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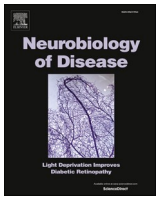

Review

Targeting dysregulated lipid metabolism for the treatment of Alzheimer's disease and Parkinson's disease: Current advancements and future prospects

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ABSTRACT

Alzheimer's and Parkinson's diseases are two of the most frequent neurological diseases. The clinical features of AD are memory decline and cognitive dysfunction, while PD mainly manifests as motor dysfunction such as limb tremors, muscle rigidity abnormalities, and slow gait. Abnormalities in cholesterol, sphingolipid, and glycerophospholipid metabolism have been demonstrated to directly exacerbate the progression of AD by stimulating Aβ deposition and tau protein tangles. Indirectly, abnormal lipids can increase the burden on brain vasculature, induce insulin resistance, and affect the structure of neuronal cell membranes. Abnormal lipid metabolism leads to PD through inducing accumulation of α-syn, dysfunction of mitochondria and endoplasmic reticulum, and ferroptosis. Great progress has been made in targeting lipid metabolism abnormalities for the treatment of AD and PD in recent years, like metformin, insulin, peroxisome proliferator-activated receptors (PPARs) agonists, and monoclonal antibodies targeting apolipoprotein E (ApoE). This review comprehensively summarizes the involvement of dysregulated lipid metabolism in the pathogenesis of AD and PD, the application of Lipid Monitoring, and emerging lipid regulatory drug targets. A better understanding of the lipidological bases of AD and PD may pave the way for developing effective prevention and treatment methods for neurodegenerative disorders.

1. Introduction

Alzheimer's and Parkinson's diseases are two of the most frequent neurological diseases (Aarsland et al., 2011). AD accounts for approximately 60–70% of dementia cases worldwide, with an estimated 50 million people currently living with the condition globally (Collaborators, 2019). The latest projections indicate worrisome trends regarding the growth of dementia cases worldwide. Data shows that by 2050, the global prevalence of dementia is estimated to nearly double from current levels. However, if defined according to biological rather than solely clinical criteria for AD, the predicted rise in dementia cases may be even greater, potentially tripling in scale based on the available

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data (Nowell et al., 2023; Scheltens et al., 2021). Furthermore, PD has a significant influence on human health as the second most prevalent neurological illness after AD. In short, AD and PD are imposing increasingly weighty socioeconomic burdens. Accordingly, identifying efficacious therapeutic solutions takes on vital importance.

Lipid homeostasis dysfunction may pose a risk for AD and PD (Sarchione et al., 2021). Lipid metabolism disorders involve the accumulation of proteins caused by changes in lipid content and oxidative damage caused by lipid peroxidation, which are different from the metabolic behaviors of normal individuals. In the body fluid and brain tissue samples of AD and PD patients, we can detect differences in the levels of cholesterol, phospholipids, and other lipids between normal people and patients. The accumulation of abnormal tau protein and β-amyloid protein (Aβ) is the central feature of AD. The build-up of lipids like cholesterol and sphingolipid is linked to the accumulation of Aβ and tau protein (Flores-Leon and Outeiro, 2023; Hashemi et al., 2022). In addition, abnormal lipid metabolism may indirectly affect the onset of AD through secondary pathological mechanisms. α-synuclein (α-syn) aggregation is the main feature of PD, and the accumulation of lipids such as polyunsaturated fatty acids (PUFAs) and cholesterol is involved in the misfolding and aggregation of α-syn (Sarchione et al., 2021). Abnormal attachment of α-syn to oxidized lipid metabolites also causes damage to organelles such as mitochondria (Ruipérez et al., 2010). Many studies have also found that lipid peroxidation is strongly associated with ferroptosis, which causes neuronal death (Pope and Dixon, 2023). As was previously mentioned, research shows a role for disruption of lipid homeostasis in the etiology and development of neurodegenerative diseases such as AD and PD.

By targeting specific aspects of lipid metabolism, it may be possible to develop novel therapeutics that help restore metabolic balance in the brain and slow cognitive and motor decline. Great progress has been made in targeting lipid metabolism abnormalities in order to cure PD and AD in recent years. Some common antidiabetic drugs like metformin (Li et al., 2012), insulin (Kellar and Craft, 2020), glucagon-like peptide-1 (GLP-1) receptor agonists (Lourenco et al., 2013), and dipeptidyl peptidase-4 (DDP4) inhibitors (Kosaraju et al., 2013) have shown potential therapeutic effects on AD and PD through enhancing brain synaptic plasticity and cognitive function. In addition, regulating key enzymes such as HMG-CoA reductase (Bar-On et al., 2008) and stearoyl-CoA desaturase (Vincent et al., 2018) can also affect cholesterol and fatty acid synthesis and metabolism. Moreover, peroxisome proliferator-activated receptors (PPARs) agonists (Comerota et al., 2023; Sastre et al., 2003) can inhibit amyloidogenesis by improving insulin sensitivity. Monoclonal antibodies targeting lipid metabolism-related proteins like apolipoprotein E (ApoE) (Wang et al., 2018) and triggering receptor expressed on myeloid cells 2 (TREM2) (Zhao et al., 2022a) have demonstrated good anti-amyloidogenic effects by optimizing lipid transport and microglial cell functions respectively. This review comprehensively summarizes the participation of lipid metabolism in the development of AD and PD, the application of Lipid Monitoring, and emerging lipid regulatory drug targets. Greater knowledge of the lipidological roots of both AD and PD may pave the way for developing effective prevention and treatment methods for neurodegenerative disorders.

2. Dysregulated lipid metabolism leads to AD

Alzheimer's disease (AD) is a prevalent form of neurodegeneration commonly affecting the elderly which can lead to the progressive degeneration and death of neurons, particularly within regions of the brain instrumental for memory and cognition. Despite the current study, the precise cause of Alzheimer's disease is unknown. Plaques composed of aggregated Aβ (Roca-Agujetas et al., 2021; Wu et al., 2022) and twisted threads of tangled tau protein (Merrick et al., 1997) are hallmarks of the disease pathology. According to current research, unusual lipid metabolism has been linked to Aβ deposition and tangled tau protein. Based on these two characteristics, we will discuss the connections between lipid metabolism and AD (see Fig. 1).

2.1. Abnormal lipid levels accelerate Aβ deposition

2.1.1. Elevated cholesterol levels

One of the most typical features of AD is Aβ accumulation. Aβ is generated through the successive hydrolysis of amyloid precursor protein (APP) by the enzymes β-secretase and γ-secretase (Hur, 2022). Aβ formation is promoted by the up-regulation of lipids, particularly cholesterol in the brain, which increases the ability that APP to bind to β-secretase and γ-secretase (Mett, 2021; Wang et al., 2021). Furthermore, cholesterol impacts the polymerization of APP and γ-secretase's processing of APP, leading to the generation of Aβ with diverse levels of toxicity and aggravation of Alzheimer's Disease (Wu et al., 2022). High cholesterol levels in neurons encourage Aβ-induced oxidative stress in mitochondria and impede the fusion of the dysfunctional mitochondria with lysosomes (de Dios et al., 2023; Howe et al., 2022), which increases the number of dysfunctional mitochondria and causes nerve cell death (Roca-Agujetas et al., 2021).

