

Altered Brain Cholesterol Metabolism is Related to Disease Severity, Neurodegeneration and Atrophy in AD

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Abstract

Alzheimer's disease (AD) is the most progressive neurodegenerative disorder of the aging population after Parkinson's disease (PD). The pathogenesis of AD is complex and obscure till date. Recent epidemiological and molecular studies have linked the disruption of cholesterol homeostasis to increased risk for developing AD. Oxysterols are oxidized derivatives of cholesterol that are formed enzymatically or via reactive oxygen species or both. Oxysterol levels are implicated in the pathogenesis of numerous neurodegenerative diseases like AD, PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), Multiple sclerosis (MS). The blood brain barrier (BBB) effectively prevents uptake of lipoprotein-bound cholesterol from blood circulation. Here the relationship between alterations in brain cholesterol metabolism and AD pathogenesis is reviewed.

Keywords: Brain Cholesterol; Oxysterol; Homeostasis; Neurodegeneration; Alzheimer's Disease

Abbreviations

LDLR: Low Density Lipoprotein Receptor; VLDLR: Very Low Density Lipoprotein Receptor; ApoER2: Apolipoprotein E Receptor 2; LRP: LDL Receptor Related Protein; MEGF: Multiple Epidermal Growth Factor-Like Domains; SorLA: Sorting-Related Receptor With A-Type Repeats; LR: Lipoprotein Receptor; ABC: ATP-Binding Cassette Transporter

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that occurs primarily in the aging population [1]. Histopathological characteristics include extracellular deposits of amyloid- β ($A\beta$) senile plaques, $A\beta$ deposits in cerebral blood vessels, intracellular neurofibrillary tangles that consist of hyperphosphorylated tau proteins along with neuronal loss in the neocortex and hippocampus [1,2]. AD typically affects memory initially, but atypical presentations can occur, particularly in younger patients [3]. Based on Alzheimer's Disease International Federation (ADI), at least 46.8 million people are affected by dementia worldwide, that anticipated to be 74.7 million by 2030 and 131.5 million by 2050 [4]. Researchers believe pathogenesis of AD is complex which includes mechanisms like microgliosis, immunoreactivity, oxidative stress and dysregulation of protein homeostasis [5], apart from traditional amyloid cascade hypothesis [6], ultimately leading to neuroinflammation and neurodegeneration.

Cholesterol is an important constituent of eukaryotic membranes [7]. Different concentrations of cholesterol regulate membrane fluidity, and thereby functional specificity and structural integrity of various cellular locations, including trans-membrane signaling and membrane trafficking [8]. Especially, membrane cholesterol levels play a key factor in determining the stability and organization of microdomain termed lipid rafts [9]. Cholesterol is also the precursor of all steroid hormones and bile acids [7]. Cholesterol and its

oxidized form oxysterol are implicated as the initiation and progression of many chronic diseases in the literature like osteoporosis, age related macular degeneration, cataract, atherosclerosis, neurodegenerative diseases (e.g. AD, PD, MS etc.).

Chemically, the addition of one or more oxygenated functional groups to 27-carbon cholesterol molecule changes its behaviour and receptor recognition. Commonest oxysterols implicated with cognitive changes are 24-hydroxycholesterol (24-OHC), 27-hydroxycholesterol (27-OHC), 7-ketocholesterol (7-KC) and 7 β -hydroxycholesterol (7 β -OHC) [14-18]. Non-heme iron-containing oxidoreductase, cholesterol 25-hydroxylase (CH25H), has recently received attention due to the involvement of its product, 25-hydroxycholesterol (25-OHC) in immunity control [19].

