipid-rich organ in the body, after adipose tissue. Instead of being used for energy storage, brain lipids are critical building blocks for the cell membranes of neurons, astrocytes, and myelin sheaths of oligodendrocytes. Lipids account for half of the dry matter of the brain (13). The brain can synthesize only a few fatty acids; thus, most fatty acids must enter the brain from the blood across the blood–brain barrier (BBB) (16). Over one-third of brain lipids are long-chain PUFAs (17). DHA (22:6), an ω -3 PUFA, constitutes about half of the PUFA content of the

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Abbreviations used: AD, Alzheimer disease; ABCA7, ATP-binding cassette transporter A7; BBB, blood–brain barrier; FABP, fatty acid binding protein; FATP, fatty acid transport protein; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPCAT, lysophosphatidylcholine acyltransferase; MFSD2A, major facilitator superfamily domain-containing 2A (sodium-dependent LPC symporter 1); PLA₁, phospholipase A₁; PLA₂, phospholipase A₂; TG, triacylglycerol.

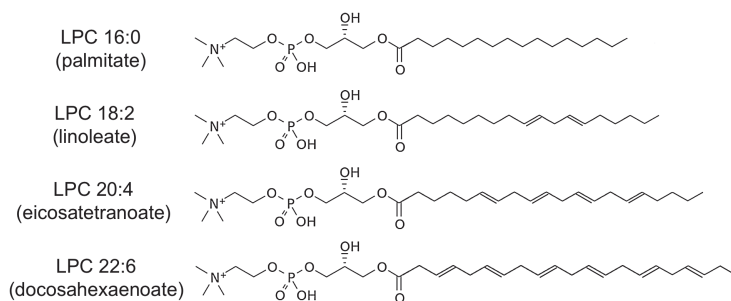


FIGURE 1 Examples of LPC species, showing fatty acid chains in the *sn*-1 position. LPC, lysophosphatidylcholine.

brain (17) and must be obtained from the circulation, since synthesis of DHA in the brain is negligible (17). Lower DHA concentrations have been described in regions of the brain most affected by AD (18–25).

Cholesterol and nearly all lipoproteins cannot cross the BBB under normal physiological conditions (16, 26–29). There are at least 2 pools by which plasma fatty acids supply the brain: free (nonesterified) and esterified in the form of lysophosphatidylcholine (LPC). Since the 1990s, studies showed that fatty acids bound to LPCs are more efficiently transported across the BBB into the brain than free fatty acids (30–33); however, the biological mechanism was not clear. In 2014, Nguyen and colleagues (28) discovered that major facilitator superfamily domain-containing 2A (MFSD2A), an orphan transporter, now known as sodium-dependent LPC symporter 1, is a specific receptor for LPC. LPCs transport long-chain fatty acids such as DHA across the BBB (28).

The aim of this Perspective is to present the potential role of circulating LPCs in the pathobiology of AD. I will review the structure of LPC, the main pathways in LPC metabolism, biological functions of LPC, emerging knowledge of MFSD2A, and transport of long-chain fatty acids across the BBB, and how these new findings relate to observations from epidemiological, clinical, and pathological studies of AD. Of the PUFAs, the emphasis is placed on DHA, as this PUFA has been the main fatty acid that has been studied in relation to LPC metabolism and AD. The biological pathways involving LPC are potentially amenable to intervention.

Current Status of Knowledge

Metabolism of LPC: how does it affect PUFA bioavailability?

Chemistry, digestion, and absorption of LPC.

The chemical structure of LPC is a phosphocholine head-group and glycerol backbone linked to a variable fatty acid bound at either the *sn*-1 or *sn*-2 position (Figure 1). In tissues and plasma, PUFAs are predominantly bound at the *sn*-2 position in LPC, whereas SFAs are mostly bound at the *sn*-1 position (29). The metabolic pathways by which DHA in the diet enters the pool of circulating LPC that is available for transport across the BBB by MFSD2A are shown in Figure 2. Seafood and fish are the major dietary source of DHA, especially cold-water fatty fish such as salmon, herring, tuna, anchovies, and sardines (30). A large

