LIPID METABOLISM AND METABOLIC DISORDERS IN NEURODEGENERATION: IN THE ERA OF ALZHEIMER'S

Pooja kumari and Preeti sharma

Abstract

Abnormal protein aggregates are the hallmarks of many neurodegenerative diseases, among the topmost prevalent neurodegenerative illnesses, are Alzheimer's and Parkinson's disease (AD and PD respectively). The main contributors to neurodegeneration are protein accumulation, excitotoxicity, neuronal apoptosis, swelling, mitochondrial malady, oxidative stress, and metabolic disease. Since protein accumulation is the primary cause of these neurological illnesses and this area of research is currently at the cutting edge of science. Growing data indicates that dysregulation of extracellular vesicles (EVs) and changes in lipid metabolism, both hasten the propagation of protein aggregate and the development of neurodegeneration in neuronal cells. However, lipids form more than 50 percent of the dry weight and roughly 10-12 percent of the moist weight of the brain, respectively. Phospholipids, sphingolipids, glycerolipids, fatty acids, and sterols are the main lipid species found in the brain. The myelin sheath and synapses both depend on these lipids as structural elements. Additionally, they function as bioenergy and signal transducers that control biological activities. There is growing evidence that lipid metabolism contributes to AD. Even the diseases associated with AD can be effectively treated or prevented using lipid-targeting therapies. The review delves further into the lipids connected to AD and metabolic disorders related to neurodegeneration.

Keywords- Alzheimer's disease, lipids, metabolism, neuroinflammation, fatty acids.

1. INTRODUCTION

Our aging population is facing an increasing medical burden from age-related neurological disorders. PD, the second-highest prevalent neurodegenerative disease, influences roughly one percent of persons aged 60 or above, whereas Alzheimer's disease (AD), the prior most common neurodegenerative disorder, influences 11.3 percent of individuals over the age of 65. As AD progresses, neurofibrillary tangles advance in a predictable pattern, beginning in the trans-entorhinal cortex and moving on to the hippocampus and cortical areas. Development of Aβ plaques is the other histological sign of AD, which does not adhere to the same rigid spatiotemporal pattern and has a poor correlation with cognitive impairment. Instead, soluble Aβ oligomers have drawn more interest as potential pathogenesis-inducing agents. Genetically, three genes, APP, PS1, and PS2, are linked to AD. AD may result from more than 50 distinct APP gene mutations. A single mutation in the APP at position 717 is the mutation that occurs most frequently. This one mutation causes an isoleucine, phenylalanine, or glycine residue to take the place of a valine residue. Increased levels of the Aβ proteins are deposited in neuritic plaques because of APP mutations (Dimakopoulos et al 2005; Li et al 2007)

Additionally, recent investigations suggest that exosomes and synaptic vesicles (SVs), the types of extracellular vesicles (EVs) perform a critical role in the spread of protein accumulation linked to neurodegeneration in the brain. It has been established that ceramide plays a function in increasing the accumulation of Aβ near lipid rafts and the dissemination of tau and Aβ through exosomes. Changes in ceramide metabolism have also been connected to the risk and development of AD. The evidence on how lipid metabolites affect exosome biogenesis, recipient cell uptake, and the rate of disease progression will be looked at next in this review. All of them indicate that the etiology of neurodegenerative illnesses is influenced by the vehicle, not simply the payload of EVs. (Mielke et al 2010; Czubowicz et al 2019)

Studies investigating the connection between dementia and metabolic conditions such as diabetes, obesity, hypertension, and dyslipidemia have proliferated in recent years. Finding connections between metabolic illnesses is difficult due to etiological complexity and co-morbidity. This review emphasizes recent research that identifies convergent pathways, such as insulin resistance, that may be responsible for co-morbid metabolic diseases and hence raise the risk of dementia. In addition to offering crucial insights into the causes and interconnections of late-life dementias, the discovery of such convergent elements will also inspire new approaches to the treatment and prevention of these conditions.

2. LIPID CLASSIFICATION AND BRAIN LIPID TRANSPORT

The primary macromolecular component of the brain is lipid. After adipose tissue, the CNS has the second-highest lipid concentration. (Hamilton et al 2007)
The lipid may wrap the axons of the cerebrum and the spinal cord or serve as the myelin sheath. Five different types of lipids are transported in the brain: triacylglycerols, fatty acids, phospholipids, sterol lipids, and sphingolipids.

Indispensable, polyunsaturated fatty acids (PUFAs) emulate a crucial function in the upkeep and development of the brain. Neuropsychiatric conditions such as significant misery, AD, and bipolar disease have been associated with aberrant PUFA status.

The polyunsaturated fatty acids (PUFAs) that are essential emulate the important part in the formation and preservation of the brain. The deformity of PUFA status has been associated with neuropsychiatric illnesses example severe depression, AD, and bipolar disorder. Docosahexaenoic acid, or DHA, is found in foods and is a key component of the family of omega-3 polyunsaturated fatty acids. It provides neuroprotection by particularly lowering the amount of beta-amyloid that is deposited in an AD mice model (Zhu et al. 2019). Two different pathways allow fatty acids to permanently pass the blood-brain barrier. The passive transport method is one of them.

There was a time when scientists believed that the majority of lipids crossed the BBB through the passive dispersal of albumin-associated free fatty acids. Fragmentation of the non-esterified fatty acid from albumin is an essential first step in the three-part process of passive diffusion across endothelial cell membranes: adsorption, and transmembrane movement. In terms of their relative compatibility, an FA for albumin in the blood circulation, the rate of separation between the FA and albumin, and the metabolic flow and FA utilization by endothelial cells and nerve cells are the three main factors that determine the absorptivity of the BBB for an FA (Pifferi et al 2021). The brain is especially susceptible to harm ROS-induced injury because of its greater lipid and iron concentrations, high oxygen intake, and subsequent ROS generation. Various macromolecules may be affected by reactive oxygen species (ROS) in different ways, depending on factors such as the kind of ROS generated, the reactivity of the ROS, the diffusion distance, and the location of formation (Jaganjac et al 2016). The bis-allylic site of polyunsaturated fatty acids (PUFAs) is particularly vulnerable to ROS-induced damage, making PUFAs a common ROS target. An overabundance of iron in the brain, in addition to its involvement in carcinogenesis and the promotion of cellular proliferation, may trigger a chain reaction of lipid peroxidation (Jaganjac et al. 2020). Mutagenic and carcinogenic effects of elevated lipid peroxidation have been postulated. Arachidonic acid (omega-6) and docosahexaenoic acid (omega-3), both important fatty acids, are present in high amounts in the brain. Linoleic acid (omega-6 PUFA) and alpha-linolenic acid (omega-3 PUFA) are the primary precursors for the production of long-chain PUFAs. If these PUFAs are peroxidized without an enzyme, reactive aldehydes are produced as a byproduct; these aldehydes have a significantly longer half-life and may travel much farther than reactive oxygen species (ROS), particularly if they bind to (extra)cellular proteins(Zhang et al 2002).

