Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders

BBA - Molecular and Cell Biology of Lipids

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Abstract:	High-density lipoproteins (HDL) play a key role in cholesterol homeostasis maintenance in the central nervous system (CNS), by carrying newly synthesized cholesterol from astrocytes to neurons, to support their lipid-related physiological functions. As occurs for plasma HDLs, brain lipoproteins are assembled through the activity of membrane cholesterol transporters, undergo remodeling mediated by specific enzymes and transport proteins, and finally deliver cholesterol to neurons by a receptor-mediated internalization process. A growing number of evidences indicates a strong association between alterations of CNS cholesterol homeostasis and neurodegenerative disorders, in particular Alzheimer's disease (AD), and a possible role in this relationship may be played by defects in brain HDL metabolism. In the present review, we summarize and critically examine the current state of knowledge on major modifications of HDL and HDL-mediated brain cholesterol transport in AD, by taking into consideration the individual steps of this process. We also describe potential and encouraging HDL-based therapies that could represent new therapeutic strategies for AD treatment. Finally, we revise the main plasma and brain HDL modifications in other neurodegenerative disorders including Parkinson's disease (PD), Huntington's disease (HD), and frontotemporal dementia (FTD).
Response to Reviewers:	See enclosed point-by-point answers to reviewers.

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DIPARTIMENTO DI SCIENZE FARMACOLOGICHE
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Direttore: Prof.ssa Monica DiLuca

Milano, February 1, 2022

Dear Editor,

Please find enclosed a new version of the review titled "Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders", MS BBALIP-21-275, which has been revised according to the Reviewer's suggestions. A detailed point-by-point response to the Reviewers' comments is also included.

We hope that this revised version will be considered of interest for the readers of *BBA - Molecular and Cell Biology of Lipids.*

Best regards,

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ANSWERS TO REVIEWERS

Reviewer #2

The authors have adequately responded to all the comments.

We thank the Reviewer for the appreciation of our work.

There are still three minor issues to be addressed as follows:

1) please use identical units to express lipid and protein concentrations in CSF throughout the manuscript whenever possible.

Unites have been modified as suggested.

2) CSF lipoproteins only contain vitamin E but not vitamin C which is a hydrophilic antioxidant (p. 14) - this sentence should be rephrased.

We apologize for the mistake. The sentence has been modified accordingly.

3) seminal study of Miyata and Smith Nat Genet. 1996; 14:55-61 should be cited when discussing antioxidative properties of apoE isoforms.

We thank the Reviewer for the suggestion; the citation, with a comment, has been added (page 14).

Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders

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ABSTRACT

High-density lipoproteins (HDLs play a key role in cholesterol homeostasis maintenance in the central nervous system (CNS), by carrying newly synthesized cholesterol from astrocytes to neurons, to support their lipid-related physiological functions. As occurs for plasma HDLs, brain lipoproteins are assembled through the activity of membrane cholesterol transporters, undergo remodeling mediated by specific enzymes and transport proteins, and finally deliver cholesterol to neurons by a receptor-mediated internalization process. A growing number of evidences indicates a strong association between alterations of CNS cholesterol homeostasis and neurodegenerative disorders, in particular Alzheimer's disease (AD), and a possible role in this relationship may be played by defects in brain HDL metabolism. In the present review, we summarize and critically examine the current state of knowledge on major modifications of HDL and HDL-mediated brain cholesterol transport in AD, by taking into consideration the individual steps of this process. We also describe potential and encouraging HDL-based therapies that could represent new therapeutic strategies for AD treatment. Finally, we revise the main plasma and brain HDL modifications in other neurodegenerative disorders including Parkinson's disease (PD), Huntington's disease (HD), and frontotemporal dementia (FTD).