The brain contains the highest level of cholesterol in the body, approximately 20% of whole body cholesterol [20,21]. Cholesterol in the brain is present mostly in the unesterified form, and the concentration in the brain is higher than that in any other tissues (~23 mg/g) [22]. The blood brain barrier (BBB) effectively prevents the uptake of lipoprotein-bound cholesterol from peripheral circulation. Cholesterol level in the brain is independent from that in peripheral tissues, and thus de novo synthesis is considered responsible for practically all cholesterol in the brain [2,21]. Cholesterol is mainly observed in glial cells [23] and is produced at higher rates in astrocytes than in neurons [22,23]. During embryogenesis, both neurons and glia actively synthesize cholesterol for myelinogenesis. Neuronal cell cholesterol uptake promotes dendritic growth and synaptic formation [24]. However, in adults, differentiated neurons gradually lose their de novo synthetic ability and rely on lipoprotein-conjugated cholesterol produced by glia [22]. Conditional ablation of cholesterol synthesis in neurons shows no specific neurodegeneration or inflammation and no change even in the amount of cholesterol uptake receptors such as Low-density lipoprotein (LDL) receptor-related protein 1 (LRP1) [25]. However, the amounts of cholesterol produced by glia and taken up by neurons increase significantly [25], supporting the dependency of neurons on cholesterol produced by astrocyte lineage. Some studies showed elevated transcript level of cholesterol synthesis enzymes in neurons compared to that in astrocytes [26]. The recovery of de novo synthesis of cholesterol to some extent is by stimulation of neurons by brain-derived neurotrophic factor (BDNF) [27]. Studies using radioactive labels have reported glia synthesize cholesterol through the Bloch pathway, as do other cholesterol forming peripheral tissues, whereas neurons synthesize cholesterol mainly through the Kandutsch-Russell (K-R) pathway [23,28], indicating that the K-R pathway is activated in neurons to maintain homeostasis. Although cholesterol cannot cross the BBB, some cholesterol are absorbed into the brain in the form of plasma lipoprotein-bound cholesterol [29,30]. Scavenger receptor, class B type 1 (SR-B1), which plays an important role in the selective absorption of high density lipoprotein (HDL) cholesterol in hepatocytes, is also present in brain capillary endothelial cells [30,31], thereby mediating the uptake of cholesterol from plasma HDL and LDL [30]. Surprisingly, brain endothelial cells have the potential to take up LDL cholesterol through luminal LDL receptor and translocate this LDL across the cells [32].

Most lipoproteins in plasma are not found in the brain owing to BBB [29]. Instead, a hybrid protein containing phospholipid, cholesterol, and apolipoprotein sized approximately 8~12 nm is identified [33]. This lipoprotein is called 'HDL-like particle' because it is similar in size and density to plasma HDL [29]. Astrocytes are suspected to be mainly responsible for most of lipoprotein production in the brain [34-36]. Most of the lipoproteins found in cerebrospinal fluid (CSF) are spherical in form and different in size from nascent poorly-lipidated HDL secreted from astrocytes, suggesting that the lipoproteins secreted from astrocytes are modified as in plasma HDL maturation [37]. Some cholesterol remodeling enzymes, such as lecithin: cholesterol acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), and phospholipid transfer protein (PLTP), known to promote spherical HDL formation from nascent HDL were found in the brain. These proteins may play a significant role in brain lipoprotein maturation, although this role needs clear elucidation [38-41].

Apo E and Apo A-I are major forms of apolipoprotein found in the brain and other apolipoproteins, such as Apo J, Apo A-II, Apo A-IV, Apo D, and Apo H are observed in human CSF samples [37,42]. These apolipoproteins form HDL-like particles, and undergo cell membrane remodeling and repair through internal rearrangement of cholesterol and phospholipids in differentiated adult neurons [20]. Apo E is synthesized in the brain [43], which is the second largest producer of Apo E after the liver [44]. Apo E is mainly produced in astrocytes, followed by oligodendrocytes, microglia, and ependymal layer cells [45]. Apo E is produced when a specific stress condition or

damage to neuron occurs [46]. The main function of Apo E is to regulate lipid transport between neurons and glia, as well as metabolism of lipoprotein-bound cholesterol [38]. ApoA-I is not synthesized in the brain, but most may be transported from plasma HDL through SR-BI-mediated uptake via the choroid plexus [30], however, this transport mechanism is not fully understood [47]. Lipoprotein-bound cholesterol is taken up by cells via receptors in peripheral tissues. In the brain, there are seven core members including LDLR, VLDLR, ApoER2/LRP8, LRP4/MEGF7, LRP1, LRP1B, and megalin/LRP2, and three subgroups of the LDLR family, including LRP5, LRP6, and SorLA/LR11 [48,49]. Apo E acts as a ligand for these LDLR family members expressed in the brain [49]. Among these receptors, LRP1 and LDLR are the major receptors related to ApoE-containing lipoproteins carrying cholesterol between neurons and glia [50]. LRP1 is a large endocytic receptor with various functions. In the brain, LRP1 is expressed by both neurons and glia, but predominantly by neurons [51]. LDLR is also present in both neurons and glia, however, contrary to LRP1, LDLR is more expressed in glia than in neurons [52].