Some other mechanisms are influenced by four different types of transport proteins. These proteins are as follows: fatty acid transport proteins 1-6 (FATP1-6), fatty acid translocase/CD 36 (FAT/CD36), intracellular fatty acid binding proteins 1-9 (FABP), plasma membrane fatty acid binding protein (FABPpm), and caveolin-1. These two pathways may work together to control the pace at which the brain metabolizes fatty acids.

3. LIPID METABOLISM IN ALZHEIMER'S-

Artificially produced phospholipid vesicles with an elevated membrane curvature (30 nm width (Sugiura et al., 2015) have been demonstrated to expedite Ab fibrillization and improve binding in AD. The degree to which the Ab accumulation shown in this in-vitro investigation is similar to that seen in vivo with exosomes or SVs has not been documented.

There is mounting evidence that lipids are involved in neurodegenerative disorders clearly explained in Table 1. The primary changed function in patients was lipid metabolism, with high-density lipoprotein serving as a prominent node in the network analysis, interacting with some proteins. By Mendelian inheritance, genome-wide association studies (GWAS), and transcriptomic research, an increasing number of genes that are engaged in lipid metabolism have been identified. These genes have been connected to neurodegenerative illness example AD and PD. According to Huang and Mahley (2014), the Apolipoprotein epsilon4 allele is the most frequent genetic liability for Alzheimer's disease. This allele is also essential for delivering cholesterol into the cerebrum. GWAS investigations for AD have led to the uncovering of a huge number of risk genes linked to lipid metabolism. One such study was recently evaluated by Chew et al. (2020). Lipidomic examination of tissues taken from AD sufferers besides animal models of the disease has shown that the levels of a variety of lipids, such as fatty acids, glycerolipids, and glycerophospholipids, are altered in AD (Mesa-Herrera et al., 2019; Chew et al., 2020). Postmortem examination of the brain tissue of AD patients revealed phospholipid deficits, such as an elevated amount of ethanolamine plasmalogen in comparison to phosphatidylethanolamine levels. Given the paradigm of the ceramide-sphingosine-1-P (S-1-P) rheostat, which suggests that the equilibrium between these two nearly connected and produced lipids may examine whether or not a cell lives or dies (Hait et al., 2006; Taniguchi and Okazaki, 2020), ceramide has garnered a lot of attention in recent years. S-1-P, on the other hand, has a pro-survival impact that is arbitrated by G-protein coupled receptor signaling, in contrast to ceramide, which has been demonstrated to have effects that are pro-apoptotic, autophagic, and inflammatory. Ceramide is also suspected of playing a crucial role in the etiology of AD because it encourages the aggregation of Amyloid beta by facilitating its interaction with lipid rafts and ceramide-rich exosome membranes. Lipid rafts are high in cholesterol and sphingolipids (Czubowicz et al., 2019). Several studies that analyzed tissue from AD patients besides rat models of Alzheimer's disease revealed higher ceramide levels. According to Han et alresearch's from 2002, the neuron tissues of AD patients with mild to severe indications were related to greater total ceramide levels than age-matched controls. Immunohistochemistry of the frontal cortex demonstrated higher ceramide levels in astrocytes in Alzheimer's disease patients. Ceramide levels were also shown to be elevated in the cerebrospinal fluid of Alzheimer's patients when differentiated from ALS patients and controls (Satoi et al., 2005). Greater baseline stage of the long-chain ceramides C22:0 and C24:0 were predictive of cognitive decrease and hippocampus shrinkage, according to an analysis of plasma taken from a small sample of people with Alzheimer's disease, moderate cognitive impairment (MCI), and healthy controls (Mielke et al., 2010).

A longitudinal research that included 99 women in their eighth decade demonstrated, once again, that the greater baseline stage of long-chain ceramides was related to an enhanced risk

of AD (Mielke et al., 2012). The investigation was conducted on the analysis of serum. Both AD and dementia-related leukemia patients have elevated amounts of ceramide in their serum (Savica et al., 2016). It has also been discovered that there is an increase in ceramides in the brain tissue of animal experiments of AD (Alessenko et al., 2004; Wang et al., 2008).

3.1 THE NEURODEGENERATIVE EFFECTS OF CERAMIDE IN AD

In the AD brain, oxidative damage, changed redox signaling, mitochondrial malfunction, glucose hypometabolism/other metabolic stressors, Ca2+ dysregulation, and inflammatory response are well-known processes that cause neuronal and synaptic degeneration. Solvent oligomers of the Aβ peptide work on neurons and glia to start and spread several of these pathways. The function of ceramide/S1P was examined in both these damage pathways and the amyloidogenesis process(Czubowicz et al. 2019).

Ceramides are a diverse class of lipids that are both the main metabolic byproducts of sphingomyelin catabolism and the main bioactive particles of sphingolipid pathways. They are made of various fatty acids with carbon atom lengths ranging from 14 to 26 connected to sphingosine. Sphingosine is typically joined to the non-hydroxy fatty acids palmitic (C16) and stearic (C18)(Pant, D. C., Aguilera-Albesa, S., & Pujol, A 2020)

Along with playing a crucial part in signal transduction, sphingolipids in lipid rafts also have a regulatory role in synaptic function, helping to maintain synapses, dendritic spines, and neuronal transmission.

Ceramides also stimulate the generation of ROS forming a connection with oxidative stress and sphingolipid metabolism causing negative effects on neuronal survival.

Sphingolipid ceramide is a metabolite with a role in both cellular differentiation and death. Apoptosis induction studies have been performed on many mammalian cell lines, and it has freshly been linked to apoptosis in neurons. The involvement of proline-directed kinases, phosphatases, phospholipases, transcription factors, and caspases, as well as other signal transduction pathways, seems to be necessary for ceramide-induced cell death, the mechanisms of which need to be completely explored(Hannun, Y. A., & Obeid, L. M. 2008). Ceramide, when administered at certain doses and/or developmental phases, seems to increase survival and differentiation in specific neural systems.

