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Towards a whole-body systems [multi-organ] lipidomics in Alzheimer's disease

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SUMMARY

Preclinical and clinical evidence suggests that docosahexaenoic acid (DHA), an omega-3 fatty acid derived from diet or synthesized in the liver, decreases the risk of developing Alzheimer's disease (AD). DHA levels are reduced in the brain of subjects with AD, but it is still unclear whether human dementias are associated with dysregulations of DHA metabolism. A systems biological view of omega-3 fatty acid metabolism offered unexpected insights on the regulation of DHA homeostasis in AD¹. Results of multi-organ lipidomic analyses were integrated with clinical and gene-expression data sets to develop testable hypotheses on the functional significance of lipid abnormalities observed and on their possible mechanistic bases. One surprising outcome of this integrative approach was the discovery that the liver of AD patients has a limited capacity to convert shorter chain omega-3 fatty acids into DHA due to a deficit in the peroxisomal D-bifunctional protein. This deficit may contribute to the decrease in brain DHA levels and contribute to cognitive impairment.

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of adult dementia, affecting an estimated 35 million of elderly people worldwide². As life span increases, this number is expected to climb to over 80 million by 2040. This neurodegenerative disorder is characterized clinically by progressive memory impairment, deterioration of language, and visuospatial deficits³. Age is the most important factor that predisposes to the non-familial or sporadic form of the disease. How aging might interact with other pathogenic factors for AD, such as abnormal accumulation of beta-amyloid (A β) peptides and hyperphosphorylated tau protein in the brain⁴, is still unknown. It appears, however, that obesity, diabetes, and atherosclerosis – age-related pathologies that are closely associated with systemic dysfunctions in lipid metabolism – may be involved^{3, 5}.

DHA in subjects with AD

Epidemiological studies and animal experiments have provided evidence that increased docosahexaenoic acid (DHA) consumption decreases the risk of developing AD^{6–17}. It is still unclear, however, how the metabolism of DHA is affected in AD. A comprehensive

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description of the DHA metabolism in AD requires placing DHA in the context of the interconnected network of its substrates and products. Thus, the development of a lipidomic approach that considers the entire omega-3 fatty acids system, rather than its individual components in isolation, is essential to elucidate a role for DHA in AD. Such an approach cannot be limited to the brain. Indeed, in conditions of low dietary omega-3 fatty acids intake (e.g. Western diets), DHA brain levels depend on the liver's capacity to metabolize diet-derived omega-3 fatty acids^{18–20}. Therefore, a systems biological approach that includes the liver-brain axis is required to investigate DHA regulation in AD.

Biological roles of DHA

DHA is an omega-3 essential fatty acid that is highly enriched in the brain and the eyes, where it accumulates during late fetal and early neonatal life. Because of its high degree of unsaturation, the accumulation of DHA-containing phospholipids affects membrane biophysical properties such as fluidity, permeability and compressibility, and alters the function of many integral and membrane associated proteins^{21–23}. High levels of DHA have been found in growth cones²⁴, synaptic plasma membranes and synaptic vesicles²⁵; however, the functional significance of this localization is still unclear. For example, it has been suggested that the increased membrane fluidity may regulate the speed of signal transduction²⁶, neurotransmission²⁷, and formation of lipid rafts²⁸, mediating essential processes for the neurodevelopment and functional synaptic plasticity of the brain. In addition to altering the structural functionality of neural cell membranes, DHA can be released from phospholipids due to PLA₂ activation^{29, 30}, acting as a signaling molecule. Non-esterified DHA may bind Retinoid X Receptor, a ligand-activated transcription factor³¹, or it may be oxygenated to produce various bioactive lipids. DHA oxygenation is thought to proceed through two main pathways: *i*) a lipoxygenase-mediated pathway converts DHA to resolvins and neuroprotectins such as neuroprotectin D1³², two families of lipid signals with marked antiinflammatory and neuroprotective effects^{33–35}; and *ii*) free radical-mediated peroxidation of DHA produces neuroprostanes, which are involved in oxidative stress³⁶. Both mechanisms may be relevant to the alterations in DHA levels observed in aging and AD^{33–35, 37–40}. It is likely, however, that the positive effects excited by DHA are the result of multiple signaling events, many of which remain to be discovered.

