Review Article

The Link between Cholesterol and a Brain Disease

Sujeetha Purushothaman[1], Arumugan Vijaya Anand[1]

From, [1]Medical Genetics and Epigenetics Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore, Tamil Nadu, India.

Correspondence to: Sujeetha Purushothaman, Medical Genetics and Epigenetics Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore - 641046. Tamil Nadu, India. **Email:** suji648@yahoo.co.in

ABSTRACT

Lipids comprise the immensity dry mass of the brain and these have been allied with healthy function as well as the most common pathological circumstances of the brain. Genetics and lifestyles are the most important factor that influences the lipid metabolism and the key components of lipid disruption in Alzheimer's disease (AD). Additionally, the most common genetic risk factor of AD, *APOE E4* genotype, is involved in lipid transport and metabolism. Under healthy conditions, lipid homeostasis bestows a balanced cellular environment that enables the proper functioning of brain cells. However, under pathological conditions, dyshomeostasis of brain lipid can result in disturbed BBB, abnormal processing of APP, dysfunction in endocytosis/exocytose/autophagocytos is, altered myelination, disturbed signaling, unbalanced energy metabolism, and enhanced inflammation. This lipid instability may contribute to abnormalities in brain function that are the hallmark of AD. In this Review, we focus on the lipid and cholesterol metabolism, with an overview of the various lipid and cholesterol metabolic pathways and changes that have been linked to AD.

Key words: Alzheimer's disease, Lipid homeostasis, Inflammation, Apolipoprotein E

Deregulated lipid and cholesterol homeostasis in the body and particularly in the brain has been demonstrated in neurodegenerative diseases such as Alzheimer's disease (AD), as well as Parkinson's disease (PD) and Huntington's disease (HD) [1]. The changes in lipid metabolism may affect the disease progression or pathogenic mechanism. Amyloidogenic peptide is believed to play a key role in the AD pathogenesis mounting the evidence that dyslipidemia provoke the production or reduce of amyloid beta (Aβ) clearance [2]. Moreover, other dyslipidemic-related conditions have also been linked in the AD pathogenesis, including obesity, hypertension, inflammation, insulin resistance, and type 2 diabetes [3]. In this review, we focus on the lipid and cholesterol metabolism, with an overview of the various lipid and cholesterol metabolic pathways and changes that have been linked to AD.

Cholesterol and Lipid Metabolism

Rising evidence suggest the changes in the metabolism of lipids, predominantly cholesterol, is implicated directly in the pathogenesis of many neurodegenerative disease including AD [2]. This part describes the cholesterol synthesis and metabolism followed by some vital information about the lipid transport and metabolism, in order to explain the normal roles of these lipids in the body and the brain. Some changes in lipid metabolisms which have been detected in AD [4].

Cholesterol Synthesis and Metabolism

Cholesterol plays a vital function in the structure and function of cell membranes. It influences the inflexibility of lipid bilayers, there in affects the transfer and process through the membrane. Cholesterol in the brain accounts for 25% of the total body cholesterol [5]. About 70% of its cholesterol is there in the myelin, 20% is present in the glial cells, while the remaining 10% is present in the neurons [6]. The cholesterol requirements in the body are met by dietary intake of animal fats, or by synthesis. Cholesterol productiongets activated when acetyl-CoA is transformed into 3-hydroxy-3methylglutaryl-CoA (HMG-CoA). Cholesterol is formed when its precursor lanosterol is channeled into either the Bloch pathway to generate desmosterol or lathosterol respectively; these are then converted to cholesterol [7].