2.1.2. Sphingolipid breakdown to ceramides

Sphingolipids are a key component of lipid rafts and help regulate the production and accumulation of Aβ. Normal levels of sphingolipids inhibit the formation and buildup of Aβ peptides, thereby preventing Alzheimer's disease progression. Research has found the increased breakdown of sphingomyelin, a type of sphingolipid, in the brains of AD patients. The enzyme sphingomyelinase catalyzes the breakdown of sphingomyelin to produce ceramides, which was shown to stabilize the accumulation of Aβ. Therefore, abnormal sphingomyelin breakdown in Alzheimer's disease patients further exacerbates the accumulation of Aβ, leading to further worsening of AD, and the above process is also linked with sphingomyelinase activity (Czubowicz et al., 2019; Xing et al., 2023).

2.1.3. Other lipids

Research has found that 27-hydroxycholesterol, a lipid that can easily pass the blood-brain barrier, increases expression of the enzyme β-site amyloid precursor protein cleaving enzyme 1 (BACE1), which is known to play a significant part in Aβ production via causing the cleavage of APP. IκB phosphorylation and degradation were triggered by 27-OHC in SH-SY5Y cells at the molecular level, whose degradation product p65-p50 dimer was able to translocate to the BACE1 promoter region's κB site in the nucleus, thereby upregulating the synthesis of BACE1 (Wu et al., 2022). Studies have shown omega-3 polyunsaturated fatty acids can inhibit the activity of β-secretase and γ-secretase and can also increase the activity of α-secretase, (Chen et al., 2021), which may have the potential to reduce the formation and accumulation of toxic Aβ. Furthermore, it has been shown that certain ratios of phospholipid vesicle constituents contribute to the reduction of amyloid (Chaparro Sosa et al., 2020). This finding also points to a relationship between phospholipids and Aβ formation.

2.2. Abnormal lipid levels promote tangled tau protein

In AD patients' brains, levels of the tau protein are elevated and abnormally hyperphosphorylated tau comprises a significant proportion. Phosphorylated tau loses its normal function as supporting microtubule stability. This disrupts the cytoskeleton leading to defects in axonal transport and neural connectivity (Merrick et al., 1997). Studies have now linked imbalances in lipid metabolism to excessive tau phosphorylation. Disturbances to lipid metabolism can trigger inflammatory responses within the brain which promotes the formation and activation of different kinases and phosphatases involved in phosphorylation signaling cascades. Through these inflammatory mechanisms, imbalances in lipid processing may elevate tau phosphatase and kinase

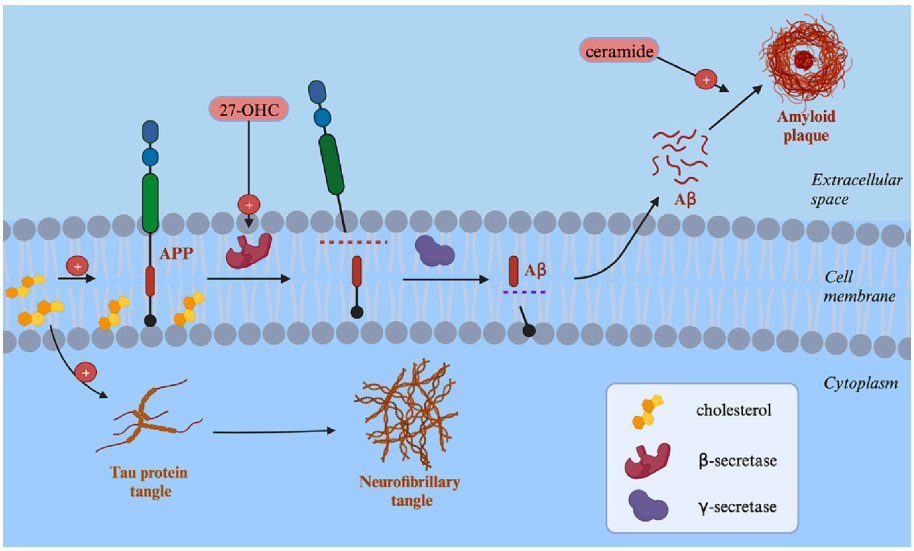

Fig. 1. Dysregulated lipid metabolism leads to AD.

activity, thereby enhancing aberrant tau hyperphosphorylation (Chen and Yu, 2023; Ismail et al., 2020). Dysregulation of PI3K-Akt signaling, which can result from imbalances in phosphatidylinositol levels and structural integrity of lipid rafts, may therefore promote aberrant tau phospho-regulation at multiple nodes (Yang et al., 2020). This is achieved by activating downstream GSK3β and Cdk5, which function as tau phosphokinases (Yang et al., 2020).

Cholesterol metabolism has additionally been linked to the modulation of tau phosphorylation levels. Research has shown depleting cholesterol levels within lipid rafts can activate the raft-dependent Ras/MEK/ERK signaling cascade, leading to phosphorylation of tau protein at multiple sites (Mai et al., 2022). This goes against what we previously concluded and therefore requires further investigation.

2.3. Imbalances in lipid metabolism indirectly accelerate AD

Research indicates elevated cholesterol and imbalanced lipid processing increase the risk of atherosclerosis, whereby plaques accumulate within arteries. Over time, this atherogenic process can generate cerebrovascular lesions that diminish blood flow to the brain, exacerbating the underlying pathologies of AD (Cortes-Canteli and Iadecola, 2020).In addition, imbalanced lipid metabolism is linked to insulin resistance (Kerr et al., 2023), a driving factor behind impaired glucose metabolism. When energetic pathways are compromised by insulin insensitivity, neural excitability may become diminished. This could lead to dysregulated neurotransmitter release and reuptake (Sędzikowska and Szablewski, 2021). Over time, sustained excitatory/inhibitory imbalance poses injury risks to neurons. Triacylglycerols and very low-density lipoproteins, as two markers of lipid metabolism, have been flagged as likely contributors to diminished insulin sensitivity based on their metabolic profiles (Rhee et al., 2011). Recent evidence points out that cholesterol is essential for maintaining typical synaptic architecture given its physical contribution to membrane composition. When cholesterol levels stray outside an optimal range, this destabilizes synaptic structures. Over time, such injuries to synaptic organization at the molecular level are likely to impair communication between neurons. If unaddressed, progressively deteriorating synapse structures and functions may therefore exacerbate disease progression (Li et al., 2022a).