For example, DHA is known to play important roles in the cardiovascular system, which in turn may contribute to the clinical manifestation and the pathology of AD in the brain^{5, 41}. The roles of DHA on the vascular component and the cerebral parenchyma itself, however, have not been systematically explored⁴². Therefore, the contribution of liver-derived DHA in vascular dementia and, more generally in cardiovascular diseases, should be object of further investigation.

DHA in brains of subjects with AD

Numerous studies indicates that DHA serves important neurotrophic functions during the last trimester of fetal life and the first two years of childhood⁴³, but it is still unclear whether this fatty acid plays similar roles in aged subjects. Several, albeit not all, epidemiological and clinical studies suggest that higher intake of DHA decreases the risk of cognitive decline and dementia in elderly adults⁴⁴. Animal experiments support this conclusion^{7, 8, 13} and further indicate that DHA might exert these effects by promoting, directly or through biologically active metabolites, the survival and repair of neuronal cells^{45, 46}.

The cognate question of whether changes in brain DHA levels might accompany cognitive decline has been addressed using *post mortem* brain tissue from AD patients and age-matched control subjects^{34, 38, 47–52}. With some inconsistency, deficits in DHA-containing phospholipids have been reported in AD brains, but only as localized to selected brain

regions^{38, 47, 48, 50, 51, 53}. Discrepancies may be due to both 1) very small number of subjects in each series (<10 per cohort); and 2) variations in sampling and methodology. Furthermore, only one reports described the levels of non-esterified DHA, which was reported to be lower in hippocampus of AD patients than control subjects³⁴.

In conclusion, despite some disparities, the results of these investigations generally support the possibility that AD is associated with lower than normal levels of DHA in the brain⁶. In the following sections, we describe how we reexamined this possibility and searched for supporting correlative evidence that a disruption in brain DHA integrity might result from defective omega-3 fatty acid metabolism in liver.

DHA biosynthesis in human liver

Like other mammals, humans obtain DHA directly from dietary sources, especially fish, but can also produce it in liver from omega-3 fatty acid precursors present in green plant leaves^{20, 54, 55}. When food does not provide a sufficient supply of these nutrients, the liver's capacity to generate DHA may become critical to keep brain levels of this fatty acid within a normal range^{19, 55}.

A properly functioning liver synthesizes DHA from shorter-chain omega-3 precursors, such as α -linolenic acid (C18:3 omega-3) and eicosapentaenoic acid (C20:5 omega-3). A cascade of elongase and desaturase enzymes localized in the endoplasmic reticulum of the hepatocyte progressively add carbon units and double bonds to shorter-chain omega-3 fatty acids, producing the very-long-chain tetracosahexaenoic acid (C24:6 omega-3). This fatty acid is transported into peroxisomes and then converted to DHA by the sequential action of acyl-coenzyme A oxidases, D-bifunctional protein (DBP) and peroxisomal thiolases^{56–59}. Liver-derived DHA reaches the brain through the general circulation, most likely as a complex with lipid-binding proteins (e.g., albumin) that are also synthesized in the hepatocyte²⁰. Notably, whole-body β -oxidation of a single dose of ¹³C-DHA in healthy, young adults is <5% in one-month period follow-up⁶⁰, suggesting that the human body does not rapidly catabolize DHA. Recent evidence also indicates that the half-life of DHA in the human brain approximates 2.5 years¹⁸, with a consumption rate of 3.8 mg/day¹⁸. These observations indicate that the need for DHA in humans might be covered by dietary α -linolenic acid when liver metabolic conversion machinery is intact and the diet has a high α -linolenic acid content¹⁹. For example, it has been calculated that assuming an average ingestion of 1,400 mg/day of α -linolenic acid^{61, 62}, and that 0.5–10% of ingested α -linolenic acid is converted to DHA^{63–67}, the liver is able to synthesize DHA at rates of 7–140 mg/day, 1.8–36-fold, respectively, the human brain requirement¹⁸. This evidence suggests that liver-mediated DHA biosynthesis may be sufficient (and indeed essential) for normal brain activity.