Cholesterol is used widely in the body, particularly by the cell membrane structures. Other important physiological functions include the production of bile by the liver and hormone synthesis. Brain cholesterol metabolism is different and independent from that of peripheral tissues, due to the blood–brain barrier (BBB) preventing rapid transport into and out of the brain [8]. In the adult brain, cholesteroloriginate in the form of non-esterifies form, rest being in the form of desmosterol and cholesteryl esters [9]. Major part of cholesterol (about 70–80%) is seen in the myelin sheaths formed by

oligodendrocyte that insulates the axons and in the plasma membranes of astrocytes and neurons, where it maintains cellular morphology, plays important roles in lipid rafts, and helps in the synaptic transmission [10]. During adolescence, the cholesterol turnover reduces because of myelin sheath formation with the half-life between six months and five years. This is a contrast turnover that occurs during the general circulation [6].

The role of lipid rafts in neurodegenerative diseases

Lipid rafts are buoyant membrane glycolipoprotein micro domains rich in cholesterol and sphingolipids [11]. These provide the frame for signaling molecules and protein transduction, trafficking and immunoglobulin functions and neurotransmitters [12]. Lipid rafts have been linked to various diseases conditions including cardiovascular disease and certain cancers. They are also important for the entry, replication, assembly, and budding of various types of viruses [13]. Some proteins are linked with lipid rafts include GPI-anchored proteins, Src family kinases, components of the heterotrimeric G-proteins and many of the proteins linked to AD linked with the metabolism of APP [14]. Some of the later include the γ-secretase complex (processes over 20 proteins, including γ-site cleavage of APP), BACE-1 (β-site APP cleaving enzyme, the enzyme responsible for βsite APP cleavage), ADAM10 (A Disintegrin and Metalloprotease-10, enzyme which cleaves APP at the α-site, also cleaves TNF-α and E-cadherin), and neprilysin, an Aβ-degrading enzyme [15]. Studies have demonstrated that by increasing the dietary cholesterol content, Aβ production can be elevated [16].

In animal studies where rabbits were placed on a high-cholesterol diet, a greater level of brain Aβ accumulation was found [17]. Lim et al., [18] concluded that a high-fat and high-cholesterol (HFHC) diet results in increase in brain cholesterol esters, These effects were seen in older *APO E E4* knock-in mice compared to *APO E E3* mice. Conversely, the reduction of cell membrane cholesterol has been shown to reduce γ-secretase activity and also to increase the non-amyloidogenic α-secretase cleavage of APP [19, 20]. Studies have shown that the membranes of the lipid content raft, from early-stage AD brain frontal and entorhinal cortex tissue, has greater microviscosity which correlated with BACE-1/APP interaction levels [21]. This was found not to be due to increased cholesterol or sphingomyelin levels, but due to a lower content of unsaturated fats [14]. This adds to the evidence that dyslipidaemia is central in AD neurodegeneration and that a diet high in polyunsaturated fatty acids may provide benefit in slowing or preventing AD pathogenesis. Transgenic AD mouse models and mathematical modeling studies support this theory, with evidence suggesting that increasing the cholesterol and long-chain polyunsaturated fatty acid (mainly DHA) content of membranes may delay the onset and/or progression of AD [22]

Alzheimer's disease

AD is the most common type of dementia, characterized by the progressive loss of memory and other cognitive functions of the brain. An affected individual gradually becomes totally dependent upon others, culminating in their death approximately 3– 10 years after diagnosis [23]. The neurodegenerative changes that are characteristic of an AD brain include widespread synaptic and neuronal loss, the accumulation of extracellular Aβ fibrils and plaques, intracellular neurofibrillary tangles (NFT) composed of hyper-phosphorylated tau filaments, microglial infiltration, and brain atrophy, particularly in the regions important for memory, such as the hippocampus, amygdala, and frontal cortex [24]. Genetic mutations in genes whose proteins are involved in the processing of the APP to Aβ peptides, such PS1 and PS2, as well as AD-related APP mutations, are predisposing risk factors for AD. However, these mutations are involved only in earlyonset familial Alzheimer's disease (EOAD) which occurs before age 65, but sometimes as young as 30. These cases are relatively rare and account for less than 5% of all AD cases [25].