portion of ω -3 PUFAs in fish muscle is esterified in LPC and in phosphatidylcholine (31–33). In phosphatidylcholine occurring in fish and seafood, DHA is predominantly found in the *sn*-2 position, but in roe (34) and krill (35), a small portion of DHA has been described in the *sn*-1 position. The position of DHA at either the *sn*-1 or *sn*-2 position of phosphatidylcholine in food or supplements is relevant to the metabolism of DHA. In the proximal intestinal lumen, pancreatic phospholipase A₂ catalyzes the hydrolysis of the ester bond at the *sn*-2 position of phospholipids to yield free fatty acids and *sn*-1 LPC (36) (Figure 2). LPCs in the lumen are then absorbed into enterocytes by simple diffusion and enter the portal circulation (36, 37). In the liver, some LPCs are re-esterified to phosphatidylcholine by LPC acyltransferase (LPCAT) 3 (LPCAT3) (38). Some of the phosphatidylcholine that is esterified with DHA is remodeled in the liver and secreted into blood as LPC with DHA at the *sn*-2 position (39). Small amounts of LPC with DHA at the *sn*-2 position can also be formed from triacylglycerols (TGs), but the conversion is not efficient (39).

LPC in the circulation.

Albumin is the primary transporter of LPC in plasma (40), with a smaller amount of LPCs transported by lipoproteins (41) and α 1-acid glycoprotein (42). Total LPCs circulate in the 100–300- μ M range in plasma. The most abundant LPCs in human plasma are LPC palmitate (16:0), LPC stearate (18:0), LPC oleate (18:1), LPC linoleate (18:2), and LPC eicosatetraenoate (20:4), and other species include LPC eicosapentaenoate (20:5) and LPC docosahexaenoate (22:6; DHA) (41). The distribution of LPC species in human serum is shown in Figure 3. The sources of LPCs in human plasma include LPC directly absorbed from the diet (28, 39, 43), LPC generated by phospholipase A₂ (PLA₂) activity on phosphatidylcholine during digestion and then absorbed in the gut, LPC generated by PLA₂ activity on phosphatidylcholine in membranes (Lands' cycle) (44), and phospholipase A₁ (PLA₁) activity on phosphatidylcholine in the liver (45, 46). Endothelial lipase cleaves fatty acids from HDL phosphatidylcholine at the *sn*-1 position (47), generating LPC with a fatty acid at the *sn*-2 position. The fatty acid is then released from LPC through lysophospholipase activity of endothelial lipase (47). Lecithin-cholesterol acyltransferase can also generate LPC by deacylation of phosphatidylcholines primarily at *sn*-2 on the surface of HDL (48).

