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Review Article

Lipid Metabolism in Neurocognitive Disorders: Current Update

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Abstract

The physiology and the pathology of the Central Nervous System (CNS) is very complex, and only by understanding it the scientific research might develop effective treatments. Neurocognitive Disorders, extremely diffused diseases, have a multifactorial aetiology, in which lipid homeostasis plays an important role, as known.

The aim of this mini review is focus on interesting recently published researches on the topic, in order to put together some pieces of the puzzle of such an enormous physiopathology chapter.

After a brief introduction, we will describe important aspects of CNS lipid metabolism, then we will examine the conclusions of recent articles relating to lipid role in neurodegeneration. The recent scientific literature has strengthened the position of some well-known "biological agents" – i.e. lipid peroxidation and apolipoprotein E4 allele –but also detailed the importance of new promising diagnostic and therapeutic targets.

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Keywords

Lipids; Lipid Metabolism; Neurocognitive Disorders; Dementia

Abbreviations

A: Acyl-coenzyme; ACAT: Cholesterol Acyltransferase; AD: Alzheimer's Disease; BBB: Blood Brain Barrier; CNS: Central Nervous System; d-PUFA: Deuterated Polyunsaturated Fatty Acids; Fp: Ferroptosis; LML: Lipid Metabolism; MD: Mixed Dementia; NCDs: Neurocognitive Disorders; PO1: Paroxonase 1; PBMNCs: Peripheral Blood Mononuclear Cells; PUFA: Polyunsaturated Fatty Acids; VCI: Vascular Cognitive Impairment; VaD: Vascular Dementia.

Introduction

Global population growth is increasing, and people over 65 will rise to 1.5 billion (16% of the population) by 2050 [1]. Demography inevitably affects public health: the median age increase will cause also chronic pathologies' incidence increase: among them, Neurocognitive Disorders (NCDs) [2]. Physiology of aging has been extensively studied in order to demarcate it from pathology [3], and so has been NCD pathophysiology. Several different conditions may cause NCD [4], which therefore are considered multifactorial diseases. The key moment in brain damage is considered the accumulation of misfolded proteins, and

various hypothesis try to explain misfolding and accumulation genesis: e.g. genetics [5], microvascular disease [6], environmental factors [7], oxidative stress [8] are involved. Also, lipid metabolism (LM) plays a fundamental role in cognitive decline [9], as a growing number of researches on the topic confirms. In this mini review, we will briefly summarize the most important brain lipid metabolism aspects, and then we will present some recent studies about its correlation with NCDs.

Central Nervous System Lipid Metabolism

Central Nervous System (CNS) presents a lipid metabolism quite different from the other systems. The blood brain barrier (BBB) presents the passage of several molecules [10], letting pass throw hydrophobic ones. Though lipids are commonly considered hydrophobic molecules, many of them present a hydrophilic component, like hydroxyl radical: the presence of both polar and non-polar parts defines the lipid "amphiphilic" - e.g. phospholipids and cholesterol. Phospholipids are the major component of the plasma membrane, and their modifications correlate with histological and electrophysiological changes in aging [11], as demonstrated in the Fischer 344 rat. Among them, phosphatidylserine is particularly represented. It derives form phosphorylated molecules, and its synthesis involves the intervention of endoplasmic reticulum enzymes: phosphatidylserine synthase 1 and 2 [12]. Phosphatidylserine is required for plasma membrane and myelin constitution and its homeostasis is necessary to support many cognitive functions [13]. Cholesterol metabolism is related to CNS damage, as we will describe in next section, so it's important to describe it. Due its inability to cross the BBB, brain cells have to synthetize their own cholesterol [14]. Astrocytes - a glial cell type – synthetize cholesterol: apolipoprotein E (ApoE) molecules present in the cerebrospinal fluid (CSF) receive it by ATP-binding cassette transporter 1 (ABCA-1) and ATP-binding cassette sub-family G 1 (ABCG-1). Neurons, due their poor synthesis capacity, receive cholesterol by these lipoproteins. As for its elimination by CNS, neurons convert it in 24S-OH-cholesterol, which is a polar molecule, therefore able to cross the BBB [15, 16, 17].