3.2 THE NEURODEGENERATIVE EFFECTS OF SPHINGOSINE-1-PHOSPHATE IN AD

Accompanying neuroinflammation, gliosis, synapse damage, and cognitive impairment, AD is characterized by amyloid accumulation produced from amyloid precursor protein (APP), and neurofibrillary tangles (NFTs) containing hyperphosphorylated tau. When the illness progresses, significant neuronal death and atrophy of the brain come in the inevitable outcomes (Yuyama, K., Mitsutake, S., & Igarashi, Y. 2014). The current scientific literature on the involvement of S1P in Alzheimer's disease is contentious, with some findings showing a protective role and others proposing a causal role in the pathogenesis of Alzheimer's disease. A study revealed that the expression of SK1 was lowered and S1PL was elevated in

the brains of persons with Alzheimer's disease. This finding suggests that S1P content is adversely connected with Aβ deposits (Pyszko, J. A., &Strosznajder, J. B. 2014). The research was conducted post-mortem. Another post-mortem investigation in human AD brains indicated a drop in the S1P/sphingosine ratio in the hippocampus and inferior temporal cortex of AD brains, and this decrease was related to the loss of SK1 activity. This decline occurred in both regions of the AD brain. Another study established the interaction of S1P with the beta-secretase BACE1, indicating that it plays a direct role in the production of Aβ in neurons (Pyszko, J., &Strosznajder, J. B. 2014). Experiments that indicated a clear association between the production of S1P and that of A added more support to these facts, which were previously established as being accurate. Therefore, lowering the amount of enzymes that generate S1P and increasing the amount of enzymes that degrade S1P led to a reduction in the amount of A that was produced. Specifically, the relative activity of SK2 was shown to be higher in Alzheimer's disease brains. Neuronal mortality was shown to be strongly related to increased levels of S1P in primary cultured neurons produced from S1PL-deficient mice, according to research carried out by our laboratory (Czubowicz et al. 2019). This neurotoxic impact was brought about through a process that was mediated by calcium, calpain, and CDK5. In addition to this, there was a correlation between S1PL deficit and tau hyperphosphorylation. Additionally, it was found that S1PL knockout cells had decreased lysosomal activity in addition to an accumulation of APP and amyloidogenic APP C-terminal fragments (Motyl et al. 2018). On the other hand, the immunomodulatory analog of S1P known as fingolimod (FTY720) was shown to ameliorate neuronal damage and cognitive impairment caused by A in rat hippocampus. Notably, the neuroprotection afforded by fingolimod was shown to be linked to changes in the expression of mitogen-activated protein kinases as well as certain inflammatory markers (Sentelle et al 2012). Additionally, vaccination of AD mice with the vaccine EB101, which is a mixture of synthetic human A42 and liposomes carrying S1P, was shown to be more successful compared to immunization with synthetic A42 plus Freund's adjuvant. This was the conclusion reached after comparing the two methods. In mice inoculated with EB101, researchers observed improved Aβ clearance, lower swelling in the hippocampus and cortical areas, and fewer plaque neurites. These results were seen in mice.

4. LIPID BUILDUP IS CORRELATED WITH INFLAMMATION-INDUCED NEUROTOXICITY.

A rising amount of evidence supports the notion that lipid metabolism and inflammation are inextricably related. Recent research found that a high-fat/high-cholesterol diet increased microglial activation while decreasing neuronal growth (Moloney EB et al. 2018; Nalls MA et al. 2019; Diaz-Ortiz ME et al. 2022). It is interesting to note that lipid buildup, and not overexpression of alpha-synuclein, was enough to duplicate the patient's biochemistry in mice. This finding suggests that GPNMB levels may reflect lipid levels in the brain. Microglia is responsible for the removal of broken synapses and dead cells from the brain at the cellular level. Infections and recurrent tissue injury induce microglia to activate beyond their homeostatic range, upregulate lipid droplets, and fundamentally modify metabolism and function (Deleidi M, Isacson O. Viral 2012; Marschallinger J et al. 2020). Once the inflammatory trigger is removed, microglia will revert to their homeostatic range. Microglial

function is changed as a result of repeated activation, which in turn causes altered gene expression patterns, the accumulation of lipofuscin, senescence, and myeloid recruitment of nonmicroglial cells to the brain. This ultimately results in a shift in the immune status of the brain. In addition, macrophages collect lipids in GD and NPC1, which is consistent with the malfunctioning of myeloid cells that are connected to more frequent forms of neurodegenerative illness (Van Eijk M, Aerts J. 2021). TREM2 is a receptor at the plasma membrane that is abundantly expressed by myeloid cells. Variation in the chromosomal sequence of TREM2 is associated with an increased risk of Alzheimer's disease (AD), and TREM2 can bind to apolipoproteins, including APOE (Fig. 1).

Microglial cholesteryl esters and monosialodihexosylganglioside (GM3) accumulate due to the accumulation of microglial cholesteryl esters when TREM2 is deleted (Nugent AA et al. 2020; Griciuc A et al. 2019). This reduces the responsiveness of mouse microglia to extend beyond adaptive homeostasis, which in turn alters the expression of ApoE and lipoprotein lipase. Reduced brain glucose metabolism is seen in mice lacking either Trem2 or Grn, which is compatible with prodromal stages of human neurodegenerative illness (Reifschneider A et al. 2022; Gotzl JK et al. 2019). Furthermore, a variety of lipids can activate a nuclear factor of activated T cells (NFAT) reporter in vitro; however, the TREM2 R47H allele, which is linked with the rising risk of AD, suppresses this kind of immunological activity. Alterations in lipid metabolic genes that are TREM2-dependent are detected in a community of mice macrophages that rise in adipose tissue when they are fed a high-fat diet. The potential healing effects of the antibody on lipid metabolism are unknown, monoclonal antibodies against TREM2 have been shown to enhance microglial activity and reduce plaque burden in preclinical models of Alzheimer's disease (Jaitin DA et al 2019; Wang S, et al 2020; Schlepckow K, et al 2020; Price BR et al 2020). This suggests that these antibodies may be used as a healing perspective to stabilize TREM2.

Additionally, the Liver X receptor (LXR) appears to be involved in the integration of lipid metabolism and neuroinflammation in Alzheimer's disease. Indeed, LXR regulates ABCA1 and apoE, both of which are involved in Aβ transport and clearance. The activation of these genes in the brain by LXR agonists may have a considerable influence on Aβ deposition and the development of amyloid/neuritic plaques. In APP/PS1 AD-Tg mice, deletion of either LXR or LXR resulted in increased amyloid plaque burden and aggravated AD pathogenesis. This impact was ascribed to abnormalities in brain cholesterol metabolism as well as LXR's capacity to control microglia inflammatory responses in the presence of fAβ. Furthermore, high-fat/high-cholesterol diets have been shown in mice models to exacerbate AD-like neuropathology by increasing neuroinflammation and APP processing. T0901317, a synthetic LXR agonist, raises ABCA1 and apoE protein levels, reduces Aβ levels in the brain, and thereby ameliorates amyloid pathology and memory impairments produced by high-fat/high-cholesterol diets in APP23 mice. These findings, along with the capacity of LXR agonists to reduce the expression of inflammatory genes in the presence of LPS, suggest a probable link between LXR anti-inflammatory actions and AD protection (Jihong Kang and Serge Rivest, 2012).

