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Review

Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: Potential novel targets for treatment

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia and it is characterized by the deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain. However, the complete pathogenesis of the disease is still unknown. High level of serum cholesterol has been found to positively correlate with an increased risk of dementia and some studies have reported a decreased prevalence of AD in patients taking cholesterol-lowering drugs. Years of research have shown a strong correlation between blood hypercholesterolemia and AD, however cholesterol is not able to cross the Blood Brain Barrier (BBB) into the brain. Cholesterol lowering therapies have shown mixed results in cognitive performance in AD patients, raising questions of whether brain cholesterol metabolism in the brain should be studied separately from peripheral cholesterol metabolism and what their relationship is. Unlike cholesterol, oxidized cholesterol metabolites known as oxysterols are able to cross the BBB from the circulation into the brain and vice-versa. The main oxysterols present in the circulation are 24S-hydroxycholesterol and 27-hydroxycholesterol. These oxysterols and their catalysing enzymes have been found to be altered in AD brains and there is evidence indicating their influence in the progression of the disease. This review gives a broad perspective on the relationship between hypercholesterolemia and AD, cholesterol lowering therapies for AD patients and the role of oxysterols in pathological and non-pathological conditions. Also, we propose cholesterol metabolites as valuable targets for prevention and alternative AD treatments.

1. Hypercholesterolemia and Alzheimer's disease

Dementia is one of the major health problems worldwide and it comprises a broad range of signs and symptoms associated with the loss of cognitive functioning that eventually leads to a devastating loss of autonomy in the person´s everyday activities. The nearly estimated 46.8 million patients suffering from dementia worldwide in 2015 are believed to double every 20 years and predicted to reach 131.5 million by 2050 [1]. Alzheimer disease (AD) is the most common dementia which accounts for 80% of cases followed by vascular dementia (VaD, 15%) [2]. This prevalence increases when accounting for Mixed Dementia, a condition in which AD patients present blood vessel dysfunctions associated to VaD (33%) [3]. The remaining types of dementia such as Lewy bodies (DLB, 2,5%), Parkinson's disease (PD, 1%) and Frontotemporal dementia (FTD, 5,4%) account for a smaller fraction of the cases.

AD is an irreversible neurodegenerative disease that progressively destroys memory and other important brain functions. To date, AD has neither cure nor treatment. This disease is molecularly characterized by protein misfolding in the brain with the accumulation of amyloid β (Aβ) in senile plaques and hyperphosphorylation of tau protein [4]. Most of the patients present the first clinical symptoms by the age of 65 (late onset AD or LOAD) and affect about 30–50% of those by 85 years; while only about a 2–10% of patients develop earlier onset of AD [5].

AD is a multifactorial disease that results from the combination of genetic and environmental risk factors. The presence of risk factors in midlife such as hypertension [6], diabetes mellitus [7], arteriosclerosis [1], obesity and hypercholesterolemia [8,9] are associated with

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cognitive decline in late life [2,10]. Epidemiological studies suggest that specific risk factors can be potentially controlled and thus may delay the onset of dementia in old age [11]. Moreover, these environmental factors can combine with specific alleles to contribute to the risk of developing AD, with many of them related to energy metabolism and lipid transport. For example, the presence of the ε4 allele of Apolipoprotein E (APOE), a protein involved in cholesterol transport, is the fourth genetic factor implicated in the risk of developing both early-onset and late-onset AD and accounts for 45–65% of AD patients [12]. The etiology of late-onset AD is complex, due to the fact that environmental risk factors also contribute to the pathogenesis. For instance, the combination of human ApoE4 isoform in mice with a dietary risk factor based on high carbohydrates or high fat induce impairments in memory, metabolism and higher vulnerability of hippocampal synaptic plasticity when compared to ApoE3 mice [13–15]. Other cholesterol-related genes such as clusterin (also known as APOJ), an apolipoprotein present in high-density lipoprotein (HDL), represents the third most important risk gene in AD [16,17]. The acyl-CoA cholesterol acyltransferase (SOAT1) is an enzyme that helps with cholesterol storage and a single nucleotide polymorphism (rs1044925) has been related to decreased risk of developing AD. Both clusterin and SOAT1 have been proposed as therapeutic targets for AD recently [18].

In the last decade, the relationship between cholesterol and AD has been greatly investigated in prospective epidemiological studies [8]. Several studies point out a relationship between increased risk to develop AD and high levels of cholesterol in plasma [8,19–21]. Nevertheless, questions arose when epidemiological evidence showed a decreased risk and even a protective effect for hypercholesterolemia when evaluated in elderly patients [9,22]. Higher levels of serum cholesterol have been found to positively correlate with an increased risk of dementia. However, a recent meta-analysis comparing data on more than 23,000 patients from 17 studies show that the highest risk for developing AD in relationship with hypercholesterolemia happens in midlife and early stages of aging, while there is no significant correlation with hypercholesterolemia in late life [23]. In fact, low total cholesterol in late life is associated with cognitive decline [9,24]. This study points out that the late life hypercholesterolemia has to be separated from chronic hypercholesterolemia starting from midlife and continued over the years, since these conditions often overlap with obesity, metabolic syndrome and diabetes, which are important risk factors to develop AD and other dementias [25].