Keywords: High-density lipoproteins, cholesterol, Alzheimer's disease, apolipoprotein E, apolipoprotein A-I, central nervous system, neurodegenerative diseases

1. Cholesterol in the brain

1.1. Cholesterol role and regulation in the brain

The central nervous system (CNS) accounts for only 2% of the whole body weight but it contains approximately 25% of the total pool of cholesterol [1]. Most of the cholesterol (about 80%) exists in the adult brain in the form of myelin [2], produced by oligodendrocytes and surrounding axons. Besides, brain cholesterol is an important constituent of neuronal membranes. It is the major component of synaptic vesicles, whose formation, shape, and release properties are controlled by cholesterol content. In addition, on the postsynaptic side, cholesterol has an important role in the organization and the correct positioning of neurotransmitter receptors; therefore, a reduced amount of cholesterol at this level can impair neurotransmission and induce a loss of dendrite spines and synapses [3]. The brain relies on endogenous local cholesterol since the blood-brain barrier (BBB) strictly regulates the transport of lipoprotein-associated lipids to the brain and vice versa [4]. Differently from cholesterol, oxysterols can flux across the BBB [5], as discussed below (see section 3).

Findings on the ontogenesis and regulation of cholesterol turnover in the brain in mice revealed that the CNS grows rapidly during the first three weeks after birth and equalled about 5% of the total body weight. The brain cholesterol pool at this stage increases at a rate of 0.26 mg/day and the pool of total sterols of about 0.28 mg/day [6]. On the opposite, in adult mice, starting from week 13, the trend dramatically switches with a reduction in the size of the CNS to 1.7% of body weight and in the rate of cholesterol synthesis that drops to 0.035 mg/day [6]. Neuronal cells are able to synthesize cholesterol during the prenatal period but progressively lose this capacity in the postnatal period and become dependent on cholesterol produced from other cell types, mainly astrocytes [4, 7], which display 2-3 higher biosynthetic capacity compared to neurons in adulthood [8, 9]. However, cholesterol synthesis rate in neurons may not always be low, depending on the brain region, as well as on the neuronal cell type [1, 9].

Cholesterol is not uniformly distributed in biological membranes, but concentrated in lipid rafts, together with other lipids [4]. Lipid rafts are commonly defined as cholesterol- and sphingolipid-enriched membrane microdomains acting as a platform to modulate cell signaling and membrane fluidity, to regulate membrane trafficking of proteins and cellular processes, such as neurotransmission [10]. Since cholesterol is a key component of lipid rafts also in the CNS, its depletion and disruption could be relevant for age or disease-related cognitive impairment [11].

1.2. Brain lipoproteins

Brain cholesterol metabolism and transport are for the most part segregated from the peripheral circulation by the BBB and cholesterol transport is carried out by lipoproteins that have been identified in the brain [12]. In human plasma, four major lipoprotein classes have been described: chylomicrons, VLDL, LDL, and HDL. The role of circulating apolipoprotein B (apoB)-containing lipoproteins, including LDL, VLDL and chylomicrons, is to distribute cholesterol and triglycerides (TG) from the liver and gut to peripheral tissues. Since CNS does not use TG as an energy source, apoB-containing lipoproteins are not present in healthy brains and this leads to a transport system of lipids reliant exclusively on "HDL-like particles" (called HDL throughout the paper), which absolves all lipid transport duty in the brain [13, 14]. While plasma HDL have been extensively studied, cerebrospinal fluid (CSF) HDL are still poorly characterized, mainly because of their very low amount. Indeed, the main constituents of brain lipoproteins have been reported to be markedly lower than in plasma; CSF cholesterol content ranges between 0.1 and 0.6 mg/dl, and apoA-I concentrations between 0.1 and 0.4 mg/dl [15] [16].