3. Dysregulated lipid metabolism leads to PD

Neuropathologically, a defining feature of Parkinson's disease (PD) is the presence of proteinaceous inclusions known as Lewy bodies (LB), comprised primarily of aggregates of the protein α-syn (Spillantini et al., 1997). Multiple biochemical processes are involved in PD, including mitochondrial or lysosomal malfunction and endoplasmic reticulum oxidative stress. In many recent studies, ferroptosis, a particular kind of lipid peroxidation-induced regulatory cell death, has also been gradually confirmed to be closely related to Parkinson's disease (Dixon et al., 2012; Dong-Chen et al., 2023). Recently, researchers have observed changes in lipid metabolism in PD patients including sphingolipid metabolism, arachidonic acid metabolism, and fatty acid biosynthesis (Galper et al., 2022; Sinclair et al., 2021). Based on the above, we will discuss the connections between lipid metabolism and PD.

3.1. Abnormal lipid levels accelerate the accumulation of α-syn

Lipid accumulation observed in patients with PD is involved in α-syn aggregation (see Fig. 2). Mutations in the GBA1 gene represent a major genetic risk factor for PD. GBA1 mutant reduces the activity of the enzyme β-glucocerebrosidase (GCase) and leads to lysosomal dysfunction, therefore causing an abnormal build-up of cholesterol and polyunsaturated fatty acids (PUFAs) (Flores-Leon and Outeiro, 2023). PUFAs accumulate within cells due to lysosomal dysfunction and other reasons. The elevation of PUFA levels may impact the functioning of dopaminergic neurons by upregulating the expression of the α-syn gene and promoting the oligomerization of α-syn and the formation of toxic oligomers, thereby increasing the risk of PD (Assayag et al., 2007; Yakunin et al., 2012). At the same time, high levels of fatty acids can also cause α-syn aggregation, thus participating in the formation of LB (Erskine et al., 2021). The interaction between α-syn and cellular membranes may facilitate its transformation from benign, soluble forms to toxic, insoluble aggregates (Marschallinger et al., 2020). Cholesterol-rich domains such as lipid rafts may be the focal points for α-syn aggregation. Cholesterol is also thought to regulate the binding of α-syn to synaptic vesicle-like structures, potentially triggering their aggregation (Galvagnion, 2017; García-Sanz, 2021). Recent findings indicate levels of the lipid transport apolipoprotein (ApoE) are elevated in cerebrospinal fluid of early PD patients. As ApoE encodes a protein that mediates lipid trafficking, this suggests α-syn may augment its spread between neurons by interacting with ApoE (Paslawski et al., 2019).

3.2. Abnormal lipid levels lead to dysfunction of mitochondria and endoplasmic reticulum

Lipid metabolism disorders such as fatty acids and cardiolipin

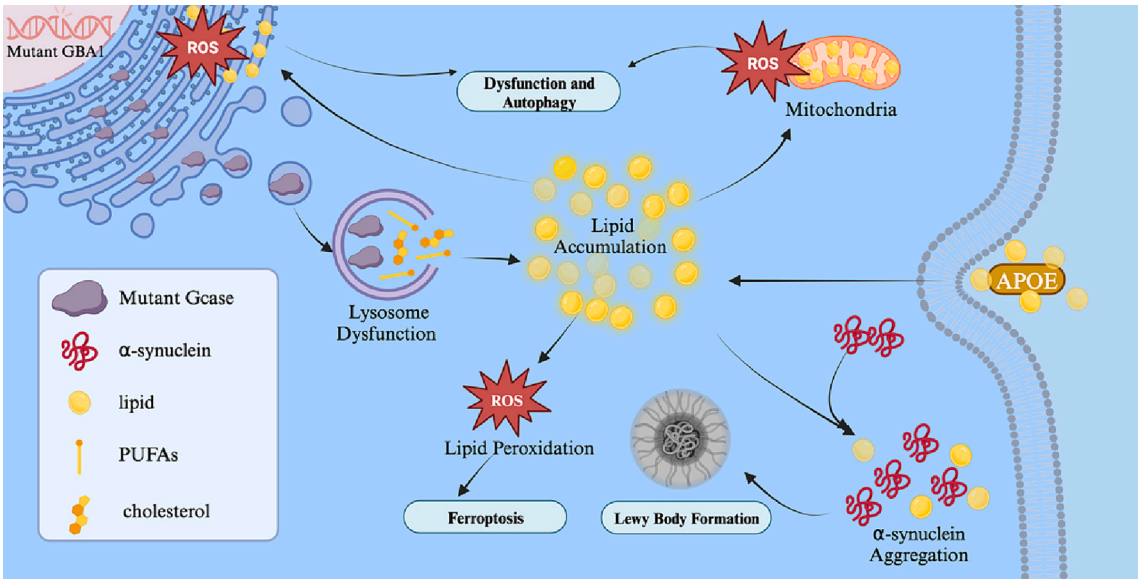

Fig. 2. Dysregulated lipid metabolism leads to PD.

participate in mitochondrial and endoplasmic reticulum dysfunction, which leads to dysfunction of neurons and plays an important role in the pathogenesis of PD. Excessive lipid accumulation can induce mitochondria-cytoplasmic stress response (MCSR), and the resulting ROS preferentially targets PUFAs, leading to the occurrence of PUFA peroxidation, thereby altering mitochondrial permeability and leading to mitochondrial dysfunction (Kim et al., 2016). Research has established that Elovl2 is a key endoplasmic reticulum-located very long-chain fatty acid elongase. Deficiency of Elovl2 may result in impaired fatty acid synthesis and accumulation of short-chain fatty acids within the endoplasmic reticulum. The build-up of free fatty acids in the endoplasmic reticulum damages its function, leading to increased unfolded or misfolded protein load, chronic endoplasmic reticulum stress, and elevated risk of mitochondrial dysfunction (Li et al., 2022c). There has been evidence of a decrease in SIRT6 activity in the brains of PD patients (Stein et al., 2021). Research has shown that a deficiency of SIRT6 can lead to decreased mitochondrial gene expression, elevating the production of reactive oxygen species (ROS), and mitochondrial decay, thereby initiating mitochondrial dysfunction (Smirnov et al., 2023). In addition, disruption to mitochondrial lipid metabolism could further influence mitochondrial structure and function. Cardiolipin (CL) is a glycerophospholipid that is present in the mitochondrial membranes of eukaryotic cells (van Meer et al., 2008). Misfolded α-syn interacting with cardiolipin has the potential to compromise the integrity of mitochondrial membranes and thereby impair mitochondrial function (Ghio et al., 2016). Additionally, research has revealed that CL mediated the targeted autophagy of abnormal mitochondria, abnormal CL content could hinder mitochondrial autophagy, and abnormal mitochondrial aggregation could trigger inflammation through the NLRP3 inflammasome and/or cGAS-cgamp-STING-TBK1-IRF3 pathway, further aggravation of neuronal cell damage (Chu et al., 2013; Doblado et al., 2021; Hsu and Shi, 2017; Tansey et al., 2022). Hence, it can be inferred that there is a delicate balance between cardiolipin (CL), mitochondria, and Parkinson's disease. Abnormal CL metabolism can lead to Parkinson's disease by affecting mitochondrial function or inhibiting abnormal mitochondrial autophagy. The disorder of lipid metabolic coupling between neurons and astrocytes is also closely related to PD (Bantle et al., 2020). Toxic fatty acids (FAs) generated in hyperactive neurons are transported to astrocyte lipid droplets via APOE-positive lipid particles and consumed through mitochondrial beta-oxidation for detoxification (Ioannou et al., 2019). Pathogenic α-syn is involved in astrocyte mitochondrial dysfunction (Braidy et al., 2013). Mitochondrial dysfunction of astrocytes can reduce FA metabolism, make neurons poisoned by FA, and aggravate the PD process.