Another study proposes that dietary intake of fatty acids and increased essential docosahexaenoic fatty acid in serum is related to preservation of entorhinal and hippocampal volumes in AD patients, with positive amyloid deposition in the brain assessed through PIB PET [26]. The fact that cholesterol and lipid levels in the blood are modifiable makes them of great interest for the generation of cholesterol modifying therapies that can potentially ameliorate the progression of AD pathology.

2. Cholesterol-lowering therapies for prevention of Alzheimer's disease

in vitro and *in vivo* experiments suggests that high levels of cholesterol in the blood increase the production of Aβ in AD [27]. Moreover, cholesterol-lowering medications, such as statins counteract Aβ production in animal models fed on cholesterol [28]. Over the past two decades, several studies explored the possibility of using lipid-lowering compounds such as fibrates, niacin, dietary supplements, statins, or bile acid sequestrants to prevent the risk of AD, however, none of them is as studied as statins for dementia prevention purposes.

Statins are the most widely prescribed FDA-approved cholesterol-lowering medications and they have been used as therapies for many cardiovascular illnesses [27]. Statins can be classified according to their solubility as lipophilic or hydrophilic: among the lipophilic statins are lovastatin, simvastatin, atorvastatin, fluvastatin and pitavastatin, while the hydrophilic ones are rosuvastatin and pravastatin [29]. These compounds block the conversion step of 3-hydroxy-3-methylglutaryl-coenzymeA (HMG-CoA) to mevalonate by inhibiting HMG-CoA reductase and thus inhibiting the biosynthesis of cholesterol. Statins target the liver leading to decreased intracellular levels of cholesterol in hepatic cells [30] and also reduce the generation and entry of LDL cholesterol into the circulation and up-regulate LDL receptor activity.

Among their multiple pleiotropic effects, statins increase the production of vasodilators such as prostaglandin I2 and nitric oxide (NO) and decrease the production of vasoconstrictors, therefore enhancing blood perfusion [31]. They also prevent the release of pro-inflammatory matrix metalloproteinases (MMP) and cytokines, including TNF-α, IL-1β and IL-6 [28], thus producing an overall anti-inflammatory effect. Finally, statins have been shown to improve the endothelial function of atherosclerotic vessels [29] and by inhibiting NADPH oxidase they may contribute to generating an antioxidant effect. Simvastatin and Atorvastatin treatments have been shown to ameliorate inflammation and memory deficits *in vivo* in APP/PS1 transgenic mice and in mice injected ventricularly with Aβ, respectively [32,33].

Several early observational studies have been carried out in patients over 60 years old in order to evaluate whether the use of statins would lead to the development of dementia later in life. The Sacramento Area Latino Study on Aging (SALSA) reported that during over 5 years of follow-up in elderly (60 years of age or older), statin users were significantly less likely to develop dementia or cognitive impairment without dementia than statin non-users [34]. Additionally, in the Indianapolis-Ibadan Dementia Project, statin non-users showed a faster decline in cognitive scores over 3 years follow-up [35]. Interestingly, patients who discontinued the use of statins showed significantly slower cognitive decline than those with a consistent statin-use group, whose cognitive decline showed no significant difference in comparison to non-users. On the opposite, in 2015, the same cohort had been studied for 8 years and authors reported that only consistent statin users over the observational period showed reduced dementia and AD risk [36].

On the other hand, the MRC/BHF Heart Protection Study (HPS) trial evaluated the effect of an individual statin, simvastatin, in the prevention of heart disease among 20,536 adults, including 5806 elder people (age 70–80) at baseline [37]. In the same line, the effect of pravastatin was evaluated in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial on 5804 elder individuals at risk of vascular disease [38]. Results in both studies showed reduced cardiovascular illnesses such as stroke and myocardial infarction among the study participants however, no changes were found for the groups of people reported to have developed dementia. In several smaller 6-month trials, the authors reported no significant improvement and even worse cognitive scores between lovastatin or simvastatin users and placebo. In these studies, they performed cognitive tests of executive function, global cognitive screening tests and evaluated attention on trial participants [39–41].

In summary, observational studies and randomized control trials in AD shows contradictory results. While some observational studies report beneficial effects of statins in the prevention of AD in late life, the most important randomized clinical trials, including the HPS trial and the PROSPER trial do not support such conclusion. These findings reflect the complexity of the relationship between cholesterol and brain cognitive decline. Therefore, further investigation of the metabolism of cholesterol in the brain may be crucial to understanding how blood cholesterol alterations affect cognition and neurodegenerative processes.

3. Brain cholesterol and oxysterols in Alzheimer's disease

The brain contains 23% of total body cholesterol [42] and brain cholesterol is considered to be essential for cell maintenance, neuronal transmission and synapse formation. Postnatally, the main source of cholesterol for neurons is provided by astrocytes through synthesis

[43]. Synthesized cholesterol is delivered to neurons by the cholesterol transporter APOE [44], which also allows cholesterol excretion. Brain cholesterol is abundantly present in myelin sheath to insulate axons and it is also a major component of dendritic spines. Removal of cholesterol membrane blocks long term potentiation (LTP) in the hippocampus [45], while chronic excitatory stimuli lead to cholesterol loss from synapses [46]. Cholesterol replenishment *in vivo* improves cognitive functions and restores LTP [47].