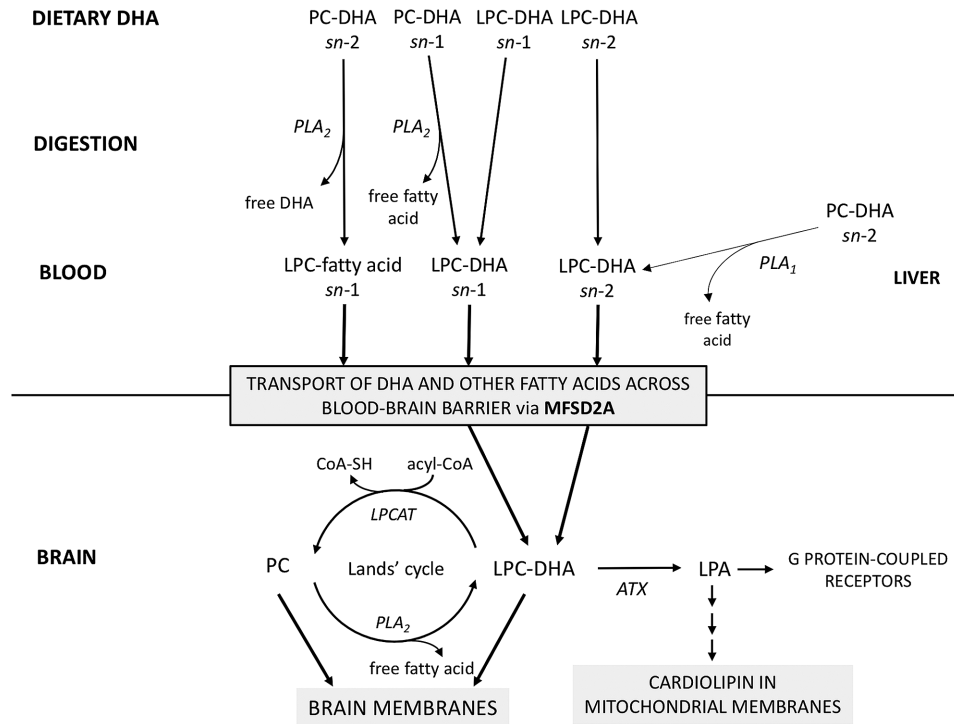


FIGURE 2 Metabolic pathway of LPC from the diet to the brain, with an emphasis on LPC-DHA because of the importance of DHA in the brain (17). Dietary sources of DHA are seafood and fish, which contain DHA esterified in LPC (31–33) or in PC. PCs in the diet generally have saturated fatty acids esterified in the *sn*-1 position and PUFAs such as DHA in the *sn*-2 position (39). During digestion, PLA₂ cleaves fatty acids from the *sn*-2 position of PC in the gut, generating LPC with fatty acids at the *sn*-1 position. LPC-DHA is absorbed by diffusion across enterocytes, circulates in the blood, and is transported by MFSD2A across the blood–brain barrier. MFSD2A transports LPCs with fatty acids at either *sn*-1 or *sn*-2 with equal efficiency into the brain (49). Through the Lands’ cycle, LPC-DHA is remodeled in brain membranes as PC via LPCAT or converted back to LPC via PLA₂. LPC-DHA can be converted to LPA by ATX, with DHA becoming incorporated in cardiolipin in mitochondrial membranes. LPA can bind to specific G protein–coupled receptors. Some LPC-DHA is generated by PLA₁ on PCs in the liver, but the conversion is not efficient (39). ATX, autotaxin; CoA-SH, coenzyme A; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPCAT, LPC acyltransferase; MFSD2A, sodium-dependent LPC symporter 1; PC, phosphatidylcholine; PLA₁, phospholipase A₁; PLA₂, phospholipase A₂.

LPC and fatty acid transport into the brain via MFSD2A.

In 2008, MFSD2A was originally described as a member of the major facilitator domain-controlling family of membrane proteins and an orphan transporter. During feed deprivation in mice, MFSD2A was induced in liver and brown adipose tissue (50). Observations in *Mfsd2a* knockout mice suggested that MFSD2A was a nutritionally regulated gene that played a role in growth and lipid metabolism (51). Although MFSD2A is ubiquitously expressed in brain and was considered to play an important role in brain functioning, no ligand for the receptor was identified at the time (51). In 2014, Nguyen and colleagues (28) demonstrated that MFSD2A is a transporter of long-chain fatty acids across the BBB that are esterified to LPC. MFSD2A is a transmembrane protein located exclusively on the luminal membrane of endothelial cells that line the blood vessels in the brain (28, 52). MFSD2A transports LPCs with fatty acids that contain ≥ 14 carbons across the BBB (Figure 2) (28). *Mfsd2a* knockout mice exhibit an $\sim 60\%$ decrease in brain DHA,

cognitive impairment, neuronal loss in the hippocampus, microcephaly, motor dysfunction, and shorter lifespan (28, 51). Brain uptake of LPC oleate and LPC-DHA was reduced by 80% and 90%, respectively, in *Mfsd2a* knockout mice compared with wild-type mice. *Mfsd2a* knockout mice had $\sim 30\%$ lower brain weight than wild-type mice (28). Free DHA supplementation did not increase brain weight or brain DHA in *Mfsd2a* knockout mice (28). In contrast, DHA concentrations in heart and liver were not significantly different between *Mfsd2a* knockout and wild-type mice (28), demonstrating that MFSD2A affected long-chain fatty acid transport and deposition in the brain but not in other organs.

The MFSD2A receptor contains 12 transmembrane helices and connecting loops, a conserved sodium-binding site, a phosphate headgroup binding site, a hydrophobic cleft to accommodate a hydrophobic hydrocarbon tail, and 3 sets of ionic locks to stabilize the outward-open conformation (52). Ligand docking studies showed that Lys-436 is a key residue for LPC transport and forms a salt bridge with the

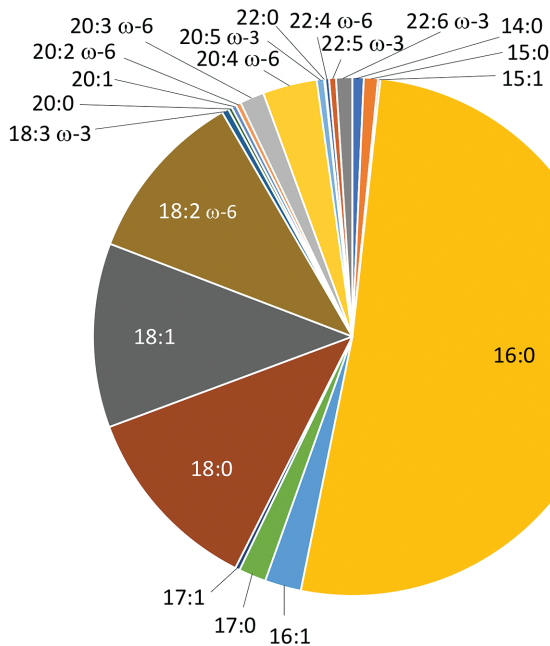


FIGURE 3 Distribution of 21 serum LPC species as measured by LC–tandem MS (53) in 100 women, aged 71–89 y, in the Women’s Health and Aging Study II, a population-based study of the two-thirds least-disabled women living in the community (RD Semba, P Zhang, LP Fried, previously unpublished data, 2019). LPC, lysophosphatidylcholine.