A lipidomic approach for the study of AD

Acquiring a broad view of lipid metabolic pathways in AD might offer unexpected insights on the regulation of DHA homeostasis, which may contribute the pathogenesis of this disease. Technical progress in lipid analysis has opened unprecedented opportunities for the field of lipidomics – the branch of metabolomics that studies large-scale lipid profiles in healthy and diseased tissues⁶⁸. AD is an especially promising area of application for lipidomics. Risk factors for AD – such as aging and genetic vulnerability – alter specific lipid pathways in brain and peripheral tissues, and these alterations may influence in turn AD progression (Fig. 1). In our studies, we used a functional lipidomic approach that has two key features. First, biological specimens from clinically characterized AD patients and closely matched controls were analyzed by liquid chromatography/mass spectrometry (LC/MS). Second, the obtained information was integrated with clinical and molecular data to

generate testable hypotheses on the functional significance of newly described lipid abnormalities, and on the possible mechanistic bases for their development. The application of this approach allowed us to uncover multiple lipid alterations in *post mortem* brain and liver tissue from AD patients, some of which strongly correlate with AD clinical symptoms.

Functional lipidomic analyses in subjects with AD

A lipidomic analysis of DHA metabolism requires (i) to analyze structurally diverse classes of lipids, and (ii) to achieve a high sensitivity of detection for low-abundance lipids. The lipid work-up procedure utilized in our studies is illustrated schematically in Figure 2⁶⁹. Organic solvent extraction and open-bed silica-gel chromatography were used to divide the lipidome into 4 fractions: *fraction 1*, which contained water-extractable polyanionic phospholipids (e.g., phosphatidylinositol-4,5-bisphosphate [PIP₂]); *fraction 2*, which included large cationic phospholipids (e.g., phosphatidylcholine [PC]); *fraction 3a*, which comprised small amphipathic and non-polar lipids (e.g., fatty acids [FA] and diacylglycerols [DAG]); and *fraction 3b*, which included large anionic phospholipids (e.g., phosphatidylethanolamine [PE]). Each lipid fraction was subjected to LC separation on appropriate C18-based columns. Following these initial steps, lipid classes and individual compounds of interest were characterized by LC/MSⁿ and then quantified using non-endogenous lipid standards. Finally, lipidomic results were integrated with clinical and gene expression profile data sets.

Lipidomics of brain tissues from subjects with AD

Our lipidomic analyses have uncovered multiple lipid alterations in the brain of AD patients¹. Some of these changes have already been documented in the scientific literature. For example, corroborating the work of Bazan and others^{45, 70}, we found that levels of non-esterified (free) DHA are reduced in brain tissues from AD patients compared to control subjects¹. Analyses of lipid fraction *3b* also confirmed that levels of DHA-containing phospholipids are decreased in AD (for review, see⁶). Our lipidome-wide search revealed, however, two aspects of AD-associated DHA deficiency, which have not been previously recognized. The first is that the positive statistical correlation between DHA content and clinical measures of dementia, which was measured by the Mini-Mental Status Examination (MMSE). Though these results do not clarify the putative role of DHA in the pathogenesis of AD, they are consistent with epidemiological surveys and animal studies corroborating the hypothesis of a link between dietary DHA intake and cognitive function (reviewed in⁶).

The second new element uncovered by our experiments is that the deficiency in DHA occurs throughout the brain, including regions such as cerebellum, which are not generally regarded as being directly involved in AD pathology. This led us to investigate a possible systemic cause for the decline in DHA levels. Previous evidence indicates a peripheral decrease of omega-3 fatty acids with AD, and suggests that increasing the levels of peripheral levels of omega-3 fatty acids may have substantial benefits in reducing their risk of cognitive decline^{71,72-76}.

Functional lipidomics of liver tissues in AD

Although AD is conceptualized as a neurodegenerative disease of the brain, there is increasing awareness that it may involve abnormalities in multiple peripheral tissues^{34, 77, 7879-83}. In this regard, several reports indicate that the liver may play an important role in peripheral A β clearance from the central nervous system⁸⁴⁻⁸⁶. To identify potential mechanisms responsible for the observed DHA deficit in AD brain, we focused our attention on the liver because of the essential contribution of this organ in supplying DHA to the brain¹ (Fig. 3). Our analyses showed that liver tissue from AD patients contains reduced

