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Research paper

The effect of lipid metabolism on age-associated cognitive decline: Lessons learned from model organisms and human

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ABSTRACT

Lipids are required as integral building blocks of cells to support cellular structures and functions. The intricate mechanisms underpinning lipid homeostasis are essential for the health and maintenance of the central nervous system. Here we summarize the recent advances in dissecting the effect of lipid metabolism on cognitive function and its age-associated decline by reviewing relevant studies ranging from invertebrate model organisms to mammals including human.

Lipids and their role in cognitive function

Lipids are chemically diverse hydrophobic molecules that play a wide variety of roles in cell biology. There are eight categories of lipids, including fatty acyls, glycerolipids, phospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketide (Kao et al., 2020). They function as an important source of energy, are major constituents of cell membranes, and participate in numerous signaling and regulatory processes (Vance and Vance, 2008).

Lipids consist ~50% of the mammalian brain's dry weight, making it the second most lipid-rich organ in the body after adipose tissue. Brain lipids are composed of ~50% phospholipids, less than 40% glycolipids, ~10% cholesterol and cholesterol ester, and traces of triglycerides (Sastry, 1985). Lipids are key to neuronal functions and dysregulated lipid metabolism drives age-related cognitive decline through mechanisms such as alterations in intestinal microbiota and the gut-brain axis, neuronal signaling pathway, blood-brain barrier disruption, mitochondrial dysfunction, oxidative stress, and inflammation, which together cause synaptic loss and eventually memory impairment (Kao et al., 2020). Disruption of lipid homeostasis has also been linked to the pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD) (Giri et al., 2016).

In this review, we are going to focus on the effect of lipid metabolism on cognitive function and its age-associated decline in animals of different complexity ranging from the invertebrates *C. elegans* and *Drosophila* to mammals including mouse and human.

C. elegans

The round worm *C. elegans* is an easy-to-handle genetic model for studying both aging and metabolism. Recently, many studies have been conducted to dissect the effects of lipid metabolism on aging using this model organism, and the role of several molecular regulators of lipid metabolism on aging and age-related diseases has been characterized (Rubio-Tomas and Tavernarakis, 2022).

By expressing human disease-causing proteins in worm tissues, *C. elegans* models of age-related neurodegenerative diseases have been established (Caldwell et al., 2020). In a cross-species study, evidence from two *C. elegans* AD models (worms expressing neuronal amyloid beta/Aβ or tau, respectively) suggested a neuroprotective role for the switch from glucose to lipid metabolism found in human AD patients (Demarest et al., 2020). In another study, removing phospholipase D,

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which catalyzes the hydrolysis of phosphatidylcholine to form phosphatidic acid and choline, partially recued the pathological phenotypes of AD worms (Bravo et al., 2018). In the case of Lewy body dementia (DLB), patients co-express Aβ and alpha-synuclein (α-syn) in their brain. Transcriptional profiling analysis of a worm model of DLB showed that genes associated with lipid metabolism and lysosomal function were down-regulated in these worms just as in the lateral temporal lobe of post-mortem brains of DLB patients (Huang et al., 2021). Together, these data suggest that cellular lipid homeostasis plays an important role in the pathogenesis of age-related neurodegeneration.

Drosophila

Over the past several decades, the genetic model fruit fly *Drosophila* has been extensively used for understanding the molecular and cellular mechanisms underlying neurodegeneration (Deal and Yamamoto, 2018). On one hand, disease models in which pathogenic factors were expressed in the fly nervous system to recapitulate some of the cellular and histological features seen in the human condition were generated (Greeve et al., 2004; Zhao et al., 2010; Frost et al., 2014) and used for identifying genes and genetic pathways that function as suppressors or enhancers of the relevant phenotypes (Lenz et al., 2013). On the other hand, forward genetic screens have been conducted to identify genes that are necessary for maintenance of the fly nervous system (Anderson, 2008; Yamamoto et al., 2014).

When characterizing mutants identified in those screens, a neuroprotective role of neuron-glia metabolic coupling in neurons experiencing oxidative stress was uncovered. In mutant flies with defective mitochondria, elevated reactive oxygen species (ROS) elicited lipogenesis in the neurons through the activation of c-Jun N-terminal kinase (JNK) and sterol regulatory element binding protein (SREBP). The lipids generated were transferred to glia, where they formed lipid droplets. This process required fatty acid transport proteins (FATPs) and apolipoproteins. Interestingly, variants of human APOE, except APOE4, the allele associated with increased risk of developing AD, were able to substitute for a fly glial apolipoprotein for this function. This result links reduced lipid transport between neurons and glia to the development of AD, providing mechanistic insights into the pathogenesis of neurodegeneration (Liu et al., 2015, 2017; Bailey et al., 2015; Cabirol-Pol et al., 2018).