Lipid Peroxidation

Lipid peroxidation (LP) is a biological process consisting in oxidant molecules attacking lipid carbon-carbon bonds. The abovementioned phospholipids and cholesterol are typical targets due to their chemical structure [18]. It's known that LP products may determine cytotoxicity and alter gene expression and cellular signaling [19] and in this section recent results deriving from these cellular mechanisms study will be taken into consideration. In 2020, Bednarz-Misa et al. [20] performed a study about paraoxonase 1 (PO1) role in protecting by LP. Patients affected by Alzheimer's disease (AD), mixed dementia (MD) and vascular dementia (VaD) were enrolled. The authors studied PO1 activity in NCD patients and healthy controls' blood, noting that it was decreased in dementia, especially in severe forms – assessed with Mini Mental State Examination and Clinical Dementia Rating scales. They also studied malondialdehyde/thiobarbituric acid reactive substances (M/T) ratio as oxidative stress markers, being malondialdehyde an abundant product of LP [21]: M/T ratio seemed to be a dementia marker too. Both the considered markers – PO1 and M/T ratio – seemed not to be able to differentiate various etiologies. LP was studied in transgenic Alzheimer's mice in 2020 by Wang et al. [22]. The aim of their interesting study was to clarify the role played by allopregnanolone – a neurosteroid – in metabolic regulation. By a transcriptome analysis, the authors found that some allopregnanolone-induced pathways collaborated in inhibiting AD linked pathways – e.g. Presenilin 1 and Tumor Necrosis Factor pathways. The conclusions also hypothesized a therapeutic role for that neurosteroid. Another research in transgenic Alzheimer's mice was

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performed by Raefsky et al. [23]. Polyunsaturated fatty acids (PUFA) were the protagonists of the study. The authors were able to demonstrate that deuterated-PUFA (d-PUFA) fed mice showed reduced brain concentration of LP products – like isoprostanes and neuroprostanes – and also of hippocampal amyloid β (Aβ) 40 and 38, compared to mice fed with hydrogenated-PUFA. d-PUFA, despite reducing lipid peroxidation, seemed not to be able to improve mice cognitive capacities. In 2015, Angelova et al. [24] also studied the relationship between d-PUFA and LP, this time in in-vitro α-synuclein-mediated damage. Rat cortex neurons and astrocytes co-cultures were used to perform the experiment. The authors found that α-synuclein-aggregates were able to induce LP and cell death, while incubating the cells with d-PUFA, LP and cell death were prevented. Further studies may deepen the clinical impact of these discoveries.

Ferroptosis

Ferroptosis (Fp) [25] falls under the oxidative stress mediated cell death. It consists of a recently discovered nonapoptotic cell death, dependent from intracellular iron levels – not depending by other metal ions – induced by brain LP. Fp is different from other known death cell forms, but a relationship with autophagy was found: though genetic relationships is unclear, it seems that autophagy, by ferritin degradation, is able to promote Fp [26]. Fp can be induced by molecules like erastin [27] and it appears that mitochondria have a role in some Fp pathways, due to their membrane hyperpolarization and increase of LP products [25,28]. Ferrostatin-1 is a small molecule able to inhibit Fp by preventing erastin-induced accumulation of reactive oxygen species [25]. The scientific literature underlines Fp role in several biological processes: it is able to promote inflammation [29] or to kill cancer cells [25,30-32], while is inhibited by cellular senescence, due its lysosomal disfunction [33]. Its impact in neurodegeneration was supposed by Dixon et al. [25] already in 2012, the year of Fp discovery, and in this section recent results will be taken into consideration. In 2020, Ayton et al. [34] conducted a neuropathology study, measuring brain iron concentration in autopsy biopsies from temporal cortex and cerebellum – two areas known to be affected and spared, respectively, in AD. The analysis brought them to suppose that, being the AD neuronal death unclear, it may depend on Fp. Another contribute about Fp in AD was given by Zang et al. [35] in transgenic mice. Starting from the assumption that Tau protein is able to induce Fp by determining iron overload, they suggested that α-lipoic acid might inhibit Tau phosphorylation, so Fp, by acting on a kinase enzymatic cascade. Lysosome disfunction was under the attention of a study conducted in 2020 by Guiney et al. [36] about α-synuclein toxicity in Parkinson's disease (PD). The authors hypothesized that α-synuclein related cell death was mediated by Fp, but the results thy obtained did not support this hypothesis. In the same year, Angelova et al. [37], on the contrary, by performing a study on human stem cell-derived models of PD, were able to demonstrate a Fp role in α-synuclein related cell death. When treating the cellular models with erastin – a Fp inducer – the authors found a dose-dependent cell death increase; when treating them with ferrostatin-1, d-PUFAs and an iron chelator - Fp inhibitors – they found a cell death reduction compared to control cells. In 2019, Yan et al. [38] studied Fp in vascular cognitive impairment (VCI). The authors, starting from the relationship involving VCI and iron, LP and oxidative stress, hypothesized Fp as a trait d'union between VCI and cell death.