levels of DHA, but elevated levels of shorter chain omega-3 fatty acids precursors – from α -linolenic to tetracosahexaenoic acid (24:6 omega-3). This profile cannot be caused by a nutritional deficit in omega-3 fatty acids. Rather, the profile suggests a defect in the last step of DHA biosynthesis – the β -oxidative conversion of tetracosahexaenoic acid into DHA, which is catalyzed by DBP in liver peroxisomes. Two additional findings support this interpretation. First, expression of the hydroxysteroid (17- β) dehydrogenase 4 (*HSD17B4*) gene, which encodes for DBP^{58, 59, 87}, is lower in AD. Second, pristanic acid and phytanic acid, two substrates for liver DBP activity, accumulate in the liver of AD patients. Notably, no other gene included in our panel was significantly altered in liver tissue from AD patients, including those encoding for proteins involved in peroxisome biogenesis, such as *PEX13*, *PEX14* and *PEX19*. These results are consistent with those of previous studies, which have shown that genetic mutations that selectively disrupt DBP activity reduce DHA levels in human plasma and brain^{88, 89}. The pathological changes that trigger the down-regulation of liver DBP expression in AD are still unknown. One possible candidate is oxidative stress, which is known to accelerate age-dependent damage to peroxisomes^{90, 91}. Additional studies should also evaluate the existence of other possible links between liver peroxisomal function and cognition. Moreover, other aspects of DHA metabolism – such as transport and ApoE genotype^{14, 92–94} – might contribute to the observed changes and await further investigation.

Importantly, the functional significance of the peroxysomal liver dysfunction is underscored by the identification of a strong positive correlation between liver DHA content and cognitive status, indicating a previously unrecognized association between hepatic DHA homeostasis and global cognition¹. Although it is well established that patients with advanced liver diseases (e.g., hepatitis C, non-alcoholic liver steatosis and end-stage liver disease) show a decline in cognitive abilities (e.g., hepatic encephalopathy)^{95–97}, our novel findings reveal that, even in the absence of overt liver pathology, subtle molecular dysfunctions in the liver can be associated with dementia and AD pathology.

It appears, however, that an overall healthy liver is required for optimal DHA biosynthesis. It has been reported that during conditions of hepatic stress such as in chronic alcohol intake^{98, 99}, and liver steatosis and injury^{100, 101}, the levels of hepatic DHA are compromised. Supplementation of DHA has been suggested as a new therapeutic approach in the treatment of these conditions^{102, 103}. Further research will be required to determine the contribution of a dysfunctional hepatic DHA biosynthesis to cognition in relation to liver injury or impaired functioning.

Role of peroxisomal metabolism in DHA deficiency

Peroxisomes are essential for the last steps of the biosynthesis of DHA (Fig.3) and have been involved in neurodevelopment¹⁰⁴, and mental and visual health. These organelles are particularly enriched in liver and kidneys, which are also the organs deputed to the DHA biosynthesis^{105, 106}. DHA levels are extremely low in brain of patients with severe peroxisomal disorders, such as Zellweger syndrome and X-adrenoleukodystrophy, where some clinical symptoms can be improved following the administration of DHA¹⁰⁷. In particular, previous reports suggest that DHA levels were reduced in plasma and brain tissue of patients carrying DBP deficiency^{88, 89}. In light of this evidence, we should consider dietary interventions to include preformed DHA, rather than its precursors, to normalize brain content of DHA in patients with AD. Moreover, it has been shown that administration of shorter-chain omega-3 precursors of DHA, such as EPA (C20:5, omega-3), for 12 weeks was ineffective in increasing the levels of DHA in AD patients, while increasing DPA (C22:5 omega-3)¹⁰⁸.

These observations add to the accumulating evidence that only a small percent of the dietary shorter-chain omega-3 fatty acids (0.5–10%) is fully converted into DHA^{63–67}. Overall, it appears that the peroxisomal step for the biosynthesis of DHA may work as a checkpoint for the control of DHA homeostasis and it could be subject to fine regulatory mechanisms. In addition, the general functionality of peroxisomes could affect DHA metabolism. Thus, further investigation should focus on determining how the integrity and number of these organelles is affected in the livers of AD patients.

Finally, because kidneys are rich in peroxisomes and together with liver contribute to DHA biosynthesis, their contribution to the DHA biosynthesis in AD patients should be object of further investigation.

A role for lived-derived DHA in cognitive aging?

Peroxisomal function is known to decline with age⁹⁰ and this may explain the decrease in the synthesis of plasmalogens^{37, 89, 109} and DHA^{54, 110, 111} observed in elderly people. Indeed, it has been observed that DHA composition progressively declines in human and rat frontal cortex with increasing age¹¹², despite the availability of dietary short chain omega-3 PUFA^{37, 113, 114}. In a recent clinical trial, supplementation of DHA as been shown to provide a net benefit roughly equivalent to having the learning and memory skills of someone 3 years younger¹¹⁵. Overall, this evidence supports the hypothesis that peroxisomal DHA biosynthesis may have a significant role in aging and that AD is an acceleration of the peroxisomal aging process.