The main risk factor linked to the much more common late-onset form of Alzheimer's disease (LOAD) is *APOE E4* allele status. Other significant risk factors include dyslipidemia, hypertension, obesity, chronic inflammation, insulin resistance, and type 2 diabetes. All of these are also risk factors for cardiovascular disease. When these conditions occur together, this is termed 'metabolic syndrome' [28, 29]. It is believed that metabolic changes caused by these conditions lead to a greater production or reduced clearance (or both) of Aβ peptides. Many of these risk factors can be prevented by altering diet and physical exercise, which are known to reduce the risk of cardiovascular disease. There is a growing body of evidence that reducing these same risk factors would considerably slow or possibly prevent AD pathogenesis [30, 31].

Effect of Amyloid-B on Lipid Metabolism

It has been suggested that APP processing affects cellular lipid metabolism [32]. In cultured neurons and in transgenic mice, Aβ with 42 amino acids (Aβ42) can activate neutral sphingomyelinases and down regulate sphingomyelin levels, whereas Aβ40 reduces de novo cholesterol synthesis by inhibiting the activity of HMG-CoA reductase. Therefore, maintaining lipid homeostasis could be a biological function of APP processing Grimm *et al.*, [33] and the pathological accumulation of Aβ could lead to abnormal lipid metabolism. Furthermore, both studies in vitro and in AD patients suggest that Aβ causes oxidative stress, leading to lipid oxidation that might contribute directly to neurodegeneration [32] Studies also suggest that Aβ induces ozonolysis of cholesterol, leading to the formation of peroxiderivatives that accelerate aggregation of Aβ monomers [35] and that Aβ oxidizes cholesterol at positions of 7-β and 3-β, thus leading to H_2O_2 production [36]. Therefore,

a deleterious feedback loop between Aβ accumulation and altered lipid metabolism could be one of the molecular mechanisms underlying the link between lipid disorders and AD.

Cholesterol metabolism-related genes and Alzheimer's disease

APO E protein plays a central role in lipid transport while possession of the *APOE E 4* allele influences AD risk. The human *APOE* gene is located on chromosome 19, and its three most common alleles are designated *E2*, *E3* and *E4*(Williams *et al*., 2020). Of these, *E3* is the most common allele in humans (78%) followed by *E4* (14%), then *E2* (8%). However, it is usually *APO E E4* which is associated with increased levels of circulating LDL cholesterol, higher triglyceride levels, and a greater risk of coronary artery disease (Linton *et al*., 2019). This is despite *APO E E4* having higher affinity for the LDL receptors than *APO E E3* and *E2*, and increased levels of lipoprotein internalization [37, 38].The increased affinity of *APO E E4* for the LDL receptor in the periphery may be a limiting factor for cellular processing of lipoproteins, for it has been observed that *APO E E4* is poorly recycled by cells, yet is readily internalized which results in raised intracellular cholesterol levels [39].

APO E in the brain

Whilst *APO E* is clearly a molecule of great importance in the CNS, it is not imported from the periphery [40] where the liver produces it in the largest amounts. Rather it is synthesized locally by astrocytes in significant quantities [41]. LRP-1 is primarily expressed in neurons, whereas glial cells mostly express the LDL-receptor [42]. These receptors (particularly LRP-1) are not only used for lipoprotein metabolism, but they also bind some proteins involved in brain development (e.g. Sonic Hedgehog, Wnt, and reelin), as well as proteases, protease inhibitors, vitamin transporters, and proinflammatory molecules [43]. Receptor-mediated endocytosis transit lipid particles to late endosomes. Immediately after endocytosis, *APO E* is detached from the lipid components and is not sent to lysosomes but recycled back to the plasma membrane [44].