negative charge on the phosphate headgroup of the LPC (52). In transport by MFSD2A, Quek and colleagues (52) proposed that LPCs are “flipped” within the transporter cavity by pivoting around Lys-436, with net transport from the outer leaflet to the inner leaflet of the plasma membrane.

In mice, dietary LPC eicosapentaenoate increased brain total ω -3 fatty acid content nearly 3-fold compared with mice receiving carrier alone or free (unesterified) eicosapentaenoate (54). Dietary LPC docosahexaenoate increased brain DHA content by >2-fold after 30 d and improved memory in mice, whereas free DHA did not alter brain DHA content and had no effect on memory (49). MFSD2A transports LPC with fatty acids esterified at either the *sn*-1 or *sn*-2 position with equal efficiency into the brain (49). Feeding studies in rats show that LPC-DHA is the preferred carrier of DHA across the BBB, as DHA in the form of LPC enriches DHA concentrations in brain (29). In contrast, DHA esterified in TGs, also known as triglycerides, did not increase DHA in brain tissues (29). After LPCs are transported into the brain, LPCs undergo physiological processes, such as the Lands’ cycle.

The consequences of disrupting LPC transport of long-chain fatty acids across the BBB are demonstrated in humans with genetic mutations in MFSD2A. In 2 families with inactivating MFSD2A mutations in conserved residues (p.Thr159Met, or p.Ser166Leu), affected individuals had a lethal microcephaly syndrome associated with inadequate

uptake of LPC from the circulation (55). Patients with MFSD2A mutations had ~80% higher total plasma LPC concentrations (LPC palmitate, LPC stearate, LPC oleate, LPC linoleate) compared with healthy age-matched controls and heterozygous parents (55). Individuals with a homozygous mutation in a highly conserved MFSD2A residue, p.Ser339Leu, had a nonlethal, progressive microcephaly syndrome characterized by intellectual disability, spasticity, and absent speech (56). Total plasma LPC concentrations were 54% higher in patients homozygous for the p.Ser339Leu variant compared with healthy controls and unaffected siblings (56). A homozygous missense mutation in MFSD2A (p.Pro402His) was characterized by microcephaly, hypotonia, appendicular spasticity, dystonia, strabismus, and global developmental delay; and neuroimaging showed a large reduction in white matter volume consistent with hypomyelination and enlarged lateral ventricles (57). Plasma LPC concentrations were elevated in the affected children compared with the mother and healthy controls (57). Elevated plasma LPC concentrations have also been noted in *Mfsd2a* knockout mice compared with wild-type mice (55). The observations from both human and rodent studies suggest that defective MFSD2A function is associated with elevation in circulating LPCs due to failed cellular uptake (55).

In *Mfsd2a* knockout mice, DHA content in brain is greatly reduced but not absent, suggesting that there are alternative mechanisms by which long-chain fatty acids such as DHA can cross the BBB and supply the brain. In human plasma, 55% of DHA circulates in LPC and 45% of DHA circulates as free fatty acids (unesterified) bound to albumin (41, 58). Free fatty acids have been proposed to cross the BBB by passive diffusion (59), fatty acid transport proteins (FATPs) (60–62), or fatty acid binding proteins (FABPs) (63, 64). The BBB is not very permeable to diffusion by long-chain fatty acids (59). FATP1 appears to facilitate fatty acid uptake across the BBB (62), but knockout of *Fatp1* has not yet demonstrated the necessity of FATP1 for fatty acid uptake by the brain (64). FABP5, a cytosolic protein, can transport DHA across the BBB (63). *Fabp5* knockout mice had a modest reduction (~15%) in brain DHA but brain weight similar to wild-type mice (64) and a normal phenotype similar to wild-type mice (65). The membrane protein CD36 was a candidate for free fatty acid transport across the BBB, but *Cd36* knockout mice had no alterations in brain PUFA concentrations (66). No differences were found in FATP1, FABP5, or CD36 mRNA expression in the cerebral cortex in DHA-deficient or DHA-supplemented rats, despite a large difference in brain DHA content, suggesting that brain DHA uptake did not require FATP1, FABP5, or CD36 for transport (67). It has been argued from kinetic studies in rats that nonesterified DHA may be the major pool of DHA supplying the brain (68). The mechanisms by which PUFAs enter the brain have been a subject of debate; animal and clinical studies suggest that multiple pathways may exist for PUFA import into the brain. Of the 2 major fatty acid pools available to the brain (41, 58, 69), supplementation studies of LPCs versus free fatty acids

(29, 54, 49, 58, 70–72), developmental studies (73), knockout models (28), and human genetic studies (55–57) suggest that the plasma LPC pool is the dominant source of long-chain fatty acids for the brain.