Cholesterol levels in the brain are independent of the levels in peripheral tissues since the BBB prevents peripheral cholesterol to enter the central nervous system. Although cholesterol levels could be highly increased in the blood due to high-fat/high-cholesterol diets, brain cholesterol remains unchanged in animal models [48]. Yet, the administration of high fat diet in AD animal models is able induces Aβ accumulation and worsen amyloid pathology and cognition [49–56]. In the same manner, high-fat diets increase the flux of oxysterols (oxidized forms of cholesterol) to the brain [50,57], and these molecules could explain the relationship between blood and brain cholesterol levels. It is believed that brain cholesterol may exert its functions in the brain also through these cholesterol metabolites. In light of this, recent evidence shows that oxysterols are signaling molecules of great importance for brain functions.

Maintenance of cholesterol homeostasis is essential for normal neuronal functioning and brain development. In neurons, a brain-specific enzyme cholesterol 24-hydroxylase (CYP46A1) converts the excess of cholesterol into 24-hydroxycholesterol (24S − OH), which may diffuse across the blood-brain barrier (BBB) [58,59]. 24 − OH levels are directly correlated to cholesterol levels in the brain and its presence in the plasma comes almost entirely from cerebral production through gradient-mediated diffusion [60]. While there is an efflux of 24 − OH from the brain to the peripheral circulation, there is also an inflow of 27-hydroxycholesterol (27 − OH) to the brain [61]. This oxysterol is a product of peripheral metabolism of cholesterol, generated by the enzyme sterol 27-hydroxylase (CYP27A1).

Both 24S − OH and 27 − OH are regarded as physiological suppressors of the brain cholesterol biosynthesis, since activity-based depletion of the 24S − OH boosts cholesterol synthesis in the brain as a compensatory response [62], same as increased 24S − OH leakage through the BBB [63]. Several studies have shown that 27 − OH, unlike 24S − OH, may accelerate brain cognitive deficits in AD under conditions of hypercholesterolemia where higher cholesterol levels result in an increased influx of 27 − OH into the brain [50,64]. Other oxysterols are present in the brain and are also linked to other risk factors and diseases like inflammation [65] or atherosclerosis [66], however the interplay between 24S − OH and 27 − OH is the main driving force of cholesterol homeostasis in the brain (Fig. 1) [43,67–70].

Disruption in cholesterol metabolism is a risk factor for the development of AD and during healthy aging, homeostasis of brain cholesterol is maintained by tight regulation of cholesterol biosynthesis and efflux of oxysterols between brain and circulation. Levels of oxysterols are modified during the development of AD. Quantification of oxysterols in AD autopsy brain shows significant reduction of 24S − OH in late stages of AD, while other oxysterols such as 27 − OH and 25 − OH are significantly increased. Accordingly, CYP46A1 levels are markedly reduced already in early stages of AD, while CYP27A1 levels are increased [71]. The decrease of CYP46A1 is probably due to selective loss of neurons expressing CYP46A1, being this enzyme present mainly in neurons. However, during AD, CYP46A1 is mainly located in astrocytes and around amyloid plaques [72]. In plasma of AD patients levels of 24S − OH are increased at early stages and decreased during late stages when compared to healthy controls. In CSF both 24S − OH and 27 − OH levels tend to be increased [73,74]. Interestingly, increased 24S − OH is also found in other neuronal pathologies such as meningitis and multiple sclerosis, probably as consequence of neuronal damage and cholesterol engulfment. In light of these findings, 24S − OH has been suggested as a CSF biomarker useful for early diagnosis of neurodegenerative diseases. Since CYP46A1 is decreased in AD brains [72,75], several studies have looked for an association of its single nucleotide polymorphisms (SNPs) to the risk of developing AD and cerebral amyloidosis [76–79]. Nevertheless, there is no consensus about such correlations [80,81]. Most studies have identified two polymorphisms in CYP46A1 intron 2 (rs754203) and 3 (rs4900442), however, two additional SNPs rs7157609 and rs4900442 can interact to increase the risk of AD and are associated with reduced CSF levels of 24S − OH [79]. The intron II CYP46A1 polymorphism is associated with the APOE genotype influencing the risk of AD [82], however, the mechanisms mediating this effect on AD pathogenesis remains unclear.