5. PATHOLOGICAL ELEMENTS THAT ENCOURAGE THE ACCUMULATION OF LIPID IN NEUROGLIA

Cargo-specified clearing of organelles via selective cell death is critical for preserving the integrity of the neuronal central milieu under normal settings.

When cells are starved for an extended length of time, the lipids that are released from membrane organelles through macroautophagy/autophagy are packed and stored in new LDs (Nguyen TB, Olzmann JA. 2017). Lipids are essential components of cell membranes. Moreover, LD formation happens in a broad range of clinical diseases, and LDs may reveal a spectrum of functional abnormalities depending on context or cell type. It has been shown that 'foamy macrophages,' that were previously unknown to bestow to atherosclerotic injury, are formed when a substantial quantity of decreased density lipoprotein cholesterol is phagocytosed by macrophages. In response to an increase in lipids, macrophages accumulate CE by combining with alcohol unesterified FC through ACAT1 (Smolic T, et al. 2021) and then binding the FC to modified lipoproteins in LDs. Lipolytic materials of triglyceride-rich lipoproteins (TGRL) were shown to boost the Blood-brain barrier transfer coefficient and stimulate astrocyte lipid aggregation in the study conducted by Lee's group. These findings show that an increase in blood triglycerides influences the development and aggregation of intracellular LDs in both the periphery and the brain.

Nutritional deficits and hypoxia are prevalent stressors in various illnesses of the central nervous system, and they have been linked to the development and progression of neurodegenerative disorders. When astrocytes were exposed to many forms of nutritional stress for 24 hours, including partial/complete nutritional deficit, excess FFA, and L-lactate, the number and/or size of LDs significantly increased [74]. Similar to what was shown by Nguyen and coworkers (Nguyen TB, et al. 2017; Dienel GA, Cruz NF 2016), DGAT1 and DGAT2 inhibitors decreased LD accumulation in starved astrocytes. Increased norepinephrine and low oxygen tension may both accelerate glycogenolysis, aerobic glycolysis, and lactate generation in astrocytes, hence favoring the buildup of LDs. Lack of ATGL, for instance, causes an increase in fat mass, and research shows that ATGL-/- murine macrophages collect a lot of TG-rich LDs. Defective lipolysis also contributes to intracellular lipid aggregation.

6. METABOLIC DISORDERS IN NEURODEGENERATION

Diseases like AD, PD, and HD all advance in an age-related but accelerated manner. Accumulation of oxidative reaction products causes extensive damage to lipids and protein in most diseases (Procaccini, C. et al 2016). The inflammatory response causes excessive oxidative stress due to the unregulated generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Appercipient and motor reduction, as well as minute signaling problems example decreased insulin signalling, are all symptoms shared by these neurodegenerative diseases and old age. Intriguingly, all three diseases have a pattern of

metabolic malfunction and a neurodegenerative pathogenesis. It is possible that hypothalamic illness, namely damage caused by aberrant protein accumulates such as mutant htt or Amyloid beta plaques, is a contributing factor in energy dysregulation, although this is not the case. variation in leptin, ghrelin, GLP-1, and insulin communication between the CNS and the periphery, which govern energy management, provide a more comprehensive and plausible explanation for the metabolic abnormalities associated with neuronal damage in these illnesses. Although these metabolic hormones have long been associated with metabolic diseases, it is now obvious that changes to these hormones may have profound effects on the etiology of several well-known forms of neurodegeneration, as noted above. There is little doubt that pharmaceutical targets that might alter these metabolic variables are promising in the fight against neurodegenerative diseases (Capucho et al. 2022). New evidence suggests that effective therapies for neurodegenerative illnesses should aim to improve function across the body, not only in the Central nervous system. Various endocrinological elements likely play a connectional role in smoothening the pathophysiology of AD, HD, and PD. As a result, experiments that aim to learn the combined outcome of these hormones, preferably their separate effects, are required. Several variables, including housing and feeding, might increase the likelihood that animals in a study will acquire metabolic dysfunctions, making it difficult to determine whether the metabolic phenotype is related to the course of the illness or the animal's lifestyle (Muddapu, V. R. et al. 2020).

8. CONCLUSION

Disease development in neurodegenerative disorders is linked to the dispersion of pathogenic protein aggregates throughout brain areas. confirmation proves that EVs play a critical role in facilitating the spread of harmful protein accumulation in various neurodegenerative illness. By encouraging the oligomerization of accumulation-prone pathogenic proteins and reducing EV biogenesis, alterations in lipid metabolism also affect illness development. Although the focus of this review was on the neuropathology of AD and PD, EVs and lipid metabolism changes are also involved in other neurodegenerative diseases with pathogenic protein accumulates, such as dementia with Lewy bodies, amyotrophic lateral sclerosis, prion illness, and other tauopathies and -synucleinopathies (Hannun, Y. A., & Obeid, L. M. (2018). Even though the proteins implicated in accumulation for each of these illnesses are distinct, there may be a shared highlight toxic mechanism that regulates the development of these accumulations that may be used therapeutically to delay or prevent neurodegenerative disease. Understanding the metabolic shifts may lead to the discovery of new biomarkers and therapeutic targets for treating neurodegenerative disorders.

Most of the strongest proof for the role of lipid metabolism in the development of dementia comes from learning of tissues from GBA carriers and GBA defective model animals and cultured cells. Cell-autonomous vesicular trafficking and autophagy, exosome formation, cell signaling, and cell survival are only some of the many cellular processes affected by lipid composition, all of which contribute to disease development. In this review, we looked at the data suggesting that the lipid content of membranes strictly interacts with neurodegenerative proteins to encourage accumulation and disease. Ceramide metabolism is intriguing because it affects so many processes that have been linked to dementia. These include membrane

fluidity and curvature, cell signaling, control of apoptosis, autophagy, inflammation, and the formation of exosomes(Marschallinger J, et al. 2020). Conclusions from these analyses imply that modifications in lipid metabolism may have a significant impact on the rate of disease development. Elucidating lipid-mediated mechanisms to bring down neurodegeneration holds great therapeutic promise because lipid abnormalities in AD, PD, and other neurodegenerative illnesses with a propensity for protein aggregation share commonalities in modifying protein aggregation. The increased complexity of the lipid landscape is a consequence of advances in the examination and annotation of lipids from human tissues, animal, or cell culture models. Key lipid changes in etiology and disease development will need to be identified by the further lipidomic study of patient tissues, model organisms subject to isogenic control, and cell culture models.