1.2.1. Heterogeneity of brain HDL

Brain HDL particles are, as plasma HDL, heterogeneous in terms of density, size, and composition. Brain HDL slightly differ from plasma HDL in terms of size and density, but the major difference is the apolipoprotein composition. The major protein component of brain HDL is apolipoprotein E (apoE), while apoA-I is the major protein component of plasma HDL. Notably, apoE is the major apolipoprotein expressed, translated, and secreted from astrocytes, microglia, and pericytes in different species [17-20]. Analysis of CSF lipoproteins by anti-apoE and anti-apoA-I immunoaffinity columns showed particles predominantly containing apoE and largely spherical (13-20 nm) with few disc-like particles, and particles containing apoA-I, spherical and smaller (10-18 nm) [16]. The apoE-containing particles are the predominant HDL subclass; the second HDL subclass is composed of apoA-I- and apoA-II-containing particles. The third class is characterized by apoE-containing large particles (18-22 nm) which also contain apoD, apoA-IV and apoJ. Finally, small HDL-like particles (10-12 nm) containing apoD, apoH, apoA-IV and apoJ have been described [15].

Plasma HDL sediment in the density region from 1.063 to 1.21 g/ml, range from 7 to 13 nm of diameter and present majorly a spherical shape [21]. Brain HDL particles identified in human CSF also mainly present a spherical shape but have a density of 1.063-1.12 g/ml and a wider diameter range (10-22 nm) [15]. Very dense HDL (VHDL), with a density up to 1.25 g/mL, mostly of spherical shape and with a diameter around 17 nm, have been also reported in human CSF [22, 23].

Plasma HDLs have been described to contain 251 individual proteins as tracked by the HDL Proteome Watch (https://homepages.uc.edu/~davidswm/HDLproteome.html accessed on 17th

November 2021) [24]. As in plasma, proteins represent the major building block of HDL found in CSF. The total CSF protein concentration ranges between 0.2% and 0.5% of the blood total protein concentration [25]. A proteomic study highlighted more than 300 proteins in CSF from healthy donors [26], and among them, only 10 apolipoproteins have been characterized in brain HDL [27, 28]. ApoE and apoA-I represent the majority of brain apolipoproteins [15]; others apolipoproteins include apoJ, apoA-II, apoA-IV, apoD, apoC-II, apoC-III, apoC-IV, and apoH. ApoE is secreted in the brain and cannot cross the BBB, as demonstrated in liver transplanted patients that presented in plasma the donor apoE phenotype but preserved their birth phenotype in the CNS [29]. ApoE is synthesized mainly by astrocytes, microglia, and oligodendrocytes. Neurons are not normally able to produce apoE, except that in response to certain conditions such as brain injuries [30, 31]. The origin of CSF apolipoproteins other than apoE remains still unknown. *ApoA-I* mRNA is not expressed by human primary brain endothelial cells, suggesting a peripheral origin [32] and the ability to cross the BBB with an endocytosis process [33] (for further details see section 3). ApoD has been reported to be expressed in neuroglial, pia mater, and perivascular cells of human brain [34, 35] and apoJ is also produced from astrocytes but secreted free of lipids [18, 36].

Lipids present in the CSF also contribute to the heterogeneity of brain HDL. The main lipids carried by brain HDL are cholesteryl esters, phospholipids (PL), and sphingolipids [13]. Five major lipid classes have been detected in CSF: free fatty acids, sphingolipids, glycerophospholipids, glycerolipids, and sterol lipids [37]. A recent untargeted lipidomic analysis has identified up to 245 lipids in CSF; these include predominantly PL (lysophosfatidylcholines, phosphatidylcholines, lysophosphatatidylethanolamines, phosphatidylethanolamine, cyclic phosphatidic acids, phosphatidylglycerols and phosphatidylinositols), ceramides, sphingomyelins, cholesteryl esters, diacylglycerols and triacylglycerols [38]. Average PL concentration in CSFhas been reported to be 0.55 ± 0.3 mg/dl [15], and phosphatidylcholine has been identified as the most represented PL (range of about 42-54%), followed by sphingomyelin (19-20%), phosphatidylethanolamine (9-13%), and minor concentrations of lysophosphatidylcholine, phosphatidylinositol, and phosphatidylserine [39, 40].