In humans, brain cholesterol has an extremely long half-life of approximately 6 months and 5 years, whereas that in plasma is only a few days [53]. Surplus cholesterol is stored in the esterified form, corresponding to 1% of total cholesterol content in the brain [54]. The level of this esterification enzyme is higher in neurons than in glia [55]. Cholesterol can be hydroxylated to 24-HC by cholesterol 24-hydroxylase and this form of oxysterol is the main form of excreted cholesterol in the brain [56]. In fact, 40% of the cholesterol released from the brain is in the 24-HC form [57]. The expression level of cholesterol 24-hydroxylase is much higher in neurons than in glia [14,58-60]. This oxysterol can pass lipophilic membranes, such as BBB [61]. Therefore, most 24-HC in plasma are released from the brain. Therefore, there are many attempts to use 24-HC as a marker of the aging process or neurodegenerative disease, but this use is still debated [62-65]. Moreover, 27-HC, which is similar in character to 24-HC, is also present in the brain; however, 27-HC is present in low amounts and most are of extracerebral origin owing to the characteristics of this oxysterol that can cross the BBB [66]. Cholesterol is also excreted from neurons through ABC transporters, such as ABCA1, ABCG1, and ABCG4. These ABC transporters are involved in the transport of various substances beyond the membrane, between the cells in the central nervous system (CNS) express these transporters [67]. Generally, neurons express more ABC transporters than astrocytes [68,69]. The cholesterol released via ABC transporters connect to the ApoAI containing lipoproteins present in the CSF, and then removed through LRP1 or SR-BI, which is expressed in brain capillary endothelial cells [37,70].

Mitochondrial oxysterol metabolism may play an important role in pathogenesis of Alzheimer's disease. Mitochondrial CYP27 plays an important role in cholesterol homeostasis. 27-OHC is the most abundant oxysterol reported in human atheroma, and the CYP27 enzyme that produces this oxysterol has been regarded as a defense mechanism to prevent macrophage cholesterol accumulation [71]. Sterols, including oxysterols, enter the cell via receptor-mediated endocytosis of low density lipoproteins (LDL) and traffic to the lysosomes, which are a major site of non-enzymatic oxysterol formation. Thus, among these oxysterols, 7-KC is found at the highest level in the endosomal and lysosomal compartments [72]. In addition, human pro-monocytic U937 cells treated either with 7-KC, 7 β -OHC, or cholesterol-5 β , 6 β -epoxide, show an important accumulation of 7-KC, 7 β -OHC. Cholesterol-5 β , 6 β -epoxide are found in acidic compartments of the cytoplasm (phagolysosomes) associated with membrane whorls designed as 'myelin figures' [73-75]. This accumulation of oxysterols in myelin figures has been considered first as a phospholipidosis process to attenuate the cytotoxic effects of oxysterols. It is now suggested that these myelin figures could also include autophagic vesicles (resulting from reticulophagy), involving the fusion of the autophagosome, containing large parts of endoplasmic reticulum, within the lysosome [76]. It is suggested that the process of phospholipidosis would prevent the intracellular accumulation of 7-KC which favours lysosomal membrane destabilization and contributes to cell death induction [75]. Increased intracellular 7-KC levels is associated with multiple conditions such as cardiovascular diseases, age related macular degeneration and Alzheimer's disease [77].

27-OHC and 24-OHC as a plasma oxysterol is being studied a lot. Neuronal derived 24-OHC is extensively researched in relation to neurodegeneration, compared to hepatically and extrahepatically derived 27-OHC. Unlike cholesterol, polar oxysterols can cross endothelial barriers including tight junction-rich blood-brain barrier (BBB) [78]. Fluctuation to plasma oxysterol levels have been described in neurodegenerative diseases such as Alzheimer's disease (AD), Multiple Sclerosis (MS) or Parkinson's Disease (PD) [79].

Discussion

Case-control studies on patients with early cognitive impairment have shown a small non-significant increase of plasma 24-OHC, 7-KC and 7 β -OHC levels [80,81] and a significant increase of 27-OHC [82], compared with cognitively normal controls. Studies that analysed AD plasma reported significantly higher absolute levels of plasma 24-OHC and 27-OHC than in healthy controls [81,83-85]. However, other studies did not make the same observation [80,86]. When AD is stratified by early versus late stage of disease, plasma 24-OHC levels are higher in the early stages compared to later stages of AD [81,87]. Accordingly, AD patients with longer disease duration had lower levels of oxysterols than patients with subjective cognitive impairment or cognitively healthy controls. In 2012, a longitudinal study reported that cognitively healthy participants with higher plasma 24-OHC were more likely to develop incident cognitive impairment over 8 years of follow up and that these differences in plasma oxysterols occurred at least four years prior to the onset of cognitive impairment [88].

It can be argued that part of the controversies reported in cross sectional studies is due to the observation that oxysterol levels can change longitudinally during the evolution of the disease. Whether increased oxysterol levels in early stages reflect that altered cholesterol metabolism is involved in the pathophysiology of AD or is just a consequence of the degenerative process is still unclear. The decrease in later stages could reflect a selective loss of neuronal cells expressing the enzyme cholesterol 24-hydroxylase, CYP46A1 [21].