A role for liver-derived DHA in neuropsychiatric disorders?

In addition to AD, DHA deficits may also occur in brain and peripheral tissues from patients with neuropsychiatric illnesses, including bipolar disorder, major depressive disorder, schizophrenia^{112, 116–121}, attention deficit (hyperactivity) disorder, suicide¹²², dyslexia, autism¹²³, neuroticism¹²⁴, stress disorders, and chronic fatigue (for review see¹²⁵). It has been suggested that deficits in peroxisomal metabolism may contribute to the DHA deficit observed in some of these patients¹¹². In particular, analogous to the AD treatment¹⁰⁸, shorter chain omega-3 precursors appear to be less efficacious than DHA in the treatment of mood symptoms in bipolar disorder patients¹²⁶. Furthermore, the symptoms of depression are sometimes indistinguishable from early AD¹²⁷ and it has been reported that depression early in life may be a risk factor for the later development of AD^{128, 129}. Similar to AD, it has been suggested that the deficits in DHA observed in neuropsychiatric diseases may contribute to (i) cognitive impairment and (ii) structural brain changes, such as reduced cerebral volume, enlarged ventricles, cerebral atrophy, and frontotemporal-sulcal widening^{130–135}. In this context, peripheral DHA supplementation has been shown effective in increasing cortical gray matter volume^{135,136}, which may explain some of the benefits of this lipid on mood. In light of this evidence, the role for liver biosynthesis of DHA in the development and progression of neuropsychiatric disorders that may accompany AD requires further examination.

Conclusions and future perspective

The use of a multi-organ lipidomic approach allowed us to identify a dysfunction in the liver's ability to synthesize DHA in subjects with AD, which possibly lessens the flux of this neuroprotective fatty acid to the brain (Fig. 4). This systemic deficiency in DHA correlates with the cognitive impairment observed in AD patients and has implications in two main areas. First, interventions with omega-3 fatty acids – both dietary and supplement-based^{9, 10, 14, 93} – should take into consideration the partial inability of AD patients to complete DHA biosynthesis. For example, future clinical studies might consider using

appropriate forms of purified DHA, DHA-delivering prodrugs, or routes of administration that bypass the liver. A similar approach was shown to improve clinical symptoms in patients with severe peroxisomal disorders^{107, 137}, and it has been previously suggested in older individuals¹¹¹ or individuals with end-stage liver disease¹³⁸. Second, the altered pattern in lipid metabolism in liver produced by DBP dysfunction might be exploited to develop peripheral biomarker strategies for AD.

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Figure 1.

Scheme illustrating the core hypothesis of our study. Risk factors for AD (which include genetic-predisposition, age and, possibly, nutritional deficits) influence interacting lipid pathways throughout the body. Over time, accumulating lipid changes compound with those factors to increase the risk for AD.

Figure 2.

Schematic flow chart of our lipid work-up procedure. 1, extraction in acidic solvent; 2, extraction in water; 3, fractionation by open-bed silica-gel chromatography; elution with 3a, chloroform/methanol (9:1); 3b, chloroform/methanol (1:1). See text for details and abbreviations.

Figure 3.

Overview of DHA biosynthesis in liver. Liver transforms diet-derived α -linolenic acid (18:3 omega-3) into DHA (22:6 omega-3). In the endoplasmatic reticulum, the serial activities of Δ^6 and Δ^5 desaturases (encoded by the *FADS2* and *FADS1* genes, respectively) and elongases (such as that encoded by the *HELO1* gene) convert alinolenic acid into tetracosahexaenoic acid (24:6 omega-3). Proteins encoded by the *ABCD1* or *ABCD2* genes transport tetracosahexaenoic acid into peroxisomes. The sequential action of acyl coenzyme-A oxidase (encoded by the *ACOX1* gene), D-bifunctional protein (encoded by the *HSD17B4* gene), and various peroxisomal thiolases (not shown) convert tetracosahexaenoic acid into DHA.

Figure 4.

Hepatic DHA biosynthesis is linked to cognition. Diet-derived ALA (α -linolenic acid, 18:3 omega-3) is absorbed by the intestine and delivered to the liver where it serves as precursor for DHA. A peroxisomal dysfunction impairs the conversion of tetracosahexaenoic acid (24:6 omega-3) into DHA in the livers of subjects with AD. This systemic deficiency in DHA possibly lessens the flux of this neuroprotective fatty acid to the brain leading to cognitive impairment.