As neurodegeneration becomes more common, researchers are more interested in learning how glia contributes to the layout of protein accumulation and illness. It is not yet known which glial cells are neuron-protective, and which are neurotoxic. It has been suggested in several studies that glia may initially have a neuroprotective role by removing gliding and EV-related proteins that are harmful and might potentially seed and spread disease in recipient neurons. Toxic effects on glia may result from the ingestion of pathogenic EVs, which can then spread pathologic proteins inside glial EVs (Laulagnier et al., 2018; Sardar Sinha et al., 2018). The complicated relationships between neurons and glia in health and illness are only now being elucidated by research utilizing custom of iPSC-acquire neurons and glia. To further understand the intricate connections between different cell types that are disturbed in neurodegenerative disorders, studies employing organoid models produced from iPSCs may be required. To further understand whether glia inhibit or promote the spread of neurodegenerative disease, more research is required. This research has the potential to uncover new treatment targets for halting the development of neurodegenerative pathology and slowing the course of illness by capitalizing on the enhanced absorption of pathogenic aggregate-prone proteins by glia (Estes, R. E. 2021).

REFERENCES

1. Dimakopoulos A. C. (2005). Protein aggregation in Alzheimer’s disease and other neuropathological disorders. Current Alzheimer research, 2(1), 19–28. https://doi.org/10.2174/1567205052772795
2. Li, M., Chen, L., Lee, D. H., Yu, L. C., & Zhang, Y. (2007). The role of intracellular amyloid beta in Alzheimer’s disease. Progress in neurobiology, 83(3),131–139.https://doi.org/10.1016/j.pneurobio.2007.08.002.
3. Mielke, M. M., Haughey, N. J., Bandaru, V. V., Schech, S., Carrick, R., Carlson, M. C., Mori, S., Miller, M. I., Ceritoglu, C., Brown, T., Albert, M., & Lyketsos, C. G. (2010). Plasma ceramides are altered in mild cognitive impairment and predict cognitive decline and hippocampal volume loss. Alzheimer’s &dementia : the journal of the Alzheimer’s Association, 6(5), 378–385. https://doi.org/10.1016/j.jalz.2010.03.014
4. Czubowicz, K., Jęśko, H., Wencel, P., Lukiw, W. J., & Strosznajder, R. P. (2019). The Role of Ceramide and Sphingosine-1-Phosphate in Alzheimer's Disease and Other

Neurodegenerative Disorders. Molecular neurobiology, 56(8), 5436–5455. https://doi.org/10.1007/s12035-018-1448-3

5. J.A. Hamilton, C.J. Hillard, A.A. Spector, P.A. Watkins, Brain uptake and utilization of fatty acids, lipids and lipoproteins: application to neurological disorders, Journal of Molecular Neuroscience, 33 (2007) 2-11. https://doi.org/10.1007/s12031-007-0060-1
6. Zhu, T. B., Zhang, Z., Luo, P., Wang, S. S., Peng, Y., Chu, S. F., & Chen, N. H. (2019). Lipid metabolism in Alzheimer's disease. Brain research bulletin, 144, 68–74. https://doi.org/10.1016/j.brainresbull.2018.11.012
7. Pifferi, F., Laurent, B., & Plourde, M. (2021). Lipid transport and metabolism at the blood-brain interface: Implications in health and disease. Frontiers in Physiology, 12, 645646. https://doi.org/10.3389/fphys.2021.645646.
8. Jaganjac, M., Cipak, A., Schaur, R.J., Zarkovic, N., 2016. Pathophysiology of neutrophilmediated extracellular redox reactions. Front. Biosci. - Landmark 21, 839–855. https://doi.org/10.2741/4423.
9. Jaganjac, M., Milkovic, L., Gegotek, A., Cindric, M., Zarkovic, K., Skrzydlewska, E., Zarkovic, N., 2020a. The relevance of pathophysiological alterations in redox signaling of 4-hydroxynonenal for pharmacological therapies of major stressassociated diseases. Free Radic. Biol. Med. 157. https://doi.org/10.1016/j.
10. Zhang, Y., Chen, S.-Y., Hsu, T., Santella, R.M., 2002. Immunohistochemical detection of malondialdehyde-DNA adducts in human oral mucosa cells. Carcinogenesis 23, 207–211. https://doi.org/10.1093/carcin/23.1.207.
11. Sugiura, Y., Ikeda, K., & Nakano, M. (2015). High Membrane Curvature Enhances Binding, Conformational Changes, and Fibrillation of Amyloid-β on Lipid Bilayer Surfaces. *Langmuir : the ACS journal of surfaces and colloids*, *31*(42), 11549–11557. https://doi.org/10.1021/acs.langmuir.5b03332
12. Huang, Y., &Mahley, R. W. (2014). Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiology of disease*, *72 Pt A*, 3–12. https://doi.org/10.1016/j.nbd.2014.08.025
13. Chew, H., Solomon, V. A., &Fonteh, A. N. (2020). Involvement of Lipids in Alzheimer's Disease Pathology and Potential Therapies. *Frontiers in physiology*, *11*, 598. https://doi.org/10.3389/fphys.2020.00598
14. Mesa-Herrera, F., Taoro-González, L., Valdés-Baizabal, C., Diaz, M., & Marín, R. (2019). Lipid and Lipid Raft Alteration in Aging and Neurodegenerative Diseases: A Window for the Development of New Biomarkers. *International journal of molecular sciences*, *20*(15), 3810. https://doi.org/10.3390/ijms20153810
15. Hait, N. C., Oskeritzian, C. A., Paugh, S. W., Milstien, S., & Spiegel, S. (2006). Sphingosine kinases, sphingosine 1-phosphate, apoptosis and diseases. *Biochimica et biophysica acta*, *1758*(12), 2016–2026. https://doi.org/10.1016/j.bbamem.2006.08.007
16. Taniguchi, M., & Okazaki, T. (2020). Ceramide/Sphingomyelin Rheostat Regulated by Sphingomyelin Synthases and Chronic Diseases in Murine Models. *Journal of lipid and atherosclerosis*, *9*(3), 380–405. https://doi.org/10.12997/jla.2020.9.3.380
17. Satoi, H., Tomimoto, H., Ohtani, R., Kitano, T., Kondo, T., Watanabe, M., Oka, N., Akiguchi, I., Furuya, S., Hirabayashi, Y., & Okazaki, T. (2005). Astroglial expression of ceramide in Alzheimer's disease brains: a role during neuronal

apoptosis. *Neuroscience*, *130*(3), 657–666. https://doi.org/10.1016/j.neuroscience.2004.08.056