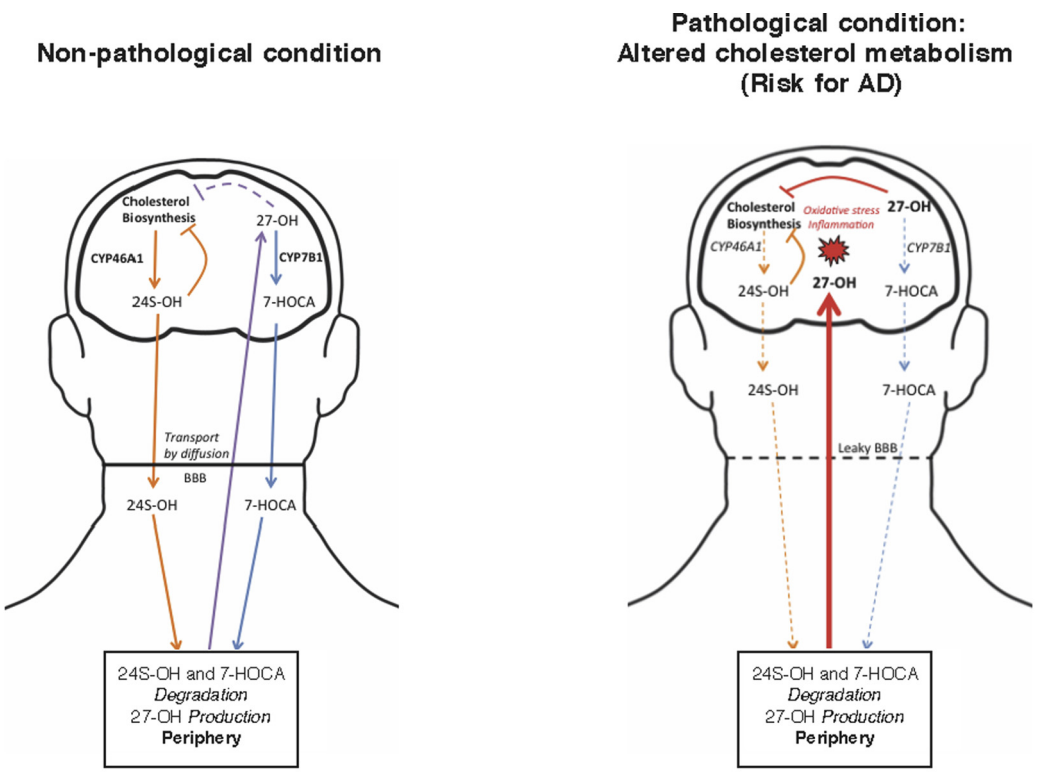
4. CYP46A1 and 24S-hydroxycholesterol

APOE-bound cholesterol is released daily to the cerebrospinal fluid (CSF) [83], however, the major route of excretion (6–7 mg per day) is the conversion to 24S − OH [59]. This conversion is mediated by the neuronal CYP46A1 producing 90% of 24S − OH present in the plasma [58,70]. After synthesis, 24S − OH crosses the BBB, enters the circulation and is cleared by the liver [84].

CYP46A1 expression in the brain seems to be insensitive to substrate regulation since replacement of cholesterol (CYP46A1 endogenous substrate) with desmosterol (not catalyzed by CYP46A1) in mice did not alter CYP46A1 expression [42]. Also, in the same study, CYP46A1 mRNA levels were unchanged by treatments with statins, cholesterol, oxysterols, steroid hormones, insulin, growth hormone, thyroid hormone, cAMP, or bile acids in primary neurons in vitro. The only insult capable to induce CYP46A1 overexpression was a cocktail of dexamethasone with Interleukin-6, simulating a condition of oxidative stress [42].

CYP46A1 is involved in memory functions and aging and therefore, modulation of CYP46A1 and its main metabolic product, 24S − OH, have been investigated in different in vitro and in vivo models. Knock out mice for CYP46A1 have marked deficiencies in learning due to impaired long-term potentiation (LTP) [85,86]. Studies on mice overexpressing CYP46A1 confirm that increased CYP46A1 activity may improve memory. CYP46A1 mice overexpress human HA-tagged CYP46A1 and have circulating levels of 24S − OH about 6-fold higher than the wild type mice [87]. Old female CYP46A1 mice have a better performance in spatial memory tests when compared to wild type animals. Moreover, CYP46A1 mice show higher activation of NMDA receptors and increased levels of postsynaptic and presynaptic proteins in hippocampus [87]. CYP46A1 overexpressing mice present higher lanosterol levels and therefore a higher rate of cholesterol synthesis, while brain cholesterol levels are comparable between transgenic mice and controls. Interestingly, 24S − OH has been described as a selective positive allosteric modulator of NMDA receptors [88].

Effects of CYP46A1 activity and 24S − OH are not only critical in memory processes but an increasing body of evidence shows that activation of CYP46A1 and 24S − OH are able to reduce the levels of Aβ generated *in vitro* and *in vivo*. 24S − OH is able to modulate APP processing in neuroblastoma SH-SY5Y cells and increases alpha secretase activity [75,89]. In line with this, Hudry and colleagues showed that injection of adeno-associated vector (AAV) encoding CYP46A1 in the hippocampus of AD mice reducesd Aβ plaques and restored spatial memory performances [90]. The same AAV strategy was used in THY Tau22 mice, where CYP46A1 and 24S − OH levels are lower than in controls. Injections of AAV-CYP46A1 in the hippocampus completely restore cognitive deficits and synaptic dysfunctions in Tau mice but did not affect Tau hyperphosphorylation, strengthening the hypothesis that memory impairment in Tau mice may be a direct consequence of lower levels of CYP46A1 and 24S − OH [91]. CYP46A1 modulation has been further investigated by using an AAV vector encoding short hairpin RNA against CYP46A1 gene in wild type animals and APP overexpressing mice. Inhibition of CYP46A1 leads to accumulation of cholesterol in neurons, neuronal death, memory impairment, increase of



24S-OH	27-OH
CYP46A1 produces 90% of 24S-OH in the plasma	Produced by CYP27A1 enzyme's activity
6-7 mg of 24S-OH secreted per day from the brain	About 5 mg 27-OH flow into the brain from the periphery per day
24S-OH outflow drives cholesterol biosynthesis	Converted into 7-HOCA by CYP7B1 in neurons

24S-OH	27-OH
Reduced levels in brain and plasma	Increased levels in the brain, CSF and plasma
Increased levels in CSF	Increased CYP27A1 levels in the brain
Lower CYP46A1 expressing neurons	Reduced cholesterol biosynthesis in the brain
	Reduced CYP7B1 levels and activity together with reduced 7-HOCA levels
	Reduced neuronal glucose uptake
	Increased inflammation and oxidative stress