Popp, *et al.* found a positive association between plasma 27-OHC levels and soluble amyloid protein precursor (APP)- β levels. However, at present, no strong correlation has been reported between plasma oxysterols and traditional AD biomarkers of amyloid, tau, p-tau [84]. When patients with cognitive complaints are stratified according to the biomarker levels, patients with AD-like pathology, that is, lower levels of amyloid and higher levels of tau, have lower plasma 24-OHC and 27-OHC [89]. In mild cognitive impairment (MCI), 24-OHC/27-OHC correlates with amyloid deposition [90]. The higher rates of atrophy are associated with a progressive reduction of the plasma levels of 24-OHC [91]. A significant correlation of 24-OHC with hippocampal volume [92] or the whole grey matter volume was found in mid-age or aged individuals [91].

In case-control studies, patients with mild cognitive impairment show higher CSF 24-OHC and 27-OHC levels than healthy controls [65,87,93-94]. Moreover, patients with MCI that progress to AD have higher levels of 24-OHC than stable MCI patients that do not progress to dementia [95]. This increase has also been described in AD patients respect to controls [84-87,93-95], but not observed in Kolsch's study [96]. Whether the increased levels of 24-OHC and 27-OHC are just a consequence of neurodegeneration or whether membrane cholesterol metabolism is involved in AD pathophysiology remains to be clarified. Increased levels of 24-OHC and 27-OHC in MCI patients could reflect both AD and cerebrovascular disorders as the underlying pathologies, suggested by Leoni and colleagues [94]. In MCI patients that progress to dementia, the proportion of subjects with altered 24-OHC levels are higher than the proportion of subjects with pathologic levels of A β 42, Tau or P-tau. In contrast, in AD subjects, the fraction of patients with pathological levels of 24-OHC is similar or even lower than the fraction of patients with pathological Tau, P-tau, and A β 42 [94,97]. While this finding could be related to the loss of 24-OHC producing neurons in the advanced stages, it could also suggest that stressed cholesterol metabolism could be involved in the pathophysiology in the early stages. Additionally, decreased activity of CYP46A1 has been also suggested to be implicated in the synaptic and memory dysfunctions caused by tau pathology [98].

With regard to the APOE genotype, both 24-OHC and 27-OHC increase proportionally to the number of e4 alleles in individuals with cognitive decline [87,94,99]. Additionally, there is a positive correlation between levels of APOE and 24-OHC in CSF from patients with AD and MCI [65,87,95]. Besga and colleagues reported that CSF 24-OHC levels were differentially associated with the white matter hyperintensity (WMH) severity. WMH load represents cerebral white matter lesions most likely related to small vessel disease whose prevalence increases with age and represent myelin damage [100]. In patients with CSF-defined AD-like pathology, CSF levels of 24-OHC was positively associated with WMH severity and in patients without AD-like pathology CSF levels of 24-OHC were negatively correlated with WMH. They suggest that in the CSF AD-like group, the positive correlation between oxysterols and white matter lesions could be understood as an increased elimination of cholesterol from ongoing demyelination [89].

Broadly speaking, hypercholesterolemia, especially in middle-aged individuals is considered a high-risk factor for the development of AD [24]. It has also been shown in rats that increased permeability of the BBB can be the result of high cholesterol diet and that AD patients who suffer from hypercholesterolemia developed BBB damage within 1 year [101,102]. Therefore, increased permeability of the BBB is the only way for peripheral cholesterol to enter the brain [24]. Both epidemiological and molecular evidence has linked disruption of cholesterol homeostasis to susceptibility to AD [1,103]. In addition, cholesterol lowering drugs, statins have been reported to exert beneficial effects in many neurodegenerative diseases, However, it is not fully known whether the underlying mechanism of statins mediated neuroprotection is associated with lowering cholesterol level due to their pleiotropic effects such as anti-inflammatory, anti-oxidant effects [104].

Conclusion

The brain is the most cholesterol-rich organ, and owing to the BBB, cholesterol metabolism in the brain is independent on that in peripheral tissues. Nevertheless, detailed knowledge on cholesterol metabolism in the brain remains incomplete, and it should be considered that altered cholesterol metabolism in the periphery does not represent that in the CNS. As we see oxysterol levels at cellular and biological fluid have an impact on pathogenesis of AD. We are beginning to see the data emerging from pre-clinical knockout of CH25H and CYP46A that point to oxysterol regulation of inflammation and neurodegeneration. Further studies are required in this emerging field which will likely provide more clues to the role of cholesterol metabolism, inflammation and neurodegeneration, and new avenues for therapeutic involvement in AD.

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