Apolipoprotein E4

ApoE4 allele is widely known to be a strong genetic factor associated with sporadic AD [39]. Its importance is mentioned in large part of the scientific literature, so, in this section, we will underline some recent findings. In 2020, Montagne et al. [40] affirmed that high CSF Platelet-Derived Growth Factor Receptor β – a

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BBB injury biomarker – might predict NCD in ApoE4 carriers (ε4/ε4 or ε3/ε4 alleles), but not in non-carriers. The authors suggested that BBB injury contributes to ApoE4-associated NCD, regardless of AD. In the same year, Area-Gomez et al. [41] performed a transcriptomics analysis on aged mice. They noticed that ApoE4 reduced mitochondrial function, but it seemed that bioenergetic regulation in entorhinal cortex was different compared to other areas. The authors hypothesized that differential stress response might have a role in AD pathophysiology. In 2020, a review conducted by Butterfield et al. [42] showing a link between ApoE4 and LP in AD developing risk. Both human and mice studies had been taken into account. The authors assessed the hypothesis that ApoE4 is less able to scavenge LP products due to its chemical structure – and in particular, the absence of two specific cysteine residues compared to other ApoE alleles. In 2021, La Joie et al. [43] performed a study on 119 Aβ-positive – assessed with positron emission tomography (PET) – symptomatic patients. They found that older age and ApoE4 seemed to promote a temporal predominant pattern assessed with PET-Tau, while amyloid pattern seemed not to be associated to different clinical phenotypes. Finally, different authors highlight ApoE role as a therapeutic target in AD patients [40,44].

Peripheral Metabolism

Central homeostasis matches peripheral lipid metabolism. Our research group produced evidence on peripheral blood mononuclear cell (PBMNC) role as NCD screening tool [45-47]. Elderly, AD, MD, VaD and HIV-associated neurocognitive disorders were the centre of our analysis. We studied neutral lipid accumulation and cluster formation using Oil Red O (ORO) staining method, measuring them with a semi-quantitative scale. We found higher accumulation in patients compared to healthy controls, but we were also able to demonstrate that the mentioned PBMNC markers are useful to identify early NCD stages. Peripheral neutral lipid accumulation was studied by François et al. [48,49] in oral mucosa cells, but the results they obtained in two studies were contradictory. In a recently published review, the role of peripheral metabolism assessment was considered a valid contribute for diagnosis and for the future of NCD therapy [50]. A possible reason of the abnormal neutral lipid accumulation is acyl-coenzyme A: cholesterol acyltransferase (ACAT), of whom two isoenzymes – ACAT1 and ACAT2 – exist [51], deriving from two different mammalian genes. ACAT is known to convert free cholesterol to cholesteryl esters (CEs), and it can be targeted in cardiovascular diseases [52]. In the past years, these genes' expression was studied in animals and humans to evaluate their role in AD. Studies were conducted, in PBMNCs, skin fibroblasts, and mice brain homogenates, among the others. Predominant role was acknowledged to be held by ACAT1 isoenzyme: its expression was higher in AD and it was correlated with higher neutral lipid accumulation. These results brought various authors to consider ACAT1 as a possible therapeutic target for AD [53-55]. Different results were instead found in Huntington's disease patients: CEs accumulation in human and murine cells in the striatum was not related to ACAT1 expression in the same areas [56].