APOE 4 and Alzheimer's disease

One of the strongest genetic risk factors for AD risk is *APOE E4* allele, the mechanisms is still implicit. A study that examined the physical distribution of the resultant *APOE E4* protein shows that it gravitates towards the larger, less dense particles of CNS lipoprotein whereas *APOE E2* and *APOE E3* tend to associate with smaller, denser lipoprotein fractions [45]. Like their peripheral counterparts, the CNS APOE proteins have differential effects, where *APOE E2* and *APOE E3* appear to be more effective than *APOE E4* [46]. Early studies showed that plasma levels of APOE may be an important factor in AD, as higher levels were observed in the plasma of AD individuals relative to non-AD individuals [47, 48]. Other early studies suggested that polymorphisms in the *APOE* promoter region may influence the probability of developing AD [49, 50].

This region, which belongs to the TATA box family, regulates the production of *APOE* protein where a genotype of -491TT produces much less APOE than -491AT and -491AA. The initial studies demonstrated that the *APOE* -491AT and AA genotypes lead to increased risk for AD independent of *APOE* allele [51]. It was soon realized that the risk for AD may be compounded when *APOE E4* alleles and the 491 AA genotype are combined [42]. These results suggested that the improved production of the *APOE* protein may boost disease progression but did not account for any mechanism of action in AD by the *APOE E4* protein itself. However, more recent studies now suggest that low plasma *APOE* levels increase the risk of AD [53]. Furthermore, Baker-Nigh *et al*., 2016 concluded that the levels of *AAPO E* and CNS are not correlated but it is well correlates CSF Aβ levels which are more relevant to AD risk.

CONCLUSION

Reducing the risk of AD will involve dietary changes and healthy lifestyles that can reduce the risk of dyslipidaemia, insulin resistance, type 2 diabetes, cardiovascular disease, and chronic inflammation, which are all known risk factors for AD. Despite the many studies on the influence of the *APOE E4* allele on Aβ aggregation, binding, and clearance, the overall pathological effect of this allele is still not known. It is hoped this will pave the way towards effective treatments, whilst highlighting the importance of preventing dyslipidaemia.

REFERENCES

1. Martín MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: sometimes determinant and frequently implicated. EMBO reports. 2014;15(10):1036-52.
2. Chew H, Solomon VA, Fonteh AN. Involvement of lipids in Alzheimer's disease pathology and potential therapies. Front Physiol. 2020:9;11:598.
3. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Canadian J of Cardiology. 2018:1;34(5):575-84.
4. Kao YC, Ho PC, Tu YK, et al. Lipids and Alzheimer's disease. International J Mol Sci. 2020;21(4):1505.
5. Björkhem I. Crossing the barrier: oxysterols as cholesterol transporters and metabolic modulators in the brain. J of Internal Medicine. 2006;260(6):493-508.
6. Zhang J and Liu Q. Cholesterol metabolism and homeostasis in the brain. Protein & Cell. 2015:1; 6(4):254-64.
7. Dietschy JM and Turley SD. Thematic review series: brain Lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. J Lipid Res. 2004:1;45(8):1375-97.
8. Orth M, Bellosta S. Cholesterol: its regulation and role in central nervous system disorders. Cholesterol. 2012.