Fig. 1. Schematic representation of 27-hydroxycolesterol and 24S-Hydroxycholesterol metabolism in non-pathological and pathological conditions. Left, 27-hydroxycholesterol (27 – OH) is produced in most cells and organs of the organism by the enzyme sterol 27-hydroxylase (CYP27A1). This oxysterol travels through the peripheral circulation into the brain crossing the Blood Brain Barrier (BBB) by diffusion. 27 – OH is then converted into 7α-hydroxy-3-oxo-4-cholestenoic acid (7 – HOCA) by the enzymes oxysterol 7α-hydroxylase (CYP7B1), CYP27A1, and 3β-hydroxy-delta-5-steroid dehydrogenase. 7 – HOCA then diffuses through the BBB into the peripheral circulation where it is finally degraded. The enzyme CYP46A1 generates 24S-hydroxycholesterol (24S – OH) in the neurons in response to an excessive cholesterol accumulation. 24S – OH then diffuses from the brain into the periphery where it is further processed and finally degraded. Right, in cases of hypercholesterolemia there is an excessive production of 27 – OH in the periphery. As a result, high amounts of 27 – OH could cross the BBB, which is damaged and impaired in AD cases. Excessive 27 – OH accumulation in the brain activates inflammatory responses and promotes an oxidative environment. Also, 27 – OH accentuates cholesterol biosynthesis inhibition. In these circumstances the levels and activity of CYP46A1 and CYP7B1 enzymes appears to be reduced producing little or no amounts of 24S – OH and 7 – HOCA respectively. Fig. 1. Schematic representation of 27-hydroxycolesterol and 24S-Hydroxycholesterol metabolism in non-pathological and pathological conditions. Left, 27-hydroxycholesterol (27 – OH) is produced in most cells and organs of the organism by the enzyme sterol 27-hydroxylase (CYP27A1). This oxysterol travels through the peripheral circulation into the brain crossing the Blood Brain Barrier (BBB) by diffusion. 27 – OH is then converted into 7α-hydroxy-3-oxo-4-cholestenoic acid (7 – HOCA) by the enzymes oxysterol 7α-hydroxylase (CYP7B1), CYP27A1, and 3β-hydroxy-delta-5-steroid dehydrogenase. 7 – HOCA then diffuses through the BBB into the peripheral circulation where it is finally degraded. The enzyme CYP46A1 generates 24S-hydroxycholesterol (24S – OH) in the neurons in response to an excessive cholesterol accumulation. 24S – OH then diffuses from the brain into the periphery where it is further processed and finally degraded. Right, in cases of hypercholesterolemia there is an excessive production of 27 – OH in the periphery. As a result, high amounts of 27 – OH could cross the BBB, which is damaged and impaired in AD cases. Excessive 27 – OH accumulation in the brain activates inflammatory responses and promotes an oxidative environment. Also, 27 – OH accentuates cholesterol biosynthesis inhibition. In these circumstances the levels and activity of CYP46A1 and CYP7B1 enzymes appears to be reduced producing little or no amounts of 24S – OH and 7 – HOCA respectively.

Table 1
Best targets for pharmacological intervention.

Target	Outcome
CYP46A1	CYP46A1 overexpression/activation in mice: Improved spatial memory Increased NMDA receptor expression Increased pre/postsynaptic protein expression Increased cholesterol synthesis Reduced Aβ peptide formation Prevented memory defects and improved synaptic processes in a tau mouse model
CYP27A1	Knockout CYP27 mice feed with a High Fat Diet (HFD): Prevented spatial learning impairment caused by the HFD in controls Prevented Arc reduction caused by the HFD in controls
CYP7B1	CYP7B1 activity is reduced in hippocampal tissue of memory impaired aged rats. Intracerebroventricular administration of a product of CYP7B1 enhanced spatial memory retention in memory impaired aged rats.

Aβ generation and atrophy in mice. The effects of such RNA interference were even stronger in AD mice [92]. Pharmacological activation of CYP46A1 obtained by chronic administration of low doses of the antiviral Efavirenz in 5xFAD mice reduces Aβ levels and glia activation and finally rescues spatial and non-spatial memory [93]. CYP46A1 is downregulated in caudate putamen of patients suffering from Huntington's Disease and restoring in vitro and in vivo CYP46A1 activity reverts neuronal dysfunction in striatal neurons and motor behavior (Table 1) [94].

As the main mechanism for elimination of cholesterol in the brain, CYP46A1 has been also linked to neuronal cholesterol loss during aging. Inhibition of CYP46A1 in hippocampal neurons seems to prevent neuronal loss and rescue cognitive and synaptic functions [95]. CYP46A1 is increased in hippocampal homogenates of a senescence mouse model SAMP8 [96] and aged mice treated with voriconazole (inhibitor of CYP46A1) showed a decrease in cholesterol loss and improved cognitive abilities [95]. Up-regulation of CYP46A1 may affect aging processes, where stress conditions could lead to hyperactivity of CYP46A1 [72,97,98]. Basal levels of CYP46A1 during development and adulthood are certainly essential for cognitive functions, but activation of CYP46A1 during aging/stress condition may also have negative effects and lead to neuronal cholesterol loss.