3.3. *Dysregulated lipid metabolism leads to ferroptosis*

Parkinson's disease-related dopaminergic neuronal degeneration is linked to ferroptosis, which is primarily brought on by problems in lipid metabolism (Dixon et al., 2012). Given the high lipid content in brain tissue, the central nervous system may be particularly vulnerable to oxidative damage caused by lipid peroxidation. Unrestricted lipid peroxidation is a hallmark of ferroptosis, and lipid peroxidation products play a key role in Parkinson's disease (Gaschler and Stockwell, 2017; Yang et al., 2016). PUFAs accumulated in PD patients are the main substrates for these peroxidation processes, and the elevated levels of peroxide substrates such as ceramide and lysophosphatidylcholine produced by peroxidation can lead to cellular oxidative damage, resulting in ferroptosis (Yan et al., 2021; Yang et al., 2016). Lipid peroxidation produces lipid free radicals and lipid peroxyl free radicals, which react with PUFAs to produce lipid peroxides, which further aggravate the oxidation process of PUFAs and accelerate the occurrence of ferroptosis (Stockwell et al., 2017). The oxidation of arachidonic acid (AA) and other polyunsaturated fatty acids in the phosphatidylethanolamine (PE) of the cell membrane can damage the membrane and induce ferroptosis (Astudillo et al., 2023). In the condition of lipid metabolism disorders, glutathione peroxidase 4(GPX4) plays a role in alleviating ferroptosis by converting lipid peroxides into lipid alcohols. GPX4 activity decreased, and the antioxidant capacity of cells decreased, making PUFAs more easily oxidized, indirectly aggravating the process of ferroptosis (Costa et al., 2023). Therefore, PD may arise as a result of abnormalities in lipid metabolism by affecting the process of desferrioxia.

Taken above, it is not difficult to see that lipid metabolism plays an important role in the accumulation of α-syn, mitochondrial dysfunction, and ferroptosis. However, these effects do not exist independently in the pathogenesis of PD. Ferroptosis can affect the metabolism of α-syn and lead to its accumulation (Castellani et al., 2000). Accumulation of α-syn can also cause mitochondrial dysfunction (Ordonez et al., 2018). This vicious cycle causes the degree of Parkinson's disease to gradually worsen, demonstrating the important role of lipid metabolism in the pathogenic process of Parkinson's disease.

4. Application of lipid monitoring in AD and PD

Previously, we summarized the relationship between lipid metabolism and AD and PD. A large number of studies have found that the levels of lipids and their metabolites in brain tissue and body fluids of AD and PD patients are different from those of healthy individuals or special patients with the disease (see Table 1 and Table 2). In AD patients, research has revealed that the degree of major membrane phospholipids in patients 'brains is considerably less than what was observed in the control group, and the related metabolites are increased. Monitoring the degree of phospholipid degeneration of brain cell membranes is an important index to judge the development of AD (Nitsch et al., 1992). At the same time, the detection results of lipid levels in AD patients are also different for different races. Ethnic background also has an impact on lipid levels in AD patients, and lipid monitoring also has racial significance (Khan et al., 2022). For patients with AD, obstructive sleep apnea (OSA) is the most prevalent type of sleep breathing disturbance. Plasma lipidomics is significantly different in these two types of patients (general AD patients versus AD patients with OSA), so lipid monitoring can be used to diagnose AD and severe OSA patients, permitting personalized management of these individuals (Dakterzada et al., 2022). In the serum of PD patients, the proportion of most lipids is too high compared with the control group, and the difference in related metabolites can feedback the metabolic process in Parkinson's disease. According to the monitored lipid changes, it can be inferred that 20 PD-related pathways such as carnitine shuttling, vitamin E metabolism, glycerol, sphingolipid, fatty acids, and aminoacyl-trNA biosynthesis have significant changes (Pereira et al., 2022). Additionally, lipid profiling can correlate specific lipid compositional features with the severity of PD. The Unified Parkinson's Disease Rating Scale (UPDRS) is used to assess symptom severity, with higher scores indicating more serious manifestations. Research shows that higher levels of glucosylceramide (GlcCer) and dihydro globotriaosylceramide (dhGB3) correlate positively with increased UPDRS scores and more severe PD symptoms. Meanwhile, elevated dihydrosphingomyelin (dhSM) and plasmenylethanolamine (PEp) are associated with lower UPDRS scoring and comparatively milder presentations of the disease (Avisar et al., 2021).

From the standpoint of brain structure and function, brain imaging methods include diffusion tensor imaging (DTI), positron emission tomography (PET), structural magnetic resonance imaging (sMRI), and functional magnetic resonance imaging (fMRI) can noninvasively identify changes in brain biomarkers (Rathore et al., 2017).In recent years, brain imaging biomarker genomics and metabolomics have been extensively utilized in the diagnosis and assessment of disease staging of AD and PD (Li et al., 2022b). In addition, there is increasing evidence that the lipidomic markers are increasingly supporting the diagnosis, prognosis, and detection of therapeutic effects of AD and PD (Chiurchiù et al., 2022). Therefore, we believe that brain imaging technology can be further used to monitor the lipid changes in the occurrence and treatment response of AD and PD, providing a new direction for future clinical research.

Table 1
Application of Lipid Monitoring in AD.