A biochemical characterization of human CSF also revealed the presence of amyloid β (Aβ) associated to brain HDL [23], as occurs for plasma HDL [41]. This interaction is probably due to the Aβ amphiphilic structure [42]. In particular, Aβ seems to be preferentially associated to large, spherical HDL [23]. Interestingly, Aβ seems to be secreted by cells already in association with apolipoproteins and lipids [43]. In this context, its specific interaction with apoE is one of the key factors in AD pathophysiology (see section 4.2.1) [44, 45].

2. HDL and cholesterol metabolism in the brain

Brain HDL have a pivotal role to carry and supply adult neurons with cholesterol to guarantee their physiological functions [13]. These lipoproteins in the CSN undergo biogenesis, maturation, and remodeling processes similar to those observed for plasma HDL, as described in detail in the following section and summarized in Figure 1.

2.1. HDL biogenesis

Although the synthesis and metabolism of plasma lipoproteins are well characterized, little is known about lipoproteins within the CNS. Brain lipoprotein metabolism involves pathways that are independent of those of the peripheral compartment. As mentioned above, HDL identified in the human CSF display apoE as a major protein component [46]. ApoE in the brain is predominantly secreted from astrocytes by the ATP-binding cassette transporter A1 (ABCA1) in the form of nascent apoE-containing HDL of about 8-12 nm, mainly composed by PL and unesterified cholesterol [20] (Figure 1). Other apolipoproteins are present in brain HDL, and the apolipoprotein composition of HDL particles may influence their lipidation degree. For example, the apoJ containing particles are lipid-poor compared to those containing apoE [36, 47].

After secretion, further synthesized cholesterol is assembled into HDL through the interaction with ABCA1 in caveolin-enriched domains, leading to the generation of discoidal particles [48, 49]. The presence in the CSF of particles mainly spherical and of different sizes indicates that nascent HDL undergo a maturation and remodeling process similar to what occurs for plasma HDL. Other ABC transporters, including ABCG1 and ABCG4, are able to promote further incorporation of cholesterol and PL in the nascent HDL [50] (Figure 1). Among these transporters, ABCG1 seems to be involved in HDL assembly at the interface between the brain and the circulation thus contributing to the generation of HDL at the BBB [51]. Another transporter sharing significant sequence similarity to ABCA1 is ABCA7, highly expressed in the brain. The physiological function of ABCA7 and its transport substrates are less known compared to those of ABCA1. It has been reported that, as for ABCA1, ABCA7 promotes the efflux of choline-containing phospholipids in the presence of apoE and apoA-I; however, differently from ABCA1, the efflux of cholesterol seems less relevant [52].

2.2. HDL remodeling

Shifting of brain HDL from discoidal to spherical particles is the result of the activity of remodeling proteins (Figure 1). HDL remodeling enzymes and lipid transfer proteins have been identified in the CNS, although little is known about the brain lipoproteins maturation process. One of the enzymes responsible for a key step in HDL maturation is the lecithin cholesterol acyltransferase

(LCAT), a soluble protein that catalyzes the conversion of unesterified cholesterol and phosphatidylcholine to cholesteryl esters and lysophosphatidylcholine on circulating lipoproteins [53]. LCAT, besides liver and testes, is also synthesized in the brain, suggesting a crucial role of this enzyme in the maturation of brain lipoproteins, although CSF LCAT concentration is very low and approximately 5% of the plasma once [17]. The primary producers of active LCAT in the brain are astrocytes, and astrocyte-derived LCAT is the only enzyme able to esterify cholesterol on nascent discoidal particles in the brain [54]. ApoE is the major LCAT activator in the CNS and both ABCA1 and apoE are required to generate glial particles substrate for this enzyme [54]. Thanks to its esterifying activity, LCAT promotes the maturation of glial-derived nascent discoidal apoE-containing particles into mature spherical ones (Figure 1).