9. Brown AJ and Sharpe LJ. Cholesterol synthesis. In: Biochemistry of Lipids, Lipoproteins and Membranes (6th Ed).328-358 (editors ND Ridgway and RS McLeod, Elsevier, Amsterdam) (2016).
10. Hussain G, Wang J, Rasul A et al. Role of cholesterol and sphingolipids in brain development and neurological diseases. Lipids Health Dis. 2019;18(1):1-2.
11. Simons K, Ehehalt R. Cholesterol, lipid rafts, and disease. J Clin Invest. 2002:1;110(5):597-603.
12. Rakesh G, Szabo ST, Alexopoulos GS et al. Strategies for dementia prevention: latest evidence and implications. Ther Advances Chr Dis. 2017;8(8-9):121-36.
13. Suzuki T, Suzuki Y. Virus infection and lipid rafts. Biolog Pharmaceut Bul. 2006;29(8):1538-41.
14. Díaz M and Marin R. Lipid Rafts and Development of Alzheimer's disease. Cerebral and Cerebellar Cortex–Interaction and Dynamics in Health and Disease. 2021: 25.
15. Vassar R, Kandalepas PC. The β-secretase enzyme BACE1 as a therapeutic target for Alzheimer's disease. Alzheimer's Res Ther. 2011; 3(3):1-6.
16. Shie FS, Jin LW, Cook DG et al., Diet-induced hypercholesterolemia enhances brain Aβ accumulation in transgenic mice. Neuroreport. 2002:25;13(4):455-9.
17. Refolo LM, Pappolla MA, Malester B et al. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiology of disease. 2000:1;7(4):321-31.
18. Lim WL, Lam SM, Shui G et al. Effects of a high fat, high-cholesterol diet on brain lipid profiles in apolipoprotein E ε3 and ε4 knock-in mice. Neuro. of aging. 2013:1;34(9):2217-24.
19. Sepulveda-Diaz JE, Alavi Naini SM, Huynh MB et al. and HS3ST2 expression is critical for the abnormal phosphorylation of tau in Alzheimer's disease-related tau pathology. Brain. 2015:1;138(5):1339-54.
20. Fabelo N, Martín V, Marín R et al. Altered lipid composition in cortical lipid rafts occurs at early stages of sporadic Alzheimer's disease and facilitates APP/BACE1 interactions. Neurobiology of aging. 2014:1;35(8):1801-12.
21. Igarashi M, Ma K, et al. Disturbed choline plasmalogen and phospholipid fatty acid concentrations in Alzheimer's disease prefrontal cortex. J of Alzheimer's dise. 2011:1;24(3):507-17.
22. Santos-Lozano A, Pareja-Galeano H, SanchisGomar F et al. Physical activity and Alzheimer disease: a protective association. InMayo Clin. Proceedings 2016:1;91:8;999-1020.
23. Van Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genetics in Medicine. 2016;18(5):421-30.
24. Serrano-Pozo A, Frosch MP, Masliah E et al. Neuropathological alterations in Alzheimer disease. Cold Spring Harbor perspectives in medi. 2011:1; 1(1):a006189.
25. Rao AT, Degnan AJ, Levy LM. Genetics of Alzheimer disease. American J of Neuroradiology. 2014:1;35(3):457-8.
26. Sorrentino G, Bonavita V. Neurodegeneration and Alzheimer's disease: the lesson from tauopathies. Neurological Sciences. 2007;28(2):63-71.
27. Razay G, Vreugdenhil A, Wilcock G. The metabolic syndrome and Alzheimer disease. Archives of neuro. 2007:1;64(1):93-6.
28. Solfrizzi V, Panza F, Frisardi V et al. Diet and Alzheimer's disease risk factors or prevention: the current evidence. Expert review of neurotherapeutics. 2011:1;11(5):677-708.
29. Dye L, Boyle NB, Champ C, et al. The relationship between obesity and cognitive health and decline. Proceedings of the nutrition society. 2017;76(4):443-54.
30. Cutler RG, Kelly J, Storie K, et al. Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. Proceedings of the Nati. Acad. of Sci. 2004:17;101(7):2070-5.
31. Grimm MO, Grimm HS, Pätzold AJ, et al. Regulation of cholesterol and sphingomyelin metabolism by amyloid-β and presenilin. Nature cell biology. 2005;7(11):1118-23.