Biological functions of LPC

The main biological functions of LPC are the transport of long-chain fatty acids to the brain, as described in detail above, remodeling of cell membranes, cell signaling, and biosynthesis of cardiolipin. In membranes of different cell types and organelles, LPCs modulate the fatty acid composition of glycerophospholipids through the Lands' cycle (44). Phospholipases, such as PLA₂, release fatty acids from phosphatidylcholines, where they are made available for β -oxidation by mitochondria. LPCATs, such as LPCAT2 or LPCAT3, catalyze the reacylation of LPCs using acyl-CoA. The actions of PLA₂ and LPCATs remodel the fatty acid composition of membranes (Figure 2) (44) and distribute fatty acids in LPCs in other phospholipids in the brain (74, 75).

LPCs can serve as ligands for specific G protein-coupled receptors such as GPR4, G2A, and GPR119 (76, 77). Autotaxin converts LPCs to lysophosphatidic acid (LPA) (78). There are specific LPA receptors, LPA_{1–6}, that are involved in growth and differentiation (79). LPCs and LPAs modulate cell migration, adhesion, growth, insulin secretion, glucose uptake, and other processes as their receptors are expressed in a wide variety of tissues (79).

Cardiolipin is a unique dimeric phospholipid that is specific to mitochondria and an essential component of mitochondrial membranes. Cardiolipin is involved in maintaining structural organization of mitochondrial membranes and facilitating normal electron transport chain function and generation of ATP. LPCs are precursors in the synthesis of cardiolipin. Autotaxin hydrolyzes LPCs to LPAs (80, 81). The acylation of glycerol-3-phosphate also generates LPAs, which are acylated to phosphatidic acid (82), and converted to nascent cardiolipin via cytidine diphosphate-glycerol, phosphatidyl-glycerophosphate, and phosphatidylglycerol. Nascent cardiolipin contains 4 fatty acid chains but then undergoes cycles of structural remodeling by tafazzin (83). Tafazzin has no substrate preference; substrate availability influences the final form of cardiolipin in mitochondrial inner membranes (84). Both linoleic acid (18:2n–6) and DHA are major constituents of cardiolipin in brain (85). Since linoleic acid is an essential fatty acid and synthesis of DHA in the brain is negligible, it is likely that the supply of linoleic acid and DHA for cardiolipin is dependent on the plasma pool of LPC linoleate and LPC docosahexaenoate for transport by MFSD2A across the BBB.

Plasma LPCs and adverse human phenotypes

Observational studies in humans show that adverse phenotypes, chronic diseases, and systemic inflammation are generally associated with low circulating LPC concentrations. These epidemiological observations contrast with in vitro studies and animal models, which suggest that LPCs have

proinflammatory and proapoptotic properties (86). In vitro studies show that LPCs have deleterious effects when there is insufficient buffering in culture (87). Injection of excessive amounts of LPC into mouse brain at 400 times greater concentration than what causes toxicity in vitro induces cell death and demyelination (87). In contrast, human studies largely suggest that adverse biological phenotypes are associated with low rather than excessive LPC concentrations.

Plasma LPCs decrease with age (88, 89) and are lower in obesity (89, 90). In cross-sectional studies, circulating LPC concentrations were lower in adults with type 2 diabetes compared with controls (90–98). Stroke patients had lower serum LPC stearate and LPC linoleate compared with controls (99). In prospective studies, low circulating LPC concentrations independently predicted adverse aging-related outcomes such as coronary artery disease (100–102), prediabetes and diabetes (93–97), and cancer (103, 104). In 504 adults, aged ≥ 50 y in the Baltimore Longitudinal Study of Aging, slow gait speed was associated with low plasma LPCs (105). Low plasma LPCs were associated with impaired skeletal muscle mitochondrial oxidative capacity (106). In healthy men, regular aerobic exercise increased serum LPC concentrations after 10 wk of intervention (107). Lower plasma LPC concentrations were associated with greater systemic inflammation (100, 108, 109). Overfeeding with a high-fat diet decreased plasma LPC concentrations (110). In contrast, consumption of a Mediterranean diet for 1 y increased plasma LPCs after 1 y in a controlled trial (111). LPCs could be related to adverse phenotypes that do not directly involve the brain and MFSD2A via LPC pathways such as the Lands' cycle (44), cell signaling (76, 77), and cardiolipin synthesis (112). It is notable that low circulating LPCs are associated with several risk factors for dementia, including obesity, physical inactivity, and diabetes (113); systemic inflammation (114); and slow gait speed (115).