Lipid	Model	[a]FC	Ref
Phospholipid			
Phosphatidylcholine	Three cortical regions in the brains of Alzheimer's patients and matched controls after death	0.90	(Nitsch et al., 1992)
Phosphatidylethanolamine		0.88	
Choline glycerophosphate	Cerebrospinal fluid samples from 12 Alzheimer's patients and 30 cognitively normal subjects	1.76	(Walter et al., 2004)
Phosphatidylserine	African American/black and non-Hispanic AD patients with mild and normal plasma samples	0.77	(Khan et al., 2022)
Phosphatidylcholine		0.81	
Cardiolipin	Clinical plasma samples from mild and moderate AD patients with and without severe [b]OSA	1.33	(Dakterzada et al., 2022)
Glycerolipids			
Diglyceride	Clinical plasma samples from mild and moderate AD patients with and without severe OSA	1.37	(Dakterzada et al., 2022)
Oxidized triglyceride		1.36	
Triglyceride		1.34	
Fatty Acyls			
Oxidized acylcarnitine	Clinical plasma samples from mild and moderate AD patients with and without severe OSA	0.72	(Dakterzada et al., 2022)
9,10-Epoxyoctadecenoic acid		1.71	
Cis-8,11,14,17-Eicosatetraenoic acid		1.40	
Linoleic acid	Brain regions in the Alzheimer's disease (AD) group ($N = 14$), control group (N = 14)	0.52	(Snowden et al., 2017)
Linolenic acid		0.84	
Docosahexaenoic Acid		1.45	
Eicosapentaenoic acid		0.16	
Oleic acid		0.34	
Arachidonic acid		0.75	
Palmitic acid		0.44	
Steroid			
Cholesterol	Brain regions in the Alzheimer's disease (AD) group (N = 14), control group (N = 14)	0.53	(Snowden et al., 2017)

[a] FC: fold change in metabolite abundance relative to controls.

Table 2
Application of Lipid Monitoring in PD.

Lipid	Model	[a]FC	Ref
Fat			
Monogalactosyl Diacylglycerols	Serums from PD patients and healthy controls	2.02	(Pereira et al., 2022)
Steroids and derivatives			
Tetrahydro aldosterone-3-Glucuronide	Serums from PD patients and healthy controls	1.73	(Pereira et al., 2022)
Estrone		1.25	
3-Deoxyvitamin D3		1.02	
Phospholipid			
Phosphatidylethanolamine	Serums from PD patients and healthy controls	1.60	(Pereira et al., 2022)
Phosphatidylcholine		1.49	
Phosphatidic acid		1.23	
Phosphatidylglycerol		1.23	
Phosphatidylserine		1.22	
Phosphatidylinositol		1.21	
Sphingolipid			
Galactosyl ceramide	Serums from PD patients and healthy controls	2.31	(Pereira et al., 2022)
Sphingomyelin		1.71	
Sphinganine-phosphate		1.37	
Sphingosine-1-phosphate		1.25	
C17 sphingosine-1-Phosphocholine		0.64	
Fatty Acyls			
6-Keto-decanoylcarnitine	Serums from PD patients and healthy controls	1.98	(Pereira et al., 2022)
Palmitoleic acid		1.96	
FAHFA		1.72	
3-octadecylenic acid		1.20	
Propionylcarnitine		1.16	
Butyrylcarnitine		1.04	

5. Therapeutic approaches targeted lipid metabolism

Taken above, it is becoming more widely acknowledged that lipid metabolic abnormalities are a major contributing factor in the etiology of AD and PD. Here we summarize the therapeutic approaches that have been explored so far to modulate lipid metabolic dysfunction in AD and PD.

5.1. Dietary supplements and related enzymes

To treat AD and PD, dietary supplements containing polyunsaturated fatty acids (PUFAs), specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have shown therapeutic promise (Strike et al., 2016). PUFA supplementation improves hippocampus synaptic plasticity (Nagaraja et al., 2021) and ameliorates (Strike et al., 2016) cognitive deficits in AD animal models. Activation of retinoid X receptors (RXRs) by natural ligands, including 9-cis retinoic acid, and DHA plays a role in these positive effects (Casali et al., 2015; de Urquiza et al., 2000). Epidemiologically, increased intake of ω-3 PUFAs, particularly DHA and EPA, is associated with a reduced risk of AD, while lower ω-3 PUFA intake increases the risk (Zhang et al., 2016) In this case, some enzyme inhibitors play a therapeutic role by inhibiting the lipid metabolism process of the enzyme (see Table 3). For example, the activity and expression of phospholipase A2 in AD are altered. Increased PLA2 activity in the cerebrospinal fluid of AD patients is accompanied by an increase in lysophosphatidylcholine (LPC), which is associated with increased inflammation(Fonteh et al., 2013). Different PLA2 subtypes have different effects on membrane remodeling and function (Chew

Table 3
Potential drugs targeted dietary supplements and related enzymes.

Drug	Disease	Mechanism	Major effect	Ref
Polyunsaturated fatty acids, *Ginkgo biloba*, phosphatidylserine, vitamin E, folic acid and vitamin B12	AD	dietary supplements	1) shorten average response time during recognition tests. 2) increase the number of words recalled during memory tests. 3) elevates walking speed.	(Strike et al., 2016)
Monophosphoryl lipid A	PD	dietary supplements	1) augments microglial phagocytic activity and mitochondrial function, eliminating deposits of α-syn. 2) protects striatal and dopaminergic neurons. 3) ameliorates motor impairment.	(Venezia et al., 2017)
Lysophospholipids	PD	dietary supplements	1) stabilize α-syn conformation. 2) inhibit α-syn aggregation.	(Karaki et al., 2022)
ab142089, CAY10566	AD	Stearoyl-CoA desaturase inhibitor	1) rescues hippocampal spine number and dendritic complexity. 2) improves learning and memory ability. 3) inhibits the activation of microglia, and reduces the damage induced by immune response.	(Hamilton et al., 2022)
Darapladib	AD	lipoprotein-associated phospholipase A2 inhibitor	1) Reduced IgG-positive material in the brain and Aβ42-containing neuron density. 2) reduces BBB permeability	(Acharya et al., 2013)
Metformin	AD	Monoacylglycerol lipase inhibitor	1) reactivates the atypical protein kinase C - CREB binding protein signaling pathway. 2) rescues memory decline.	(Syal et al., 2020)
DA1	AD	inhibits the oligomerization of ATAD3 A	1) enhances the expression of the enzyme CYP46A1, which governs cholesterol clearance. 2) restores brain cholesterol transport and integrity of MAM. 3) inhibits the accumulation of APP and prevents synaptic loss.	(Zhao et al., 2022b)
3-bromopyrimidine	AD	Hexokinase-2 inhibitor	1) upregulates lipoprotein lipase expression. 2) increases ATP production in microglia, reducing amyloid plaque deposition. 3) attenuates cognitive impairments.	(Leng et al., 2022)
Lovastatin	PD	HMG-CoA reductase inhibitor	1) reduces cholesterol by 60%, α-syn aggregates by 75%, insoluble α-syn by 45%, and oxidized α-syn by 40%. 2) relieves oxidative stress, reduces histone acetylation, and increases cell vitality.	(Bar-On et al., 2008)
Simvastatin	PD	HMG-CoA reductase inhibitor	reduces cholesterol by 50%, insoluble α-syn by 45%, and oxidized α-syn by 35%.	(Bar-On et al., 2008)
Pravastatin	PD	HMG-CoA reductase inhibitor	reduces cholesterol by 30%, insoluble α-syn by 60%, and oxidized α-syn by 50%.	(Bar-On et al., 2008)
CAY10566	PD	stearoyl-CoA desaturase inhibitor	1) reduces the ratio of unsaturated fatty acids in neurons. 2) improves mitochondrial function and oxidative phosphorylation. 3) enhances synaptic transmission and neuronal excitability.	(Vincent et al., 2018)
quetiapine	PD	β-glucocerebrosidase agonist	1) improves lysosomal function. 2) reduces the accumulation of oxidized dopamine, glucocerebroside, and α-syn. 3) improves the survival rate of neurons in PD.	(Burbulla et al., 2019; Gehrlein et al., 2023)
GZ667161	PD	Glucosylceramide synthase inhibitor	1) improves lysosomal function. 2) reduces α-syn aggregation. 3) mitigates neurodegeneration and enhances cognitive performance.	(Sardi et al., 2017)