32. Zhang Q, Powers ET, Nieva J, et al. Metabolite initiated protein misfolding may trigger Alzheimer's disease. Proceedings of the National Academy of Sciences. 2004:6;101(14):4752-7.
33. Xu PT, Li YJ, Qin XJ et al. Differences in apolipoprotein E3/3 and E4/4 allele-specific gene expression in hippocampus in Alzheimer disease. Neuro. of disease. 2006:1;21(2):256-75.
34. Williams T, Borchelt DR, Chakrabarty P. Therapeutic approaches targeting Apolipoprotein E function in Alzheimer's disease. Molecular neurode. 2020:1;15(1):8.
35. Linton MF, Yancey PG, Davies SS et al. The role of lipids and lipoproteins in atherosclerosis. End text [Internet]. 2019:3.
36. Heeren J, Grewal T, Laatsch A, et al. Impaired recycling of apolipoprotein E4 is associated with intracellular cholesterol accumulation. J Biological Chem. 2004:31; 279(53):55483-92.
37. Mamotte CD, Sturm M, Foo JI, et al. Comparison of the LDL-receptor binding of VLDL and LDL from apoE4 and apoE3 homozygotes. Am J Physiol-Endocrinol Metabol. 1999:1;276(3):E553-7.
38. Malloy P, Tremont G, Grace J, et al. The Frontal Systems Behavior Scale discriminates frontotemporal dementia from Alzheimer's disease. Alzheimer's & Deme. 2007:1;3(3):200-3.
39. Linton MF, Gish R, Hubl ST, et al. Phenotypes of apolipoprotein B and apolipoprotein E after liver transplantation. J Clin Invest. 1991:1;88(1):270-81.
40. Boyle PA, Buchman AS, Wilson RS, et al. Effect of purpose in life on the relation between Alzheimer disease pathologic changes on cognitive function in advanced age. Archives of general psychiatry. 2012:1; 69(5):Pp499-504.
41. Shinohara M, Tachibana M, Kanekiyo T, et al. Role of LRP1 in the pathogenesis of Alzheimer's disease: evidence from clinical and preclinical studies: Thematic Review Series: ApoE and Lipid Homeostasis in Alzheimer's Disease. Journal of lipid research. 2017:1; 58(7):1267-81.
42. Lane-Donovan C, Herz J. APOE, APOE receptors, and the synapse in Alzheimer's disease. Trends Endocrinol Metabol. 2017:1;28(4):273-84.
43. Petrov AM, Kasimov MR, Zefirov AL. Brain cholesterol metabolism and its defects: linkage to neurodegenerative diseases and synaptic dysfunction. Acta Naturae 2016;8(1):28.
44. Baker-Nigh A, Vahedi S, Davis EG, et al. Neuronal amyloid-β accumulation within cholinergic basal forebrain in ageing and Alzheimer's disease. Brain. 2015:1;138(6):1722-37.
45. Maezawa I, Hong HS, Wu HC, et al. A novel tricyclic pyrone compound ameliorates cell death associated with intracellular amyloid Aβ oligomeric complexes. J Neur. 2006;98(1):57-67.
46. Taddei S, Virdis A, Mattei P, et al. Hypertension causes premature aging of endothelial function in humans. Hypertension. 1997;29(3):736-43.
47. Laws SM, Taddei K, Martins G, et al. The - 491AA polymorphism in the APOE gene is associated with increased plasma APOE levels in Alzheimer's disease. Neuroreport. 1999:17;10(4):879-82.
48. Laws KR, Gale TM, Leeson VC, et al. When is category specific in Alzheimer's disease? Cortex. 2005:1; 41(4):452-63.

49. Lambert MP, Barlow AK, Chromy BA, et al. Diffusible, nonfibrillar ligands derived from Aβ1– 42 are potent central nervous system neurotoxins. Proceedings of the National Academy of Sciences. 1998:26;95(11):6448-53.
50. Rasmussen KL, Tybjærg-Hansen A, Nordestgaard BG, et al. Absolute 10-year risk of dementia by age, sex and APOE genotype: a population-based cohort study. CMAJ. 2018:4; 190(35):E1033-41.

How to cite this article: Sujeetha Purushothaman, Arumugan Vijaya Anand. The Link between Cholesterol and a Brain Disease. Indian J Pharm Drug Studies. 2022; 1(1): 10-14.

Funding: None; *Conflict of Interest: None Stated*