Lipid alterations in AD

Alterations in LPCs.

Lower LPC concentrations in blood, cerebrospinal fluid, and brain tissue have been described in adults with AD compared with controls (116–127). Although analytical platforms varied in the LPC species that were measured, LPC linoleate was measured in all studies and was consistently lower in AD compared with controls (116–120). Studies of circulating LPCs and AD have been limited by small sample sizes, use of broad, untargeted metabolomic discovery platforms (110, 111), limited coverage of long-chain LPC species, and relative rather than absolute quantification of LPC species. Cerebrospinal fluid LPC concentrations were lower in AD compared with controls (123). Lower LPC concentrations have been described in the prefrontal cortex (124), frontal cortex (125), temporal cortex (125, 126), and cerebellum (125) of patients with AD compared with controls. Lower LPC heptadecanoate (17:0) and LPC stearate concentrations were found in middle frontal gyrus, inferior temporal gyrus, and cerebellum in AD compared with controls (127).

Three abnormalities directly involving LPC metabolism have been identified in the brain in AD. In the Lands' cycle, PLA₂ activity, which generates LPCs from phosphatidylcholines, was decreased, whereas LPCAT activity, which recycles LPCs into intact membrane phosphatidylcholines, was increased in the AD brain compared with control (128, 129). Increased expression of autotaxin, which converts LPC to LPA, was reported in the frontal cortex of adults with AD (130). The ATP-binding cassette transporter A7 (*ABCA7*), a novel risk gene for AD (131), is an LPC transporter (132). Loss-of-function variants of *ABCA7* are associated with an increased risk of AD (133–136). *ABCA7* is expressed in neurons and microglial cells in the cerebral cortex (132). *ABCA7* expression was lower in AD brain compared with controls (132). *ABCA7* deficiency is associated with greater amyloid- β pathology in mouse and in vitro models (137–139).

Lipid alterations in the brain.

AD is characterized by alterations in phospholipid, sphingolipid, fatty acid, and cholesterol metabolism in the brain (11–14). Decreased phosphatidylinositol, phosphatidylethanolamine, and ethanolamine plasmalogen content have been described in frontal, temporal, and parietal cortex of AD brain compared with controls (140–147). Ceramide is a sphingolipid that serves as both a product of sphingomyelin or glycosphingolipid catabolism and as a precursor to sphingolipid synthesis (148). Elevated ceramide content was described in the frontotemporal lobe (149), temporal cortex (139), middle frontal gyrus and superior frontal cortex (15), and cerebellum in AD compared with controls (15, 150). Sulfatides, a class of sphingolipids that are abundant in the myelin sheath surrounding axons, were reduced by 93% and 58% in gray and white matter, respectively, in frontal, parietal, and temporal lobes, in early AD compared with controls (150).

The adult brain contains ~50–60% of dry weight as lipids, of which 35% are PUFAs (17). DHA comprises approximately half of PUFA content in the brain and contributes to membrane fluidity with its long carbon chain and high degree of unsaturation (17). AD is characterized by decreased DHA content in brain phospholipids by 15–60%, depending on brain region (18, 19). Lower DHA has been described in phospholipids in the frontal cortex (20–22), temporal cortex (22), and hippocampus (21, 24, 25, 144) in adults with AD compared with controls. Lipid rafts are specialized membrane microdomains that are enriched in sphingolipids and sterols and play a role in endocytosis and signal transduction (151). Decreased DHA has been described in lipid rafts in the frontal cortex and entorhinal cortex in AD compared with controls (152, 153). In addition to a structural role in membranes, DHA has anti-inflammatory properties and plays a role in neuroprotection. DHA contributes to clearance of amyloid- β in the brain (154, 155). DHA and DHA-derived metabolites such as neuroprotectin D1 (25, 156), resolvins (157), and maresins (158) protect against neurodegeneration. DHA reduces expression of transcription factor NF- κ B (159) and proinflammatory gene expression (160).

Can dietary LPCs and PUFAs protect against cognitive decline and AD?