α-syn: alpha-synuclein; SCD: Stearoyl-CoA desaturase; MAM: mitochondria-associated membranes; ATAD3 A: ATPase family AAA domain-containing protein 3A; APP: amyloid precursor protein.

et al., 2020). Lipoprotein-associated phospholipase A2 (Lp-PLA2) increases the severity of AD by oxidizing LDL and hydrolyzing it into two biologically active products, thereby promoting inflammation (Huang et al., 2020). The application of Lp-PLA2 inhibitors may play a good role in the treatment of AD (Acharya et al., 2013). The increase of cytosolic PLA2 (cPLA2) enzyme activity mainly releases arachidonic acid, thus promoting the progress of the AD pathway, while reducing the ability of microglia to phagocytose Aβ in AD brain, thus further promoting the pathogenesis of the disease (Khan and Ilies, 2023). Therefore, relevant inhibitors may play a role in reducing the course of AD by blocking these pathways(Schaeffer et al., 2011).

5.2. Antidiabetic drugs

Antidiabetic drugs have beneficial effects beyond glycemic control, as they are also able to regulate lipid metabolism. As diabetes shares certain pathophysiological similarities with neurodegenerative diseases like AD and PD, researchers have explored whether existing antidiabetic therapies may also benefit these conditions (see Table 4). Metformin is a first-line treatment for diabetes and it can penetrate the blood-brain barrier and build up to therapeutic amounts in the brain, according to studies. Metformin has gained interest for its potential neuroprotective effects in AD and PD through its ability to activate the AMP-activated protein kinase (AMPK) (Li et al., 2012; Mor et al., 2020). As a key metabolic hormone, insulin (Kellar and Craft, 2020; Novak et al., 2019) improves brain cognition and synaptic plasticity in AD and PD. Further, thiazolidinediones (rosiglitazone, pioglitazone) improve insulin sensitivity by stimulating PPARs (see Table 4). Glucagon-like peptide-1 (GLP-1) (Lourenco et al., 2013; Yun et al., 2018) and gastric inhibitory polypeptide (GIP) (Cao et al., 2018; Feng et al., 2018) are secreted by enteroendocrine L cells in the intestine in response to nutrient ingestion and could promote the release of insulin. Inhibiting dipeptidyl peptidase-4 (DPP-4) is an enzyme that can rapidly degrade GLP-1 within two minutes (Kosaraju et al., 2013; Nassar et al., 2015), thus preserving active levels of endogenous GLP-1.

5.3. Targeting nuclear receptor superfamily

The nuclear receptor superfamily controls the expression of target genes by binding to element-specific sequences located at gene promoter regions, regulating inflammation, energy balance, as well as lipid and glucose metabolism (Moutinho and Landreth, 2017). Due to their ability to lower toxic lipid products, exhibit anti-inflammatory properties, and potential neuroprotective benefits, activating these receptors with specific agonists shows great promise for AD (Moutinho and Landreth, 2017). The retinoid bexarotene synthetic agonist, which the FDA licensed for the treatment of cutaneous T-cell lymphoma, is a potent agonist of the retinoid X receptors (RXRs) and has been shown to alleviate cognitive impairments in AD (Cramer et al., 2012; Savage et al., 2015). Among all the peroxisome proliferator-activated receptors (PPARs), PPAR-α uniquely impacts excitatory cholinergic/dopaminergic signaling and glutamatergic neurotransmission in the brain. It also regulates mitochondrial fatty acid metabolism, energy homeostasis, and oxidative stress (Comerota et al., 2023; Luo et al., 2020). PPAR-γ is involved in mitochondrial biogenesis and cell differentiation relating to neurodegenerative and neuroinflammatory processes (Sastre et al., 2003; Yamanaka et al., 2012). PPAR-β/δ presides over the processes of myelination, lipid metabolism, and cellular differentiation (Chamberlain et al., 2020). Retinoic acid receptor-related orphan receptor alpha (REV-ERBα) is extensively involved in the regulation of the biological clock as well as the control of glucose metabolism and triglyceride levels (Lee et al., 2023).(see Table 5.)

5.4. Targeting APOE and TREM

Apolipoprotein E (APOE) fulfills an important function in the

Table 4
Potential drugs targeted diabetes.

Drug	Disease	Mechanism	Major effect	Ref
Metformin	AD	activates AMPK pathway	1) attenuates total tau and phosphorylation of tau at Ser396. 2) preserves synaptophysin levels.	(Li et al., 2012)
Metformin	PD	activates AMPK pathway	1) decreases astrocyte activation. 2) protects mitochondrial homeostasis and dopaminergic neurons. 3) improves motor function.	(Mor et al., 2020)
insulin	AD	intranasal insulin	1) reduces Aβ and p-tau. 2) upgrades mitochondrial function and neuronal survival rates. 3) improves memory ability and verbal fluency.	(Kellar and Craft, 2020)
insulin	PD	Intranasal insulin	improves Hoehn, Yahr scores, and Unified Parkinson's Disease Rating Scale motor scores	(Novak et al., 2019)
Exendin-4	AD	GLP-1 receptor agonist	1) decreases cerebral Aβ. 2) reduces astrocyte and microglial activation. 3) maintains dopaminergic neuronal survival in the substantia nigra. 4) preserves cognitive abilities.	(Lourenco et al., 2013)
Liraglutide	AD	GLP-1 receptor agonist	1) reduces 28 kDa and 108 kDa Aβ. 2) decreases endoplasmic reticulum stress. 3) increases synaptic density.	(Lourenco et al., 2013)
Exendin-4	PD	GLP-1 receptor agonist	1) prevents microglial activation and dopamine levels. 2) prevents dopaminergic neuronal loss. 3) improves motor function.	(Li et al., 2009)
NLY01	PD	GLP-1 receptor agonist	1) reduces phosphorylated α-syn accumulation in the ventral midbrain and striatum. 2) protects against the loss of behavioral deficits and dopamine neurons.	(Yun et al., 2018)
DA5-CH	AD	GLP-1– GIP receptor dual agonis	1) upregulates the PI3K/AKT growth factor signaling pathway and prevents GSK3β from being overactivated in the hippocampal region. 2) reduces Aβ plaques and p-tau in the hippocampus. 3) improves hippocampal synaptic	(Cao et al., 2018)