Conclusions

Lipid metabolism is a clearly interesting topic both in basic and clinical research. The passing of the years and the development of technology have resulted in new interesting discoveries and links with neuropathology. LP can be seen as the key of neurotoxicity; due to the number of biological pathways it involves. This versatility conduced various author to consider LP role in several NCD etiologies. Growing attention is given to d-PUFA, but the clinical implication of their LP products reduction is yet to be clarified. Equally great attention is currently being given to Fp: though more studies still focus on Fp in cancer, many authors are presenting evidence on Fp to play a role of primary importance in NCD pathophysiology. We consider the deepening of studies about Fp

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mechanisms to be useful to explain the biology of dementia and maybe to discover new targeted therapies. We have chosen to dedicate a section of this review to ApoE, the stronger genetic risk factor of sporadic AD. Recent research moves between precise biochemical pathways and therapeutic implications: it highlights the fact that, though much knowledge, ApoE's complexity may provide us future information. The final section of this review was dedicated to peripheral lipid metabolism. Recent findings seem to suggest that peripheral markers are of vital importance in NCD diagnosis. The international standardization of peripheral lipid metabolism assessment technique may be a valid diagnostic weapon for the physicians. In conclusion, being able to better understand the biological mechanisms of NCDs might help the scientific research to find new diagnostic and therapeutic approaches for these widespread diseases.

References

1. Why Population Aging Matters to Health: A Global Perspective. NIH. 2011;11-7737.
2. Lopez OL, Kuller LH. Epidemiology of aging and associated cognitive disorders: Prevalence and incidence of Alzheimer's disease and other dementias. Handb Clin Neurol. 2019;167:139–48.
3. Ansari Z. Homocysteine and Mild Cognitive Impairment: Are These the Tools for Early Intervention in the Dementia Spectrum? J Nutr Health Aging. 2016;20(2):155–60.
4. Diagnostic and Statistical Manual of Mental Disorders: Dsm-5. Amer Psychiatric Pub Inc; 2013.
5. Loy CT, Schofield PR, Turner AM, Kwok JBJ. Genetics of dementia. Lancet. 2014;383(9919):828–40.
6. Kalaria RN. The pathology and pathophysiology of vascular dementia. Neuropharmacology. 2018;134(Pt B):226–39.
7. Killin LOJ, Starr JM, Shiue IJ, Russ TC. Environmental risk factors for dementia: a systematic review. BMC Geriatr. 2016;16(1):175.
8. Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab. 2016;36(1):172–86.
9. Panza F, D'Introno A, Colacicco AM, Capurso C, Pichichero G, Capurso SA, et al. Lipid metabolism in cognitive decline and dementia. Brain Res Rev. 2006;51(2):275–92.
10. Dichiara M, Amata B, Turnaturi R, Marrazzo A, Amata E. Tuning Properties for Blood-Brain Barrier Permeation: A Statistics-Based Analysis. ACS Chem Neurosci. 2020;11(1):34–44.
11. Pettegrew JW, Panchalingam K, Withers G, McKeag D, Strychor S. Changes in brain energy and phospholipid metabolism during development and aging in the Fischer 344 rat. J Neuropathol Exp Neurol. 1990;49(3):237–49.
12. Kim H-Y, Huang BX, Spector AA. Phosphatidylserine in the brain: metabolism and function. Prog Lipid Res. 2014;56:1–18.
13. Glade MJ, Smith K. Phosphatidylserine and the human brain. Nutrition. 2015;31(6):781–6.
14. Anchisi L, Dessì S, Pani A, Mandas A. Cholesterol homeostasis: a key to prevent or slow down neurodegeneration. Front Physiol. 2012;3:486.
15. Pfrieger FW, Ungerer N. Cholesterol metabolism in neurons and astrocytes. Prog Lipid Res. 2011;50(4):357–71.
16. Genaro-Mattos TC, Anderson A, Allen LB, Korade Z, Mirnics K. Cholesterol Biosynthesis and Uptake in Developing Neurons. ACS Chem Neurosci. 2019;10(8):3671–81.
17. Dietschy JM, 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;45(8):1375–97.
18. Niki E. Lipid peroxidation: physiological levels and dual biological effects. Free Radic Biol Med. 2009;47(5):469–84.