18. Mielke, M. M., Bandaru, V. V., Haughey, N. J., Xia, J., Fried, L. P., Yasar, S., Albert, M., Varma, V., Harris, G., Schneider, E. B., Rabins, P. V., Bandeen-Roche, K., Lyketsos, C. G., & Carlson, M. C. (2012). Serum ceramides increase the risk of Alzheimer disease: the Women's Health and Aging Study II. *Neurology*, *79*(7), 633–641. https://doi.org/10.1212/WNL.0b013e318264e380
19. Savica, R., Murray, M. E., Persson, X. M., Kantarci, K., Parisi, J. E., Dickson, D. W., Petersen, R. C., Ferman, T. J., Boeve, B. F., & Mielke, M. M. (2016). Plasma sphingolipid changes with autopsy-confirmed Lewy Body or Alzheimer's pathology. *Alzheimer's & dementia (Amsterdam, Netherlands)*, *3*, 43–50. https://doi.org/10.1016/j.dadm.2016.02.005
20. Alessenko, A. V., Bugrova, A. E., & Dudnik, L. B. (2004). Connection of lipid peroxide oxidation with the sphingomyelin pathway in the development of Alzheimer's disease. *Biochemical Society transactions*, *32*(Pt 1), 144–146. https://doi.org/10.1042/bst0320144
21. Wang, G., Silva, J., Dasgupta, S., &Bieberich, E. (2008). Long-chain ceramide is elevated in presenilin 1 (PS1M146V) mouse brain and induces apoptosis in PS1 astrocytes. *Glia*, *56*(4), 449–456. https://doi.org/10.1002/glia.20626
22. Pant, D. C., Aguilera-Albesa, S., & Pujol, A. (2020). Ceramide signalling in inherited and multifactorial brain metabolic diseases. *Neurobiology of disease*, *143*, 105014. https://doi.org/10.1016/j.nbd.2020.105014
23. Hannun, Y. A., & Obeid, L. M. (2008). Principles of bioactive lipid signalling: lessons from sphingolipids. *Nature reviews. Molecular cell biology*, *9*(2), 139–150. https://doi.org/10.1038/nrm2329
24. Yuyama, K., Mitsutake, S., & Igarashi, Y. (2014). Pathological roles of ceramide and its metabolites in metabolic syndrome and Alzheimer's disease. *Biochimica et biophysica acta*, *1841*(5), 793–798. https://doi.org/10.1016/j.bbalip.2013.08.002
25. Pyszko, J. A., &Strosznajder, J. B. (2014). The key role of sphingosine kinases in the molecular mechanism of neuronal cell survival and death in an experimental model of Parkinson's disease. *Folia neuropathologica*, *52*(3), 260–269. https://doi.org/10.5114/fn.2014.45567
26. Motyl, J., Przykaza, Ł., Boguszewski, P. M., Kosson, P., &Strosznajder, J. B. (2018). Pramipexole and Fingolimod exert neuroprotection in a mouse model of Parkinson's disease by activation of sphingosine kinase 1 and Akt kinase. *Neuropharmacology*, *135*, 139–150. https://doi.org/10.1016/j.neuropharm.2018.02.023
27. Sentelle, R. D., Senkal, C. E., Jiang, W., Ponnusamy, S., Gencer, S., Selvam, S. P., Ramshesh, V. K., Peterson, Y. K., Lemasters, J. J., Szulc, Z. M., Bielawski, J., &Ogretmen, B. (2012). Ceramide targets autophagosomes to mitochondria and induces lethal mitophagy. *Nature chemical biology*, *8*(10), 831–838. https://doi.org/10.1038/nchembio.1059
28. Moloney, E. B., Moskites, A., Ferrari, E. J., Isacson, O., & Hallett, P. J. (2018). The glycoprotein GPNMB is selectively elevated in the substantia nigra of Parkinson's disease patients and increases after lysosomal stress. *Neurobiology of disease*, *120*, 1–11. https://doi.org/10.1016/j.nbd.2018.08.013

29. Nalls, M. A., Blauwendraat, C., Vallerga, C. L., Heilbron, K., Bandres-Ciga, S., Chang, D., Tan, M., Kia, D. A., Noyce, A. J., Xue, A., Bras, J., Young, E., von Coelln, R., Simón-Sánchez, J., Schulte, C., Sharma, M., Krohn, L., Pihlstrøm, L., Siitonen, A., Iwaki, H., … International Parkinson's Disease Genomics Consortium (2019). Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *The Lancet. Neurology*, *18*(12), 1091–1102. https://doi.org/10.1016/S1474-4422(19)30320-5
30. Diaz-Ortiz, M. E., Seo, Y., Posavi, M., Carceles Cordon, M., Clark, E., Jain, N., Charan, R., Gallagher, M. D., Unger, T. L., Amari, N., Skrinak, R. T., Davila-Rivera, R., Brody, E. M., Han, N., Zack, R., Van Deerlin, V. M., Tropea, T. F., Luk, K. C., Lee, E. B., Weintraub, D., … Chen-Plotkin, A. S. (2022). GPNMB confers risk for Parkinson's disease through interaction with α-synuclein. *Science (New York, N.Y.)*, *377*(6608), eabk0637. https://doi.org/10.1126/science.abk0637
31. Deleidi, M., &Isacson, O. (2012). Viral and inflammatory triggers of neurodegenerative diseases. *Science translational medicine*, *4*(121), 121ps3. https://doi.org/10.1126/scitranslmed.3003492
32. Marschallinger, J., Iram, T., Zardeneta, M., Lee, S. E., Lehallier, B., Haney, M. S., Pluvinage, J. V., Mathur, V., Hahn, O., Morgens, D. W., Kim, J., Tevini, J., Felder, T. K., Wolinski, H., Bertozzi, C. R., Bassik, M. C., Aigner, L., & Wyss-Coray, T. (2020). Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nature neuroscience*, *23*(2), 194–208. https://doi.org/10.1038/s41593-019-0566-1
33. van Eijk, M., &Aerts, J. M. F. G. (2021). The Unique Phenotype of Lipid-Laden Macrophages. *International journal of molecular sciences*, *22*(8), 4039. https://doi.org/10.3390/ijms22084039
34. Nugent, A. A., Lin, K., van Lengerich, B., Lianoglou, S., Przybyla, L., Davis, S. S., Llapashtica, C., Wang, J., Kim, D. J., Xia, D., Lucas, A., Baskaran, S., Haddick, P. C. G., Lenser, M., Earr, T. K., Shi, J., Dugas, J. C., Andreone, B. J., Logan, T., Solanoy, H. O., … Di Paolo, G. (2020). TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge. *Neuron*, *105*(5), 837–854.e9. https://doi.org/10.1016/j.neuron.2019.12.007
35. Griciuc, A., Patel, S., Federico, A. N., Choi, S. H., Innes, B. J., Oram, M. K., Cereghetti, G., McGinty, D., Anselmo, A., Sadreyev, R. I., Hickman, S. E., El Khoury, J., Colonna, M., &Tanzi, R. E. (2019). TREM2 Acts Downstream of CD33 in Modulating Microglial Pathology in Alzheimer's Disease. *Neuron*, *103*(5), 820–835.e7. https://doi.org/10.1016/j.neuron.2019.06.010
36. Reifschneider, A., Robinson, S., van Lengerich, B., Gnörich, J., Logan, T., Heindl, S., Vogt, M. A., Weidinger, E., Riedl, L., Wind, K., Zatcepin, A., Pesämaa, I., Haberl, S., Nuscher, B., Kleinberger, G., Klimmt, J., Götzl, J. K., Liesz, A., Bürger, K., Brendel, M., … Haass, C. (2022). Loss of TREM2 rescues hyperactivation of microglia, but not lysosomal deficits and neurotoxicity in models of progranulin deficiency. *The EMBO journal*, *41*(4), e109108. https://doi.org/10.15252/embj.2021109108
37. Götzl, J. K., Brendel, M., Werner, G., Parhizkar, S., Sebastian Monasor, L., Kleinberger, G., Colombo, A. V., Deussing, M., Wagner, M., Winkelmann, J., Diehl-Schmid, J., Levin, J., Fellerer, K., Reifschneider, A., Bultmann, S., Bartenstein, P., Rominger, A., Tahirovic, S.,