(continued on next page)

Table 4 (*continued*)

Drug	Disease	Mechanism	Major effect	Ref
			plasticity and spatial learning abilities.	
DA-JC4/ DA-CH5	PD	GLP-1– GIP receptor dual agonist	1) increases neurotrophic factors like GDNF. 2) reduces inflammatory factors like IL-1β, TNF-α. 3) increases synaptophysin levels, protects dopaminergic neurons, and reduces motor deficits.	(Feng et al., 2018)
Saxagliptin	AD	DDP4 inhibitor	1) increases GLP-1 levels and decreases Aβ42, p-tau, and total tau in the hippocampus. 2) protects hippocampal neurons. 3) improves spatial memory and learning abilities.	(Kosaraju et al., 2013)
Linagliptin	AD	DDP4 inhibitor	1) reduces oxidative stress and mitochondrial dysfunction. 2) prevents caspase-3 and PARP activation. 3) protects neurons from Aβ-induced cytotoxicity by restoring impaired insulin signaling.	(Kornelius et al., 2015)
Saxagliptin	PD	DDP4 inhibitor	1) inhibiting reductions in cyclic AMP levels and ADP/ ATP ratio. 2) prevent reductions in tyrosine hydroxylase-positive neurons in the substantia nigra and levels of TH and dopamine in the striatum. 3) suppresses apoptosis by inhibiting caspase-3 and cytochrome *c* activation. 4) reduces lipid peroxidation and inflammation. 5) improves motor deficits.	(Nassar et al., 2015)
vildagliptin	PD	DDP4 inhibitor	1) suppresses microglial activation and oxidative stress, and reduces pro-inflammatory factors like TNF-α, and iNOS. 2) restores tyrosine hydroxylase immunoreactivity and increases striatal levels of dopamine. 3) improves mitochondrial function and motor deficits.	(Abdelsalam and Safar, 2015)

Aβ: amyloid-beta; GIP: gastric inhibitory polypeptide; AMPK: AMP-activated protein kinase; p-tau: phosphorylated tau; α-syn: alpha-synuclein; GLP-1: glucagon-like peptide-1; DDP4: dipeptidyl peptidase-4.

Table 5
Potential drugs targeted nuclear receptor superfamily.

Drug	Disease	Mechanism	Major effect	Ref
bexarotene	AD	RXR agonist	1) upregulates expression of MerTK and Axl receptors, enhancing microglial phagocytosis, and reducing Aβ levels by 40%. 2) restores nesting behavior, olfactory sensing, cognition, and memory functions. 3) Treatment of an individual human patient for 6 months resulted in approximately 40% improved memory and around 20% reduction in tau levels in cerebrospinal fluid with no significant side effects.	(Cramer et al., 2012; Savage et al., 2015)
Oleoylethanolamide	AD	PPARα agonist	1) improves lipid metabolic disturbances and elevates levels of phospholipid lipids. 2) reduces activation of astrocytes and microglia, and enhances Aβ phagocytosis and lysosomal clearance. 3) increases synaptic plasticity, and improves cognitive function.	(Comerota et al., 2023)
WY14643	AD	PPAR-α agonist	1) enhances the autophagy capacity of microglia by 4-fold. 2) augments neuroplasticity. 3) improves learning, and memory, and mitigates anxiety symptoms.	(Luo et al., 2020)
gemfibrozil	AD	PPAR-α agonist	1) enhances the autophagy capacity of microglia by 3.5-fold. 2) rescues	(Luo et al., 2020)

(*continued on next page*)

Table 5 (*continued*)

Drug	Disease	Mechanism	Major effect	Ref
			spatial memory deficits.	
aspirin	AD	PPAR-α agonist	1) enhances expression of CREB and BDNF neurotrophic factors in the hippocampus. 2) augments calcium influx mediated by AMPA and NMDA receptors. 3) increases dendritic spine density and plasticity. 4) improves learning and memory abilities.	(Patel et al., 2018)
pioglitazone	AD	PPAR-γ agonist	1) enhances the phagocytic capacity of microglia, reducing $A\beta_{1-42}$ and $A\beta_{1-40}$. 2) activates microglia and astrocytes in the hippocampus. 3) augments neuronal plasticity in the hippocampus, and improves learning and memory abilities	(Sastre et al., 2003; Yamanaka et al., 2012)
Ibuprofen	AD	PPAR-γ agonist	1) enhances autophagy capacity, reducing Aβ1–42 and Aβ1–40. 2) mitigates learning and memory impairment. 3) no evident hepatic toxicity.	(Sastre et al., 2003)
Rosiglitazone	AD	PPAR-γ agonist	1) doubles IDE expression, and reduces serum corticosterone levels by 42%. 2) decreases Aβ42 by 40%. 3) mitigates learning and memory impairments.	(Pedersen et al., 2006)
DSP-8658	AD	PPARα/γ agonist	1) decreases SDS-soluble $A\beta_{1-42}$ by 32% and $A\beta_{1-40}$ by 30%. 2) enhances infiltration of microglia and astrocytes surrounding Aβ plaques. 3) improves spatial learning abilities.	(Yamanaka et al., 2012)
T3D-959	AD	PPAR-δ/γ agonist	1) enhances the phagocytic capacity of microglia. 2) reduces expression of tau, p-tau, Aβ, and ubiquitin. 3) improves cognitive function.	(Chamberlain et al., 2020)
/	AD	REV-ERBα	1) promote the formation of lipid droplets within microglia. 2) exacerbates accumulation of Aβ and tau. 3) REV-ERBα deficiency can reverse this phenomenon.	(Lee et al., 2023)

AMPK: AMP-activated protein kinase; IDE: insulin-degrading enzyme; NMDA: *N*-methyl-D-aspartate; REV-ERBα: retinoic acid receptor-related orphan receptor alpha; PPARs: peroxisome proliferator-activated receptors.

reallocation of cholesterol and additional lipids to nerve cells by fastening to receptors on the cellular membrane. A clinical study displayed that carriers of the APOEε4 variant demonstrate heightened Aβ accumulation within the cerebral cortex (Mishra et al., 2018). APOEε2 and APOEε3 are discovered to clear Aβ， but the influence of APOEε4 in propelling the process of AD and PD appears poised to surpass the protective impact of APOEε2 and APOEε3 (Jansen et al., 2015). Major approaches to treating Alzheimer's disease by targeting APOE include modulating APOE's expression levels, structure, receptors, or interactions with other molecules such as amyloid-beta (reviewed in Table 6). Triggering receptor expressed on myeloid cells 2 (TREM2) is predominantly expressed as a type-1 transmembrane protein, and it is targeted to the plasma membrane together with its co-receptor DAP12, has been prone to bind to APOE4 (Schlepckow et al., 2023). TREM2 agonistic antibodies act by binding to the TREM2 receptor, activating its downstream SYK signaling pathway, thereby enhancing microglial chemotaxis and energy metabolism, increasing phagocytosis, and thus clearing pathological products such as Aβ (Ellwanger et al., 2021; Zhao et al., 2022a).