Taken together these evidence, it is fair to propose that CYP46A1 stability in the brain is crucial for the maintenance of cognition; therefore, sustained expression of CYP46A1 is key to counter the detrimental effects of AD pathology [87]. Gene target therapies with CYP46A1 have been discussed in the last years and tested in AD mouse models with improvements in amyloid pathology and cognition [99,100].

5. CYP27A1 and 27-Hydroxycholesterol

27 − OH is the most abundant cholesterol metabolite in plasma and it is produced by CYP27A1 catalytic activity [64], with this enzyme expressed in many tissues, all of them with capabilities for 27-hydroxylation [101,102]. This metabolite then is secreted to the body where its concentration is directly related to cholesterol levels in plasma [103,104].

Due to the capacity of 27 − OH to cross lipophilic membranes, there is a flux of this oxysterol through the BBB, from the circulation into the brain [64,105]. However, in non-pathological conditions, 27 − OH remains at very low levels in the brain as a result of a very efficient metabolism [106]. 27 − OH is degraded mainly by the enzymes CYP27A1, oxysterol 7α hydroxylase (CYP7B1) and 3β-hydroxy-C27-steroid dehydrogenase/isomerase (HSD3B7). As a result, 27 − OH is metabolized in 7α-hydroxy-3-oxo-4-cholestenoic acid (7 − HOCA), which is then excreted through the BBB and has a net outflux from the brain into the circulation [107,108].

A mutation in the enzyme CYP7B1 leads to the accumulation of oxysterols in the brain, CSF and serum of human patients and progressive neurodegeneration of motor neurons in a disease known as hereditary spastic paraplegia (SPG5). A recent study reports that 27 − OH is most likely a key pathogenic factor in SPG5 [109]. In this study, impairment of the metabolic activity and viability of human cortical neurons was found, together with a direct correlation between 27 − OH levels in serum and disease severity. In the same work, the possibility of reducing 27 − OH levels in the body was explored using atorvastatin, however, there was no significant improvement possibly due to the short duration of the treatment. Additionally, levels of 27 − OH in the CSF are directly linked to levels of 27 − OH in the plasma [110], although this relationship is apparently disrupted in SPG5, where atorvastatin decreases serum 27 − OH levels but do not affect CSF levels of 27 − OH [109]. The authors discuss the possibility of a reduced brain ability to degrade 27 − OH in SPG5 patients, which could be the driving force in the flux of 27 − OH to the CSF from the plasma. This hypothesis is supported by the fact that CYP7B1 levels in the brain are higher than in other organs [111] and could potentially explain the reduced risk associated with hypercholesterolemia in late life, where the brain has a reduced drive for oxysterols flow into the brain, despite elevated cholesterol and 27 − OH in plasma.

In the periphery, the function of 27 − OH covers different systems. One of the most important functions is to be a risk factor for breast cancer. 27 − OH is a selective estrogen (E) modulator and induces the growth of estrogen receptor (ER)-positive high-grade tumors [112,113]. Additionally, 27 − OH could stimulate metastasis by its action on liver X receptor (LXR) signaling [114]. Due to its action through ERs, 27 − OH increases bone reabsorption reducing bone formation and mineral density in bones [115]. Moreover, the relationship between 27 − OH and cardiovascular diseases (CVD) has been widely studied. It is known that patients with advanced atherosclerosis often have increased levels of 27 − OH in their circulation [103,116]. In atherosclerotic plaques 27 − OH is the most common oxysterol found and its accumulation correlates with the severity of the lesion and the affluence of macrophages [117]. Interestingly, a recent study has shown that 27 − OH can induce instability of atherosclerotic plaques by mediating an inflammatory cascade [118].

The function of 27OH in the brain remains unknown, but some studies suggest it is a modulator of the brain cholesterol homeostasis. Several groups show that 27 − OH influences the synthesis of cholesterol *in vitro* [106,119,120]. Additionally, in a preclinical study, 27 − OH has been suggested as an inhibitor of brain cholesterol synthesis [62]. Several studies find an association between high levels of 27 − OH and memory deficits, Alzheimer's disease (AD) and other neurodegenerative processes [50,64,121–125]. Knocking out CYP27A1 gene in mice ameliorates memory deficits induced by high-fat diet and restores cholesterol-decreased levels of the activity-regulated cytoskeleton-associated protein (Arc) [122]. This finding suggests that 27 − OH is the main contributor to the memory impairment caused by dietary cholesterol (Table 1). As to the mechanism of 27 − OH harmful effects on cognitive functions, our group has recently described for the first time a dendritic spine density loss under high levels of 27 − OH in vivo and in vitro through the retinoid X receptor gamma (RxRg) [126]. The dendritic spines constitute the major postsynaptic elements of glutamatergic synapses and are essential for memory, learning, and cognition [127,128]. Morphological alterations on dendritic spines have been described in relation with AD pathology [129] and other neurodegenerative diseases, however, the effect of 27 − OH on synaptic plasticity and function requires further exploration.

High levels of 27 − OH are found in brains and CSF of early-onset AD as well as in sporadic AD [107,130]. Also, 27 − OH is associated with mild cognitive impairment in the elderly [131]. Due to this, there is an increasing interest in understanding whether high levels of 27 − OH could play a role in AD pathogenesis. Several groups show that 27 − OH

treatments *in vitro* increase production of Aβ and phosphorylation of tau [89,132,133]. Also, 27 − OH treatment on neuroblastoma cells induces endoplasmic reticulum stress and mediates downregulation of leptin, which is associated with AD [134]. Additionally, higher levels of 27 − OH have been found in old APP mice brains, a transgenic model for AD [107]. Moreover, a recent study shows increased activity of CYP27A1 in AD brains and suggests CYP27A1 as a modulator of neuroinflammation in AD [71].