As it occurs for plasma HDL, other two proteins seem to be involved in the remodeling of brain HDL: cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) [55, 56]. CETP has been detected in human CSF at a concentration of about 12% of that of plasma. CETP was also identified in the conditioned medium of human neuroblastoma and neuroglioma cells, clearly suggesting that this transfer protein is synthesized and secreted in the CNS, where it may contribute to the transport and redistribution of lipids [55]. However, other authors did not demonstrate any detectable CETP activity or mass in human CSF [28], leaving still open the question about the relevance of this protein in brain HDL remodeling. PLTP is also produced by neurons, astrocytes and microglia and its CSF levels represent about 15% of plasma concentration. It has been demonstrated that PLTP is highly expressed and secreted also by brain capillary endothelial cells and is actively involved in HDL biogenesis and remodeling at the BBB [56].

2.3. HDL-mediated delivery of cholesterol to neurons

Once reached the completed maturation, brain HDL particles can finally deliver cholesterol to neurons through the interaction with specific lipoprotein receptors, including the low-density lipoprotein receptor (LDLR), the very low-density lipoprotein receptor (VLDLR), the apoE receptor 2 (apoER2) and the low-density lipoprotein receptor-related protein 1 (LRP1) (Figure 1) [9, 57]. This process seems essential for the supply of cholesterol to neurons to exploit their physiological functions, such as synaptogenesis and repairing of damaged membranes. In fact, the deletion of the *Ldlr* gene in mice significantly increases apoE levels in the brain parenchyma and CSF, as a clear consequence of an impaired brain HDL internalization by neurons [58]. Similarly, conditional deletion of the *Lrp1* gene in mouse forebrain neurons increases apoE levels [59], suggesting that both receptors are involved in the internalization of HDL-apoE secreted by astrocytes. The apoE receptors show different binding affinity to apoE and lipidated apoE; in particular, nascent lipoprotein particles

secreted by astrocytes display a higher affinity for LDLR, whereas apoE-enriched lipoprotein particles and HDL isolated from CSF bind more strongly to LRP1 [60]. The other apoE receptors, VLDLR and apoER2, are structurally very similar to the LDLR and are also receptors for other ligands like the neuromodulatory signaling protein reelin, that plays a pivotal role in neurodevelopment and synaptic functions [61].