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DOI: https://doi.org/10.37191/Mapsci-2582-385X-3(4)-075

19. Luca M, Luca A, Calandra C. The Role of Oxidative Damage in the Pathogenesis and Progression of Alzheimer's Disease and Vascular Dementia. Oxid Med Cell Longev. 2015;2015:504678.
20. Bednarz-Misa I, Berdowska I, Zboch M, Misiak B, Zieliński B, Płaczkowska S, et al. Paraoxonase 1 decline and lipid peroxidation rise reflect a degree of brain atrophy and vascular impairment in dementia. Adv Clin Exp Med. 2020;29(1):71–8.
21. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev. 2014;2014:360438.
22. Wang T, Yao J, Chen S, Mao Z, Brinton RD. Allopregnanolone Reverses Bioenergetic Deficits in Female Triple Transgenic Alzheimer's Mouse Model. Neurotherapeutics. 2020;17(1):178–88.
23. Raefsky SM, Furman R, Milne G, Pollock E, Axelsen P, Mattson MP, et al. Deuterated polyunsaturated fatty acids reduce brain lipid peroxidation and hippocampal amyloid β-peptide levels, without discernable behavioral effects in an APP/PS1 mutant transgenic mouse model of Alzheimer's disease. Neurobiol Aging. 2018;66:165–76.
24. Angelova PR, Horrocks MH, Klenerman D, Gandhi S, Abramov AY, Shchepinov MS. Lipid peroxidation is essential for α-synuclein-induced cell death. J Neurochem. 2015;133(4):582–9.
25. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060–72.
26. Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ, et al. Autophagy promotes ferroptosis by degradation of ferritin. Autophagy. 2016;12(8):1425–8.
27. Dolma S, Lessnick SL, Hahn WC, Stockwell BR. Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells. Cancer Cell. 2003;3(3):285–96.
28. Gao M, Yi J, Zhu J, Minikes AM, Monian P, Thompson CB, et al. Role of Mitochondria in Ferroptosis. Mol Cell. 2019;73(2):354-363.e3.
29. Sun Y, Chen P, Zhai B, Zhang M, Xiang Y, Fang J, et al. The emerging role of ferroptosis in inflammation. Biomed Pharmacother. 2020;127:110108.
30. Mou Y, Wang J, Wu J, He D, Zhang C, Duan C, et al. Ferroptosis, a new form of cell death: opportunities and challenges in cancer. J Hematol Oncol. 2019;12(1):34.
31. Hassannia B, Vandenabeele P, Vanden Berghe T. Targeting Ferroptosis to Iron Out Cancer. Cancer Cell. 2019;35(6):830–49.
32. Bebber CM, Müller F, Prieto Clemente L, Weber J, von Karstedt S. Ferroptosis in Cancer Cell Biology. Cancers (Basel). 2020;12(1).
33. Masaldan S, Clatworthy SAS, Gamell C, Meggyesy PM, Rigopoulos A-T, Haupt S, et al. Iron accumulation in senescent cells is coupled with impaired ferritinophagy and inhibition of ferroptosis. Redox Biol. 2018;14:100–15.
34. Ayton S, Wang Y, Diouf I, Schneider JA, Brockman J, Morris MC, et al. Brain iron is associated with accelerated cognitive decline in people with Alzheimer pathology. Mol Psychiatry. 2020;25(11):2932–41.
35. Zhang Y-H, Wang D-W, Xu S-F, Zhang S, Fan Y-G, Yang Y-Y, et al. α-Lipoic acid improves abnormal behavior by mitigation of oxidative stress, inflammation, ferroptosis, and tauopathy in P301S Tau transgenic mice. Redox Biol. 2018;14:535–48.
36. Guiney SJ, Adlard PA, Lei P, Mawal CH, Bush AI, Finkelstein DI, et al. Fibrillar α-synuclein toxicity depends on functional lysosomes. J Biol Chem. 2020;295(51):17497–513.
37. Angelova PR, Choi ML, Berezhnov AV, Horrocks MH, Hughes CD, De S, et al. Alpha synuclein aggregation drives ferroptosis: an interplay of iron, calcium and lipid peroxidation. Cell Death Differ. 2020;27(10):2781–96.