Mouse

The formation and function of the mammalian nervous system requires molecular carriers transferring lipids in and out of designated cell types and cellular compartments. Genetic analysis of lipid transport proteins and their receptors, including apolipoproteins (e.g., APOD and APOE), Low-Density Lipoprotein Receptor (LDLR), and Low-density lipoprotein Receptor-related Protein 1 (LRP1), suggested that intact lipid trafficking is necessary for maintaining the proper function of the nervous system (Ganfornina et al., 2008; Evola et al., 2010; de Oliveira et al., 2011; Liu et al., 2010).

Another example of using knockout mice to study the role of genes involved in lipid metabolism and energy production in regulating the pathogenesis of neurodegenerative disorders is the inner mitochondrial membrane protein, Prohibitin 2 (PHB2) (Gao et al., 2021). Neuronal-specific depletion of PHB2 in the mouse forebrain led to mitochondrial morphological defects and tau hyperphosphorylation in the hippocampal neurons, causing extensive neurodegeneration and cognitive deficits (Merkwirth et al., 2012). Recently, a new purine derivative compound PDD005, potentially targeting PHB2, was reported to be able to attenuate tau pathology in the hippocampus of a 3xTg AD mouse model and to rescue cognitive and memory deficits in aging mice (Guyot et al., 2020).

Unified diets and standardized cognitive assessments in mice allowed scientists to dissect the effect of high-fat diet (HFD) on neurocognition in a controlled manner. Under a HFD with 40% energy from fat, mice developed brain insulin resistance and displayed neurological alterations associated with cognitive dysfunction such as increased Aβ deposition and neurofibrillary tangle formation, and impaired synaptic plasticity (Kothari et al., 2017). Another HFD consisting of 40% saturated fat could also induce a significant increase in visceral adiposity, which was linked to reduced visual recognition memory and flexibility in middle-aged mice (Petrault et al., 2019). In addition, FGF21 treatment has been suggested to have neuroprotective effects on HFD (60% calories from fat)-induced cognitive impairment, and might become a molecular target for early intervention of metabolic syndromes-associated cognitive decline (Wang et al., 2018).

Although most analyses revealed undesirable neurocognitive changes in HFD-treated mice, HFD might be beneficial under certain circumstances. One study reported that the same HFD regimen used in the previous analysis improved working memory and reduced anxiety in male C57BL/6J mice (Yoshizaki et al., 2020).

Human

The relationship between lipid metabolism and age-associated cognitive decline has been studied in human by investigating the correlation between blood lipid levels and cognitive impairment. Blood lipids are lipids contained in the plasma or serum, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), phospholipids and free fatty acids. Many clinical studies have been carried out to examine the relevance of blood lipid components to age-related cognitive deterioration, although no consensus has been reached. For example, some studies suggested that a higher level of TC, LDL-C, or TG is associated with increased risk of cognitive impairment, (Bai et al., 2016; Sachdev et al., 2012; Zou et al., 2014; Schilling et al., 2017; Power et al., 2018; Nagga et al., 2018; Ma et al., 2017) while others indicated that an elevated level of TC or TG is beneficial for maintaining cognitive function during aging (Yin et al., 2012; Lv et al., 2019; Stewart et al., 2007). In another study, a correlation between increased levels of TC, LDL-C, HDL-C and a lower risk of cognitive impairment was only observed in the population over 80 years old, but not in the 65–79 age group (Lv et al., 2016). Moreover, there were studies suggested that TG is irrelevant to cognitive impairment (Liu et al., 2020; Han and Kim, 2021; Yoshitake et al., 1995; Forti et al., 2010; Muller et al., 2007). The inconsistencies in these results can be attributed to factors such as sample size, demographic characteristics of the sample including age, gender, and ethnicity, time of blood testing, and length of follow-up. Similar to the mouse HFD studies, these analyses may also suggest the complexity of regulation of cognitive function by lipid metabolism.