Smith, S. T., Madore, C., … Haass, C. (2019). Opposite microglial activation stages upon loss of PGRN or TREM2 result in reduced cerebral glucose metabolism. *EMBO molecular medicine*, *11*(6), e9711. https://doi.org/10.15252/emmm.201809711

38. Jaitin, D. A., Adlung, L., Thaiss, C. A., Weiner, A., Li, B., Descamps, H., Lundgren, P., Bleriot, C., Liu, Z., Deczkowska, A., Keren-Shaul, H., David, E., Zmora, N., Eldar, S. M., Lubezky, N., Shibolet, O., Hill, D. A., Lazar, M. A., Colonna, M., Ginhoux, F., … Amit, I. (2019). Lipid-Associated Macrophages Control Metabolic Homeostasis in a Trem2-Dependent Manner. *Cell*, *178*(3), 686–698.e14. https://doi.org/10.1016/j.cell.2019.05.054
39. Wang, S., Mustafa, M., Yuede, C. M., Salazar, S. V., Kong, P., Long, H., Ward, M., Siddiqui, O., Paul, R., Gilfillan, S., Ibrahim, A., Rhinn, H., Tassi, I., Rosenthal, A., Schwabe, T., & Colonna, M. (2020). Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. *The Journal of experimental medicine*, *217*(9), e20200785. https://doi.org/10.1084/jem.20200785
40. Schlepckow, K., Monroe, K. M., Kleinberger, G., Cantuti-Castelvetri, L., Parhizkar, S., Xia, D., Willem, M., Werner, G., Pettkus, N., Brunner, B., Sülzen, A., Nuscher, B., Hampel, H., Xiang, X., Feederle, R., Tahirovic, S., Park, J. I., Prorok, R., Mahon, C., Liang, C. C., … Haass, C. (2020). Enhancing protective microglial activities with a dual function TREM2 antibody to the stalk region. *EMBO molecular medicine*, *12*(4), e11227. https://doi.org/10.15252/emmm.201911227
41. Price, B. R., Sudduth, T. L., Weekman, E. M., Johnson, S., Hawthorne, D., Woolums, A., & Wilcock, D. M. (2020). Therapeutic Trem2 activation ameliorates amyloid-beta deposition and improves cognition in the 5XFAD model of amyloid deposition. *Journal of neuroinflammation*, *17*(1), 238. https://doi.org/10.1186/s12974-020-01915-0
42. Jihong Kang , Serge Rivest, Lipid Metabolism and Neuroinflammation in Alzheimer's Disease: A Role for Liver X Receptors, Endocrine Reviews, Volume 33, Issue 5, 1 October 2012, Pages 715–746, https://doi.org/10.1210/er.2011-1049
43. Nguyen, T. B., &Olzmann, J. A. (2017). Lipid droplets and lipotoxicity during autophagy. *Autophagy*, *13*(11), 2002–2003. https://doi.org/10.1080/15548627.2017.1359451
44. Smolič, T., Tavčar, P., Horvat, A., Černe, U., HalužanVasle, A., Tratnjek, L., Kreft, M. E., Scholz, N., Matis, M., Petan, T., Zorec, R., &Vardjan, N. (2021). Astrocytes in stress accumulate lipid droplets. *Glia*, *69*(6), 1540–1562. https://doi.org/10.1002/glia.23978
45. Dienel, G. A., & Cruz, N. F. (2016). Aerobic glycolysis during brain activation: adrenergic regulation and influence of norepinephrine on astrocytic metabolism. *Journal of neurochemistry*, *138*(1), 14–52. https://doi.org/10.1111/jnc.13630
46. Procaccini, C., Santopaolo, M., Faicchia, D., Colamatteo, A., Formisano, L., de Candia, P., Galgani, M., De Rosa, V., & Matarese, G. (2016). Role of metabolism in neurodegenerative disorders. *Metabolism: clinical and experimental*, *65*(9), 1376–1390. https://doi.org/10.1016/j.metabol.2016.05.018
47. Muddapu, V. R., Dharshini, S. A. P., Chakravarthy, V. S., &Gromiha, M. M. (2020). Neurodegenerative Diseases - Is Metabolic Deficiency the Root Cause?. *Frontiers in neuroscience*, *14*, 213. https://doi.org/10.3389/fnins.2020.00213
48. Capucho, A. M., Chegão, A., Martins, F. O., Vicente Miranda, H., & Conde, S. V. (2022). Dysmetabolism and Neurodegeneration: Trick or Treat?. *Nutrients*, *14*(7), 1425. https://doi.org/10.3390/nu14071425

49. Marschallinger, J., Iram, T., Zardeneta, M., Lee, S. E., Lehallier, B., Haney, M. S., Pluvinage, J. V., Mathur, V., Hahn, O., Morgens, D. W., Kim, J., Tevini, J., Felder, T. K., Wolinski, H., Bertozzi, C. R., Bassik, M. C., Aigner, L., & Wyss-Coray, T. (2020). Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nature neuroscience*, *23*(2), 194–208. https://doi.org/10.1038/s41593-019-0566-1
50. Laulagnier, K., Javalet, C., Hemming, F. J., Chivet, M., Lachenal, G., Blot, B., Chatellard, C., &Sadoul, R. (2018). Amyloid precursor protein products concentrate in a subset of exosomes specifically endocytosed by neurons. *Cellular and molecular life sciences : CMLS*, *75*(4), 757–773. https://doi.org/10.1007/s00018-017-2664-0
51. Sardar Sinha, M., Ansell-Schultz, A., Civitelli, L., Hildesjö, C., Larsson, M., Lannfelt, L., Ingelsson, M., &Hallbeck, M. (2018). Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers. *Acta neuropathologica*, *136*(1), 41–56. https://doi.org/10.1007/s00401-018-1868-1
52. Estes, R. E., Lin, B., Khera, A., & Davis, M. Y. (2021). Lipid Metabolism Influence on Neurodegenerative Disease Progression: Is the Vehicle as Important as the Cargo? *Frontiers in Molecular Neuroscience*, *14*. https://doi.org/10.3389/fnmol.2021.788695