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DOI: https://doi.org/10.37191/Mapsci-2582-385X-3(4)-075

38. Yan N, Zhang J-J. The Emerging Roles of Ferroptosis in Vascular Cognitive Impairment. Front Neurosci. 2019;13:811.
39. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921–3.
40. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature. 2020;581(7806):71–6.
41. Area-Gomez E, Larrea D, Pera M, Agrawal RR, Guilfoyle DN, Pirhaji L, et al. APOE4 is Associated with Differential Regional Vulnerability to Bioenergetic Deficits in Aged APOE Mice. Sci Rep. 2020;10(1):4277.
42. Butterfield DA, Mattson MP. Apolipoprotein E and oxidative stress in brain with relevance to Alzheimer's disease. Neurobiol Dis. 2020;138:104795.
43. La Joie R, Visani AV, Lesman-Segev OH, Baker SL, Edwards L, Iaccarino L, et al. Association of APOE4 and Clinical Variability in Alzheimer Disease With the Pattern of Tau- and Amyloid-PET. Neurology. 2021;96(5):e650–61.
44. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol. 2021;20(1):68–80.
45. Mandas A, Abete C, Putzu PF, la Colla P, Dessì S, Pani A. Changes in cholesterol metabolism-related gene expression in peripheral blood mononuclear cells from Alzheimer patients. Lipids Health Dis. 2012;11:39.
46. Costaggiu D, Serchisu L, Abete C. Determination of Neutral Lipid and Cluster Formation for Screening Neurocognitive Impairment in Human Immunodeficiency Virus Patients. J AIDS Clin. 2015.
47. Serchisu L, Peiretti E, Costaggiu D, Barcellona D, Caminiti G, Abete C, et al. Abnormal Lipid Accumulation and Cluster Formation of Naive Peripheral Blood Mononuclear Cells: A Useful Tool for Early Detection of Central Nervous System Damage in Elderly. J Alzheimers Dis Parkinsonism. 2017.
48. François M, Leifert W, Hecker J, Faunt J, Martins R, Thomas P, et al. Altered cytological parameters in buccal cells from individuals with mild cognitive impairment and Alzheimer's disease. Cytometry A. 2014;85(8):698–708.
49. François M, Fenech MF, Thomas P, Hor M, Rembach A, Martins RN, et al. High Content, Multi-Parameter Analyses in Buccal Cells to Identify Alzheimer's Disease. Curr Alzheimer Res. 2016;13(7):787–99.
50. Salis F, Mandas A. The Role of Peripheral Cells in Neurocognitive Disorders Detection. J Alzheimer's Neurodegener Dis. 2021;7:052.
51. Chang T-Y, Li B-L, Chang CCY, Urano Y. Acyl-coenzyme A:cholesterol acyltransferases. Am J Physiol Endocrinol Metab. 2009;297(1):E1-9.
52. Li H, Jing X, Deng X, Ouyang D. [Targets of anti-hyperlipidemia drugs]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2013;38(1):101–8.
53. Pani A, Mandas A, Diaz G, Abete C, Cocco PL, Angius F, et al. Accumulation of neutral lipids in peripheral blood mononuclear cells as a distinctive trait of Alzheimer patients and asymptomatic subjects at risk of disease. BMC Med. 2009;7:66.
54. Pani A, Dessì S, Diaz G, La Colla P, Abete C, Mulas C, et al. Altered cholesterol ester cycle in skin fibroblasts from patients with Alzheimer's disease. J Alzheimers Dis. 2009;18(4):829–41.
55. Bryleva EY, Rogers MA, Chang CCY, Buen F, Harris BT, Rousselet E, et al. ACAT1 gene ablation increases 24(S)-hydroxycholesterol content in the brain and ameliorates amyloid pathology in mice with AD. Proc Natl Acad Sci U S A. 2010;107(7):3081–6.

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DOI: https://doi.org/10.37191/Mapsci-2582-385X-3(4)-075

56. Phillips GR, Hancock SE, Brown SHJ, Jenner AM, Kreilaus F, Newell KA, et al. Cholesteryl ester levels are elevated in the caudate and putamen of Huntington's disease patients. Sci Rep. 2020;10(1):20314.

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