With the help of high-throughput techniques such as mass spectrometry and nuclear magnetic resonance, the human blood metabolome, which is the total collection of small metabolites present in the plasma or serum was analyzed. It provides a direct and comprehensive readout of an individual's physiological status. As people age, the metabolic profile changes, which would suggest possible biomarkers for the age-associated functional decline. Lipid species including vitamin D2-related compound, phosphoserine (40:5), monoacylglyceride (22:1), diacylglyceride (33:2), and resolvin D6 decreased as individuals aged (Jove et al., 2016). Nontargeted metabolomic analyses detected a large number of metabolites that were significantly altered with age, gender, or race. Among which, age-related changes were the most pronounced (Lawton et al., 2008). Notably, age-associated differences were more prominent in women than in men. In a human serum metabolic profiling analysis, 34 and 71 metabolites were found to be linked to aging in men and women, respectively (Yu et al., 2012). Levels of many triacylglycerols were elevated in elderly women than in young women (Ishikawa et al., 2014). Women also had higher plasma concentrations of most ceramide and dihydroceramide species and demonstrated steeper trajectories of age-related up-regulation of these molecules

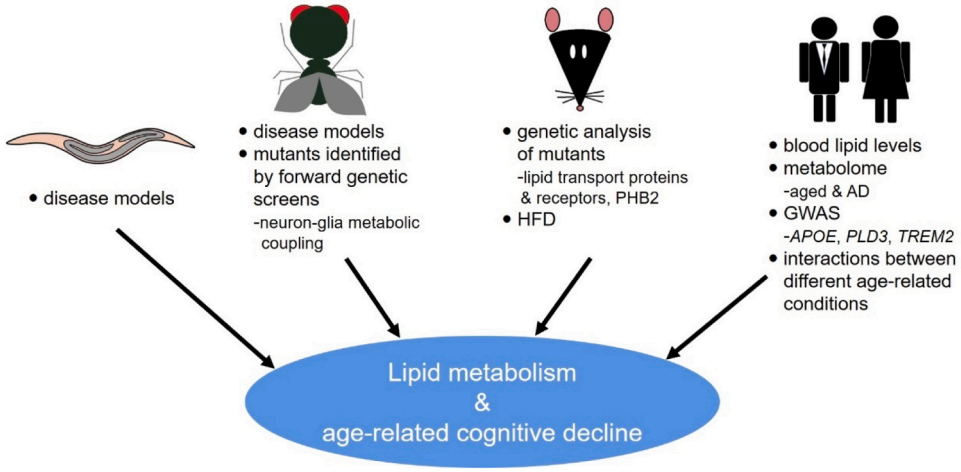

Fig. 1. Recent findings in understanding the role of lipid metabolism in regulating age-associated cognitive decline from both model organisms and human.

(Mielke et al., 2015). In addition, lipidomic analyses were conducted to identify lipid signatures correlated with extreme human longevity, and this topic has been carefully reviewed in a recent article (Johnson and Stolzing, 2019).

Likewise, lipidomic analyses were performed in order to discover biomarkers that could facilitate the risk assessment, early detection, and therapeutic monitoring of AD. Eight sphingomyelin species, especially those containing long aliphatic chains with 22 or 24 carbon atoms, were found to be significantly reduced in the plasma of AD patients, while two ceramide species (N16:0 and N21:0) were increased (Han et al., 2011). Three phosphatidylcholine (PC) molecules (PC 16:0/20:5, PC 16:0/22:6, and PC 18:0/22:6) were diminished in AD cases (Whiley et al., 2014). Major changes were observed in the levels of several species of PCs, phosphatidylethanolamines (PEs), plasmenylcholines, plasmenylethanolamines and different classes of lysophospholipids, highlighting the great importance of membrane integrity in the pathogenesis of AD (Gonzalez-Dominguez et al., 2014). Moreover, a set of ten lipid molecules from peripheral blood which could predict the risk of testee converting to either mild cognitive impairment or AD within a 2–3 year timeframe with an accuracy over 90% were identified. Such markers included PCs (PC diacyl (aa) C36:6, PC aa C38:0, PC aa C38:6, PC aa C40:1, PC aa C40:2, PC aa C40:6, and PC acyl-alkyl (ae) C40:6), lysophophatidylcholine (lysoPC a C18:2), and acylcarnitines (Propionyl AC (C3) and C16:1-OH) (Mapstone et al., 2014). For more lipidomic analyses of AD populations, the reader is directed to a recent review (Chiurchiu et al., 2022).