In recent years, our lab has been studying the effects of 27 − OH on features influencing AD pathology. It is known that glucose metabolism is downregulated in healthy older individuals [135], AD and other neurodegenerative disorders [136]. With the aim to decipher the role of 27 − OH on glucose hypometabolism, a hallmark in AD pathology, we have been working on the relationship between high levels of 27 − OH and the Renin-Angiotensin system (RAS) in the brain. The main function of the brain RAS goes beyond the regulation of several cerebral functions such as learning, memory, emotional responses and processing of sensory information [137]. We have shown that 27 − OH upregulates the RAS system and alters both cognition and glucose uptake in mice [121,123,125]. Our results point out 27 − OH as a modulator in RAS signaling in the brain, thus affecting glucose metabolism and thereby worsening memory and cognition.

6. Discussion and future directions

We have discussed the correlation between hypercholesterolemia in midlife and the risk of development and progression of AD in humans. Whereas high cholesterol levels in the blood in midlife seems to be harmful in the long term, there is evidence showing that cholesterol depletion at the cellular level is detrimental for neural function and memory [22,47,138,139]. Nevertheless, hypercholesterolemia during midlife is a modifiable risk factor, thus, there is great interest in learning how to improve cholesterol metabolism in the brain to prevent or delay the onset of AD. To the best of our knowledge, the cholesterol-lowering therapies to intervene AD progression have shown confounding results and many publications highlight the need for randomized trials, better cohort selection and longer follow up to clarify the role of statins and other lipid-lowering drugs in the cognition of AD patients.

We show the need to focus on the main regulators of cholesterol metabolism in the brain, recognizing oxysterols as key players that link blood cholesterol levels with brain dysfunction. The depletion of cholesterol in the brain with the age, evidenced by a decrease in 24 − OH in the brain with increased levels in the plasma, could also represent an important mechanism of disease in aging and in AD [107,140]. Hepatic metabolism of 24 − OH decrease with aging in relationship to brain production, thus, accumulation of 24 − OH in the plasma indirectly shows the state of cholesterol metabolism in the brain [141]. Cholesterol is essential for synaptic function [45], for the organization of proteins in the synaptic bouton [142] and for the synthesis of diverse cerebrosterols that regulate neuronal metabolism [43,143]. It has been proposed that depletion of cholesterol from neurons during aging is a leading cause of synaptic loss [144] and later, neuronal death [139]. However, to study cholesterol fluctuations in the brain is challenging due to the high content of cholesterol in other structures such as the myelin sheath. Nevertheless, the study of cholesterol regulation through analysis of 24OH levels in neurons is possible and have important implications for neurodegeneration.

We discussed how CYP46A1 activity is crucial for memory function in the brain [85,86,91] and how 27 − OH is the main metabolite linking peripheral hypercholesterolemia with negative effects occurring in the CNS, however, the link between high levels of 27 − OH and decreased CYP46A1 activity is not completely understood. Reduced cholesterol biosynthesis correlates with reduced CYP46A1 activity [145] and some evidence points that elevated levels of 27 − OH might lead to a reduction in cholesterol synthesis in the brain [146]. However, this hypothesis does not explain why statins have failed to reduce the levels of 27 − OH in the brain of SPG5 patients and have shown no improvement in memory function [109]. A possible explanation is the loss of neurons, which are the main cells expressing CYP7B1 that converts 27 − OH to 7 − HOCA. Loss of CYP7B1 would lead to increased 27 − OH levels in the brain, decreasing cholesterol biosynthesis [109] and overall worsen cognition as shown in aged [47] and 27 − OH overexpressing [121] mouse models (Fig. 1, Table 1).

27 − OH influences the relationship between angiotensin cascade proteins AngIII and IV with glucose metabolism proteins GLUT4 and IRAP respectively [121], however, their precise way of interaction requires further research. In the case of AngIV and IRAP, the effect is mediated by aminopeptidases A (AP-A) and N (AP-N) upregulation via LXR beta activation. Knockdown of LXR beta in cortical primary neurons *in vitro* prevents IRAP upregulation as well as the LXR blocker 22-S − OH [121]. The implications for developing treatments are important since blocking LXR beta activity in the brain is unviable due to its multiple functions in memory and neuronal survival [147,148]. As an alternative, statins were thought to decrease 27 − OH detrimental effects by reducing the generation of 27 − OH in the periphery, however, we have discussed how SPG5 patients with chronically elevated levels of 27 − OH in the brain have shown resistance to the lowering effects of statins [109] and how statins show mixed results in cognition in AD patients [27,149].