Figure1: -

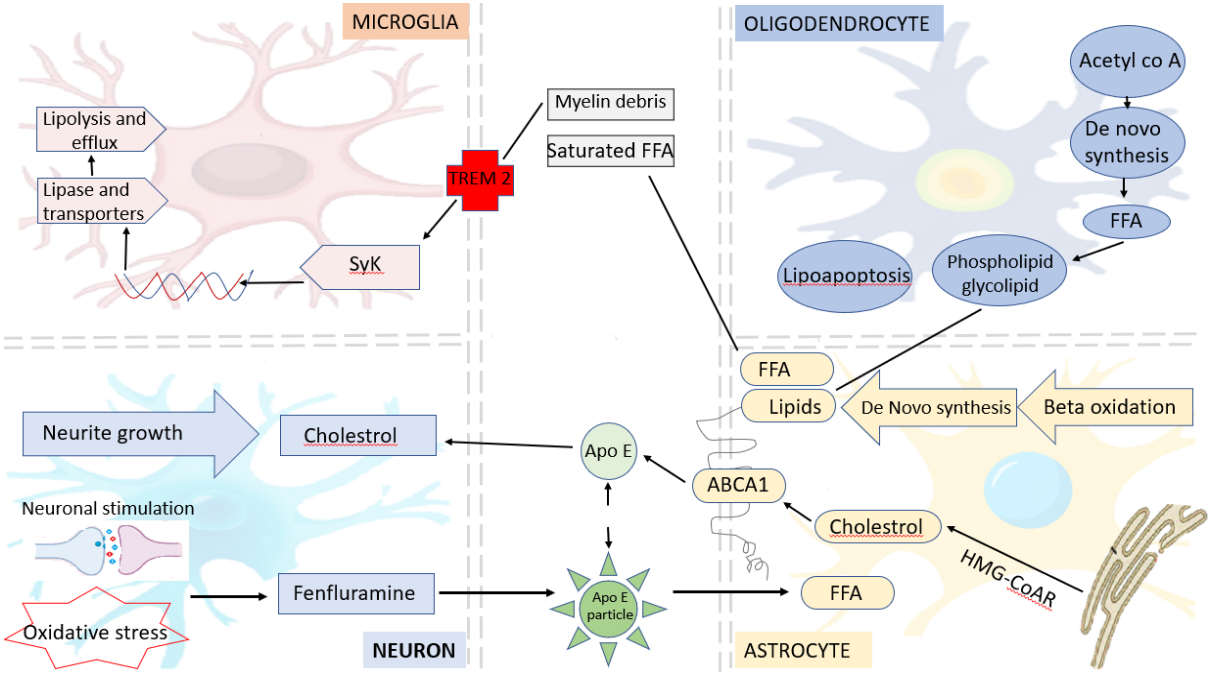

Figure 1- This figure summarizes the intricate lipid transport system in the brain. ApoE-containing lipoproteins, called ApoE-particles, transport cholesterol from astrocytes to neurons via ATP-binding cassette transporter A1 (ABCA1). Neurons use these lipoproteins for various functions, including neurite growth, synaptogenesis, and conversion to 24-hydroxycholesterol (24-OHC) by cytochrome P450 46 (CYP46). In response to specific conditions, neurons release fatty acids in ApoE-particles back to astrocytes, where they can

be degraded or stored in lipid droplets (LDs). Both oligodendrocytes and astrocytes produce essential lipids for processes like myelination and remyelination, with ApoE particles potentially aiding in lipid transfer between astrocytes and oligodendrocytes. Excessive saturated fatty acids, particularly from astrocytes, can trigger oligodendrocyte cell death through the lipoapoptosis pathway. Additionally, lipids from myelin debris can activate TREM2 signaling, promoting the expression of lipid metabolism genes. Notably, the tyrosine kinase syk is unrelated to these brain processes and is primarily found in the spleen.

Table 1: list of lipids with examples and the level changes in AD brain.

LIPIDS	EXAMPLE	LEVEL CHANGES	REFERENCES
Fatty acids (FA)	Omega 3 fatty acids (DHA, EPA, DPA, ALA)	DHA DECREASE ⬇ EPA DECREASE ⬇ DPAINCREASE ⬆ ALA INCREASE ⬆	Fonteh et al., 2020; Hosseini et al., 2020. Hosseni et al., 2020. Dyall, 2015. Leikin-Frenkel A. et al., 2022.
	Omega 6 fatty acids (AA, LA)	AA INCREASE ⬆ LA DECREASE ⬇	Fonteh et al., 2020 Snowden et al., 2017
	Saturated fatty acids (PA, SA)	PA INCREASE ⬆ SA DECREASE ⬇	Fonteh et al., 2014 Nasaruddin et al., 2016
	Eicosanoids	ANTI INFLAMMATORY DECREASES ⬇	Bringer, 2019
	Endocannavinoids	ENDOCANNAVINOIDS DECREASED ⬇	Bedse et al., 2015
Glycerolipids (GL)	Triglycerides (TG)	TG DECREASED ⬇	Bernath, M. M. et al., 2020
Glycerophospholipids (GP)	Phosphatidylcholine (PC)	PC DECREASED ⬇	Wood, 2012
	Phosphatidylethanolamine (PE)	PE DECREASED ⬇	Kosicek, M., &Hecimovic, S. 2013
	Phosphatidylserine (PS)	PS DECREASED ⬇	Kosicek, M., &Hecimovic, S. 2013.

Sphingolipids (SP)	Sphingomyelin (SM)	SM DECREASED ⬇	Fonteh et al., 2015.
	Ceramides (CM)	CM INCREASED ⬆	Kim et al., 2017.
	Sulfatides	SULFATIDES DECREASED ⬇	Qiu, S. et al., 2021.
	Gangliosides	GANGLIOSIDES DECREASED ⬇	Sipione S et al., 2020.
Sterol lipids (SL)	Cholesterol	CHOLESTEROL DECREASED ⬇	Feringa FM and van der Kant R 2021
	oxysterols	OXYSTEROLS INCREASED ⬆	Dias, I. H. K.et al., 2022
Abbreviations*DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; DPA, Docosapentaenoic acid; ALA, Alpha-linolenic acid;AA, Arachidonic acid; LA, Linoleic acid; PA, Palmitic acid; SA, Stearic acid; PC, phosphatidylcholine;PE, phosphatidylethanolamine; PS, phosphatidylserine; SM, sphingomyelin; CM, ceramide;TG, triglyceride.			