Although the heritabilities of plasma metabolites varied a lot, a median heritability as high as 36% suggested that many metabolites were influenced considerably by complex gene-environment interactions (Darst et al., 2019). Apolipoprotein E (*APOE*) is an important component of human plasma lipoprotein, which plays a pivotal role in lipid metabolism and cholesterol homeostasis. It has been recognized that the *APOE* genotype is a strong predictor of the risk for developing AD. Among the three main *APOE* alleles, ε2, ε3, and ε4, which differ at 2 single nucleotide polymorphisms (rs7412 and rs429358), ε4 was shown to be associated with increased AD risk up to 33-fold when homozygous. By contrast, the ε2 allele was often found to be protective, while ε3 seemed neutral in terms of AD incidence (Lumsden et al., 2020). Compared to non-ε4 individuals, ε4 carriers might experience earlier cognitive decline and amyloid deposition as early as age 40 (Jansen et al., 2015). In addition, synergistic effects have been observed for the ε4 allele with other cognitive impairment risk factors. For example, in a study where cognitive functions were not significantly different between ε4 carriers and non-carriers in healthy controls, the ε4 carriers showed significant cognitive decline in depressed individuals as compared to depressed non-carriers (Niti et al., 2009).

The *APOE* gene polymorphism induced cognitive impairment was linked to mitochondrial toxicity, increased Aβ deposition and tau phosphorylation, and vascular injury, which collectively contribute to the pathogenesis of AD (Refolo and L.M.F., 2004; Zhao et al., 2018). It was also shown that *APOE* ε4 expression affected cerebral structures, including hippocampus, amygdala, entorhinal cortex and led to global cerebral atrophy (Fan et al., 2019).

Recently, genome-wide association studies (GWAS) have revolutionized the analysis of genetic loci associated with late-onset AD. Next-generation sequencing technologies have been applied to identify rare disease variants with intermediate risk of AD in genes involved in lipid metabolism such as *PLD3* and *TREM2* (Giri et al., 2016). PLD3 is a neuronal lysosomal phospholipase D, (Nackenoff et al., 2021) whose removal was shown to reduce endolysosomal vesicle accumulation and axonal spheroid growth, leading to improved neural circuit function in AD (Yuan et al., 2022). TREM2, a cell surface receptor required for triggering microglial responses to conditions of neurodegeneration, did so by sustaining cellular metabolic fitness (Ulland et al., 2017).

People are more likely to suffer several conditions at the same time as they age, thus studies aimed to address the interactions between different age-related conditions such as diabetes, cardiovascular diseases, and dementia have been performed. Past studies suggested a negative correlation between cardiovascular risk factors and cognitive function. In a meta-analysis, metabolic syndrome, diabetes, and hypertension were highly associated with cognitive deficits in patients with schizophrenia (Hagi et al., 2021). Lipid accumulation product (LAP), an index calculated from waist circumference and TG levels, represents fat overaccumulation in the body and has been shown to be related to cardiovascular diseases. In a study of 5542 Chinese hypertensive patients with normal weight, higher LAP was associated with better Mini-Mental State Examination (MMSE) score, indicating a positive correlation between LAP and cognitive function (Xie et al., 2021). This phenomenon was explained as leptin produced by adipose tissue could promote neurogenesis and synaptogenesis (Marwarha and G.G., 2012). However, the relationship between LAP and cognitive function still requires further investigation, since a different study with a much smaller sample of type 2 diabetes patients (n = 220) proposed that increased LAP would indicate a risk for cognitive impairment (Yu et al., 2020).

Conclusions

In this review, we summarize the recent findings in understanding the role of lipid metabolism in regulating age-associated cognitive decline. Despite the presence of some inconsistencies in the results which can be attributed to factors such as diet and ethnicity, analyses of human samples have revealed correlations between lipid homeostasis

and maintenance of cognitive function. Moreover, genetic model organisms such as *C. elegans*, *Drosophila*, and mouse have been utilized to elucidate the mechanisms by which lipids and regulators of their homeostasis affect age-related cognitive deterioration (Fig. 1). In the future, we expect to see more studies that combine the use of both systems. On one hand, targeted lipidomic analyses of human samples will be conducted to identify specific lipid molecules that may serve as biomarkers for age-associated conditions including cognitive impairment. On the other hand, the development of more efficient genome-editing techniques such as CRISPR in model organisms will accelerate the generation of relevant mutants to facilitate the dissection of underlying mechanisms. With the help of these technological advances, evolutionarily conserved genes and pathways that mediate the effect of lipid metabolism on age-associated cognitive decline will likely be uncovered.

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