6. Conclusions and prospect

In conclusion, dysregulated lipid metabolism can lead to lipid accumulation and oxidative stress, which damages neurons and increases the risk of AD and PD. Abnormalities in cholesterol, sphingolipid, and glycerophospholipid metabolism are involved in the pathogenesis of both diseases. Abnormal lipid levels can directly accelerate the progression of AD by encouraging the deposition of Aβ as well as tau protein tangles. Indirectly, abnormal lipids can increase the burden on brain vasculature, induce insulin resistance, and affect the structure of neuronal cell membranes. Abnormal lipid metabolism leads to PD through inducing accumulation of α-syn, dysfunction of mitochondria and endoplasmic reticulum, and ferroptosis. Targeting specific steps in lipid pathways may offer novel therapeutic strategies. However, more research is still needed to fully elucidate the molecular mechanisms and identify potential drug targets. Future studies should further explore the interactions between lipid metabolism and other pathways implicated in neurodegeneration, such as protein aggregation and

Table 6
Potential drugs targeted APOE and TREM.

Drug	Disease	Mechanism	Major effect	Ref
HJ6.3	AD	Targeting APOE structure	1) decreases Aβ by 60–80% in the cortex and hippocampus. 2) recruits microglia around plaques but reduces proinflammatory cytokines levels.	(Kim et al., 2012)
Aβ12-28P	AD	Targeting APOE structure	1) reduces total Aβ and tau levels, and prevents synaptic protein decline. 2) improves memory and cognitive deficits, without inducing immune response.	(Sadowski et al., 2006)
fluvastatin	AD	Increasing APOE receptors.	1) upregulates LRP1 expression, a major receptor for apoE. 2) reduces APP-CTFs by 40% and Aβ by 20%. 3) rescues GABAergic neuron degeneration and memory deficits.	(Shinohara et al., 2010)
PH002	AD	Targeting interaction between APOE and Aβ.	1) alters the ligand-binding domain of apoE4 to make it more similar to apoE3. 2) decreases apoE4, reduces Aβ40–42 levels by 70%, and p-tau by 40%. 3) prevents synaptic protein level decline.	(Wang et al., 2018)
TREM2	AD	Overexpressing TREM2	1) reduces Aβ levels by 30.9% in the hippocampus, and 40.0% in the cortex. 2) increases synaptic proteins SYN and PSD-95, along with 30% higher NeuN-positive neurons, rescuing 20% of synaptic and neuronal loss. 3) ameliorates spatial cognitive impairment.	(Ruganzu et al., 2021)
AL002	AD	TREM2-activating antibody	1) reduces Aβ levels by 35% in the hippocampus and 40% in the cortex. 2) increases blood levels of DHA by 17%, and EPA by 71%. 3) upregulates the inflammatory response and activates microglia. 4) improves memory impairment.	(Wang et al., 2020)
HT2AB	AD	TREM2-activating antibody	1) increases the expression of chemotactic factors such as CCL4, CXCL10, and IL-1β, activating microglial proliferation. 2) reduces total amyloid plaque load by 40% in the cortex, improving cognitive function.	(Ellwanger et al., 2021)
Ab18	AD	TREM2-activating antibody	1) reduces the formation of cytokines that promote inflammation. 2) enhances the number and activity of microglia. 3) reduces Aβ aggregation and plaque load, minimizing synaptic and neuronal loss. 4) improves learning and memory deficits.	(Zhao et al., 2022a)
ATV: TREM2	AD	TREM2-activating antibody engineered with ATV	1) activates the mTOR pathway and promotes microglial proliferation and phagocytosis. 2) promotes mitochondrial fatty acid and glucose oxidation in microglia, boosting cellular energy metabolism. 3) readily accesses the brain with no evident adverse effects.	(van Lengerich et al., 2023)

ATV: antibody transport vehicle; CTFs: C-terminal fragments; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid.

mitochondrial dysfunction. Large clinical trials are also warranted to evaluate whether modulating lipid metabolism can alleviate disease symptoms or slow progression. It is suggested to utilize PET imaging and other molecular imaging techniques to longitudinally monitor changes in brain lipid metabolism in response to different therapeutic interventions. Multi-target treatment strategies should be explored to better modulate lipid metabolism at different steps in the pathogenic pathway. Gaining more insight into the lipidological underpinnings of AD and PD could lead to the development of successful preventative and therapeutic strategies for these prevalent age-related neurodegenerative illnesses.

What's more, a recent study found that sex differences(Sex generally refers to a set of biological attributes that are associated with physical and physiological features) have a profound impact on the risk of AD and PD, with women having a higher probability of AD than men and a lower probability of PD than men (Podcasy and Epperson, 2016). This may be closely related to changes in estrogen in women. Estrogen is involved in brain lipid metabolism, and the instability of its level will affect the stability of lipid metabolism (Morselli et al., 2018). At the same time, the decreased level of circulating estrogen in postmenopausal women is another risk factor for AD and is also intimately linked to the onset and progression of PD (Grimm et al., 2016; Picillo et al., 2017). Although there is no direct evidence to prove the mechanism of estrogen involvement in AD and PD processes, we further speculate that the lipid metabolism disorder caused by the instability of estrogen levels in women is an important reason for the sex difference in the incidence of AD and PD. Therefore, future studies should further investigate the influence of sex on lipid dysregulation in AD and PD.

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Not applicable.

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Not applicable.

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Bin Tong: Writing – original draft. **Yaoqi Ba:** Writing – original draft. **Zhengyang Li:** Writing – review & editing. **Caidi Yang:** Writing – original draft. **Kangtai Su:** Conceptualization. **Haodong Qi:** Conceptualization. **Deju Zhang:** Writing – review & editing. **Xiao Liu:** Supervision. **Yuting Wu:** Formal analysis. **Yixuan Chen:** Conceptualization, Data curation. **Jitao Ling:** Supervision. **Jing Zhang:** Funding acquisition. **Xiaoping Yin:** Supervision. **Peng Yu:** Overall design, review & editing, Supervision.

Declaration of competing interest

None.

Data availability

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