27 − OH mediated upregulation of AP-A, AP-N and these enzymes can also have a vascular effect through increased levels of Ang-III and reduced levels of AngIV [121]. Increased levels of Ang-III would activate AT1 receptors in blood vessels causing vasoconstriction, reducing the blood flow to the brain. On the contrary, reduced levels of AngIV due to AP-N activation means increased levels of IRAP, which can lead to pathological enzyme cleavage over vascular targets such as vasopressin [150]. Thus, the negative effects of 27 − OH in the brain can be composed of direct cascades regulating brain glucose metabolism and additional vascular components reducing blood supply to neurons, consistent with previously proposed hypotheses for AD pathogenesis [151]. Brain penetrating ACE inhibitors betters cognition in patients with mild to moderate AD [152] and combination of statins plus ACE inhibitors improve atherosclerosis [153], however the effect of mixing ACE inhibitors with statins in cognition have not yet been assessed by clinical studies. According to our hypotheses, statins would mainly have an anti-inflammatory effect previously discussed, yet those hypotheses need testing in the clinic.

A major mechanism contributing to the cognitive impairment observed in vivo under elevated levels of 27 − OH could be the loss of synapses. We have recently described a mechanism where 27 − OH reduces dendritic spines in Cyp27A1 transgenic mice [126]. In the same work, decreased PSD95 levels were found in hippocampal neurons in culture under elevated 27OH. Moreover, this is accompanied by the expression of the stem cell transcription factor REST, PTBP1 and the nuclear receptor RXRg. Under high 27OH levels, REST regulates PSD-95 expression through suppression of miR-124a, allowing PTBP1 abundance, which induces PSD-95 mRNA degradation [154]. Elevated levels of REST are abnormal in mature animals [155], and we propose this mechanism contributes to loss of synaptic function in the hippocampus under high levels of 27 − OH. Moreover, RxRg is the target of Bexarotene (BXT), a drug reported to clear amyloid beta proteins by increasing APOE levels in the brain and activating PPARgamma [156,157]. These results demand further research to describe how increased levels of 27 − OH can contribute to synaptic dysfunction in animal models.

We would like to suggest to study the targets responding to oxysterols and high fat/high-calorie diets in the diverse cell types present in the brain and not only on neurons. CYP46A1 activation by efavirenz decreases microglial activation in the cortex of an AD mouse model [158]. The treatment also reduces several genes involved in inflammation such as IL-1β and TNFα. Cholesterol metabolism is highly

regulated by the transport mediated between neurons and astrocytes through APOE and other lipid transport proteins [159–161], yet, the effects of both 24S − OH and 27 − OH in astrocytes remains largely unexplored. In addition, endothelial cells are highly responsive to proinflammatory molecules released by glia and are a major player in neurodegenerative diseases like AD. Expression profiles of endothelial cells show they have proteins related to cholesterol metabolism including LXR, CYP27A1, and CYP7B1 [162], however, their response to either 24S − OH or 27 − OH also remains unknown. Microglia should be thoroughly investigated since TREM2 represents a major non-genetic risk factor for AD related to inflammation [163,164]. Also, high 27 − OH levels can induce proinflammatory responses in AD mice models [165] and in human pathologies like type 2 diabetes and atherosclerosis [166]. Then again, the effect of 27 − OH on microglia and its role in inflammation in the brain remains unexplored.

Given the multiple proteins affected by oxysterol imbalances in the brain, together with the problem of targeting the nuclear receptors mediating 24S − OH and 27 − OH effects, specific CYP-targeting drugs might represent a better option to restore cholesterol metabolism in the brain. Multiple studies focusing on CYP-specific drugs already on the market are offering new possible therapeutics that need to be tested in animal models and clinical trials [167], such as FDA approved anastrozole, which has shown to decrease 27 − OH levels in rat brains [168]. Similarly, efavirenz is effective in enhancing CYP46A1 activity in the brain of 5XFAD mice, activating cholesterol turnover and reducing amyloid burden and microglial activation. After 8 months of administration, long-term spatial memory was improved in the 5XFAD mice (Table 1) [93]. Other neuroactive compounds have been tested in vitro for CYP46A1 activation such as L-glutamine, L-aspartate and gamma-aminobutyric acid [169]. Additionally, L-glutamine shows synergistic CYP46A1 activation when combined with efavirenz, suggesting endogenous compounds of importance in cholesterol imbalance previously ignored. Recently, van der Kant et al. performed a drug screen on hiPSC derived AD neurons and identified, among others, four statins able to significantly decrease pTau accumulation by reducing the levels of cholesteryl esters (CE). Interestingly, the same effect was mimicked by Efavirenz. The authors also found that the effects of lowering CE on pTau are mediated by the proteasome while the effect of CE on Aβ42 is mediated by the cholesterol-binding domain in APP [170]. This study is an important proof of concept that Efavirenz may be a viable drug in humans.

Lastly, proposed gene therapies upregulating CYP46A1 activity have shown improvement in the pathology and cognition of AD animal models [171]. It is possible that increase of CYP46A1 activity induces outflow of 24S − OH from the brain to the circulation, thus stimulating cholesterol biosynthesis and increasing the abundance of prenylation precursors essential for memory function such as geranylgeranyl pyrophosphate [85–87,91–93]. Thus, upregulation of CYP46A1 is a possible therapeutic strategy not only for AD but also for other neurodegenerative diseases like Huntington's disease [172]. In summary, it is the duty of the scientific community towards the millions who suffer or will suffer from Alzheimer's disease and other dementias to further understand the biology of cholesterol dysfunction in the brain. This can be improved by developing new animal models recreating key features of dementia in the metabolic aspects and by generating new therapeutic approaches based on targets from cholesterol metabolism. Altogether, these new perspectives can create alternatives to prevent, modify and improve AD onset and progression, features that could be within reach in our lifetime.

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