Observational studies show that a higher dietary intake of PUFAs is associated with a lower risk of cognitive decline and AD. In a meta-analysis of 181,580 adults from 21 studies, a 0.1-g/d increase in dietary DHA intake was associated with a lower risk of dementia (RR: 0.86; 95% CI: 0.76, 0.96) and AD (RR: 0.63; 95% CI: 0.51, 0.76) (161). DHA must be obtained from the diet, and the main dietary sources of DHA are seafood and fish as noted previously (30). The precursor of DHA, α -linolenic acid (18:3 ω -3), an essential fatty acid, is not synthesized by the body and is poorly converted to DHA in mammals (17). In a pooled analysis of 23,688 adults, aged ≥ 65 y, with median follow-up of 4–9 y, higher consumption of fish was associated with slower decline in global cognition and memory (162).

In contrast to observational studies, clinical trials have shown no impact of ω -3 PUFA supplementation on cognitive decline. In a randomized, double-blind, placebo-controlled trial of DHA supplementation in 402 older adults with mild to moderate AD, daily DHA supplementation did not slow the rate of cognitive decline compared with placebo over 18 mo (163). A randomized controlled trial of ω -3 PUFAs in 204 adults with mild to moderate AD showed no effect on cognitive decline after 6 mo (164). Supplementation with ω -3 PUFAs for 4 y duration in 1748 adults, aged 45–80 y, showed no effect on cognitive function compared with placebo (165). A meta-analysis of 12 controlled trials involving 6794 older adults showed no impact of ω -3 PUFA supplementation on cognitive decline (166).

It is important to note that the supplements used in these clinical trials provided ω -3 PUFAs in the form of TGs. In addition to phosphatidylcholines and LPCs, TGs are a major dietary source of PUFAs, and in TGs, PUFA can be distributed among the 3 positions: *sn*-1, *sn*-2, or *sn*-3. Fish oil and squid oil contain DHA primarily in the *sn*-2 position (167, 168). Fish are rich in DHA esterified in TGs. Fish oil for supplements that are rich in TG-DHA is most commonly extracted on an industrial scale by wet pressing, a process that involves 4 steps: fish cooking, pressing, decantation, and centrifugation. Algal oils are a rich source of DHA and include DHASCO-T[®] and DHASCO-S[®] (DSM Nutritional Products), which contain TGs derived from *Cryptothecodinium cohnii*, a dinoflagellate microalgae, and *Schizochytrium* spp., a unicellular eukaryote in the family Thraustochytriaceae, respectively. In algal oil, DHA is randomly distributed in any of the 3 positions of TGs (169). During digestion, pancreatic lipase hydrolyzes TGs into monoacylglycerol and free fatty acids in the jejunum, which are then taken up by enterocytes and resynthesized into TGs (170). In the blood, TGs are transported in lipoproteins and can deliver DHA to peripheral tissues (39) but not the brain (16, 26–29, 39, 49). ω -3 PUFA supplementation using TGs may have had no effect on cognitive decline because the ω -3 PUFAs were not esterified in LPCs, which transport long-chain fatty acids across the BBB via their specific receptor MFSD2A (28).

TABLE 1 Questions for future research relating to LPC and Alzheimer disease^{1,2}

- What is the fatty acid species composition of LPCs and phosphatidylcholine isomers in seafood and fish?
- In DHA-fortified eggs, which lipids (i.e., TG, phosphatidylcholine, LPC) are esterified in DHA and in what concentrations?
- Do plasma LPC fatty acid species concentrations correlate with the dietary intake of fatty acids esterified to LPC or to *sn*-1 phosphatidylcholines?
- What are plasma LPC concentrations in omnivores, pescatarians, vegetarians, and vegans?
- What is the specific concentration of DHA esterified at the *sn*-1 position in phosphatidylcholine of krill oil?
- Can LPC-DHA be synthesized from non-animal-source foods such as microalgae?
- What is the relation of the concentrations of LPC species in plasma, cerebrospinal fluid, and brain tissue in healthy adults and those with Alzheimer disease?
- Do older adults with impaired cognition have lower plasma LPC concentrations than healthy controls?
- Are plasma LPC concentrations associated with the severity of Alzheimer disease?
- Do low plasma LPC concentrations independently predict cognitive decline and incident dementia in cognitively normal older adults?
- Can LPC-DHA supplements, phosphatidylcholine-DHA supplements, or LPC-DHA-rich foods reduce the risk of cognitive decline and Alzheimer disease in cognitively normal older adults?
- Can LPC-DHA supplements, phosphatidylcholine-DHA supplements, or LPC-DHA-rich foods reduce the risk of progression to Alzheimer disease in adults diagnosed with mild cognitive impairment?

¹LPC, lysophosphatidylcholine; TG, triacylglycerol.

²LPC measurements made using highly sensitive, specific, and accurate liquid chromatography-tandem mass spectrometry platforms that provide targeted in-depth coverage of LPC species

Can diet or supplements be optimized to increase the bioavailability of DHA to the brain?

As noted previously, fish contain DHA esterified in LPC or in the *sn*-2 position of phosphatidylcholines, which would have higher bioavailability to the brain (Figure 2). To date, there have been no large, controlled, randomized trials that evaluate long-term fish consumption as an intervention to reduce cognitive decline in older adults. Animal brain is a rich dietary source of DHA, but consumption is presently limited to certain cuisines and cultures. In krill oil, processed from Antarctic krill (*Euphasia superba*), DHA is found mainly esterified in phosphatidylcholine, bound at either the *sn*-1 or *sn*-2 position (35). Krill oil may potentially have DHA that is bioavailable to the brain using LPC as a carrier if a substantial portion of DHA in krill oil is esterified at the *sn*-1 position. Some commercial supplements of ω -3 PUFAs are derived from fish roe, which contain some DHA esterified in the *sn*-1 position (34). Hen egg yolk normally contains a small amount of DHA, but the DHA content of egg yolk can be increased substantially through fortification by feeding fish oil or algal powder to laying hens (171–174). The specific lipids in which DHA is esterified in fortified egg yolks have not been well characterized. Cow milk normally contains little DHA. The DHA content of milk can be increased by adding fish oil to cow feed (175), and some commercial cow milk is available that has been fortified with DHA in the form of TGs in microalgal oil.

A synthetic preparation of oral LPC-DHA, AceDoPC[®] (LipTher), contains DHA esterified in the *sn*-2 position of LPC (176). The *sn*-1 position is blocked to prevent acyl migration of DHA from *sn*-2 to *sn*-1 (176). Acyl migration of fatty acids can occur spontaneously from *sn*-2 to *sn*-1 under physiological conditions. However, a recent study suggests that LPC with DHA esterified at *sn*-2 is stable without substantial acyl migration to *sn*-1 (177). Since MFSD2A transports LPC with fatty acids at either the *sn*-1 or *sn*-2 across the BBB with equal efficiency (49), it is

unclear whether this proprietary form of LPC-DHA will confer any advantage over naturally occurring LPC-DHA in the bioavailability of DHA to the brain. A dietary oil rich in LPC-DHA can be produced by treating squid oil with hydrolysis (178). Oral administration of this LPC-DHA-rich oil increased DHA content in the hippocampus in an experimental rat model (178).

The recent studies of LPCs raise potential concerns for vegetarians and vegans, because DHA is absent from vegan diets and is present only in limited amounts in vegetarian diets (179). Plasma, erythrocyte, and tissue concentrations of DHA are lower in vegetarians than in nonvegetarians (179). Algal oils, a rich nonanimal source of DHA, are used by some vegetarians and vegans (180); however, DHA is esterified in TGs in algal oils. Under conditions of low dietary intake of DHA, there may be compensatory increases in alternative pathways of DHA transport into the brain, such as passive diffusion (59), FATP1 (62), or FABP5 (64), but the importance of these pathways in humans has not been well characterized.

Conclusions

Animal and clinical studies suggest that the pool of circulating LPCs is a major source of long-chain fatty acids such as DHA for the brain. A low circulating pool of LPCs may play an important role in the pathobiology of AD. There are still many unanswered epidemiological and translational research questions that could provide greater insight into LPCs and AD (Table 1), including the LPC composition of seafood, fish, and fortified foods. Whether serum LPC concentrations are associated with dietary intake of LPC-rich foods, such as fish that contain high LPC-DHA content, has not been well characterized. Previous studies of circulating LPC and AD in humans have utilized broad, untargeted discovery metabolomic platforms (116–120). Highly sensitive, specific, and accurate LC-tandem MS assays that provide targeted in-depth coverage of LPC species

in biofluids and tissues (53, 181) could be applied in future clinical studies, epidemiological studies of cognitive decline and AD, and in the analysis of foods. The relation of serum LPC concentrations with cognitive decline and AD has not been well characterized in human studies. Whether adults with low serum LPC concentrations are at greater risk of developing cognitive decline and AD remains a major gap in knowledge. Preventing and treating cognitive decline and AD remain challenging. Dietary and/or lifestyle changes have shown promise in reversing or improving cognitive decline (182, 183). The LPC pathway is a promising area for future investigators to identify modifiable risk factors for AD.

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