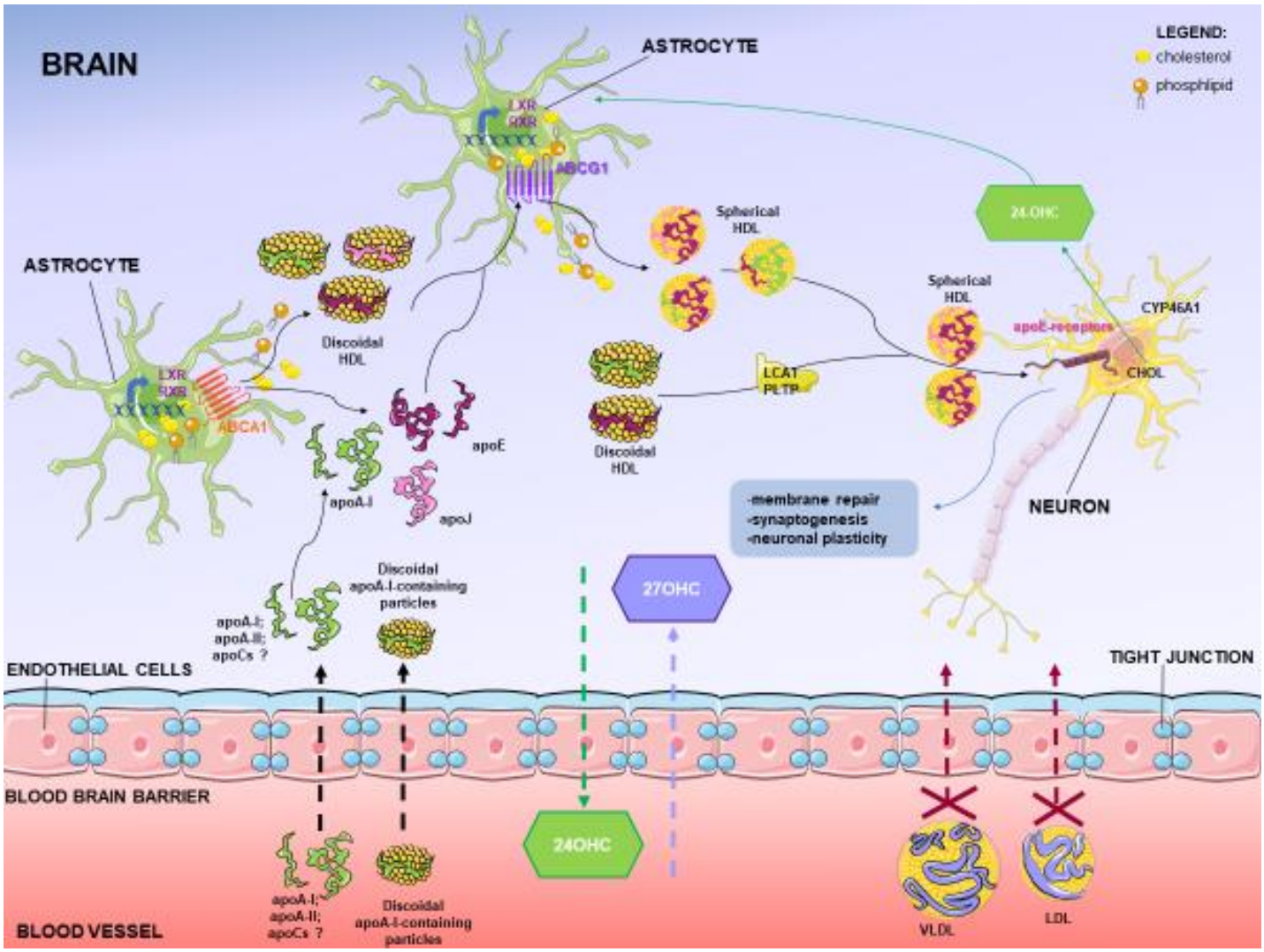

Fig. 1. Brain cholesterol transport in the CNS. In astrocytes, the ABCA1 transporter promotes the efflux of PL and UC to apoE, the major apolipoprotein in the CNS, thus leading to the formation of nascent discoidal lipoproteins. Among apolipoproteins, apoJ is also produced from astrocytes, while ApoA-I, apoA-II and apoCs are also present in the CNS, but differently from apoE are plasma-derived thanks to the ability to cross the BBB with an endocytosis process.
In addition, discoidal apoA-I-containing particles may enter the CNS via SR-BI-mediated uptake and others unknown mechanisms. Discoidal particles can further acquire PL and UC via ABCA1 and ABCG1. Maturation of discoidal particles into spherical-HDL involves the activity of remodeling enzymes like LCAT, and lipid transfer proteins, such as PLTP. These newly generated lipoproteins can be finally uptaken by neurons through the binding of apoE to apoE-receptors belonging to the LDLR family. In neurons, cholesterol overload is handled by the conversion in oxysterols, mainly 24-hydroxycholesterol (OHC) that plays a significant regulatory role. 24-OHC is produced by CYP46A1 and it upregulates ABCA1 expression via activation of LXR. 24-OHC can also cross the BBB and be found in plasma. On the contrary, 27-OHC is produced by peripheral tissues but there is a net flux from circulation to the brain., through the BBB.

ABCA1: ATP-binding cassette transporter A1, ABCG1: ATP-binding cassette transporter G1; apoA-I: apolipoprotein A-I; apoA-II: apolipoprotein A-II; apoCs: apolipoprotein C; apoE: apolipoprotein E; BBB: blood-brain barrier; CETP: cholesteryl ester transfer protein; CNS: central nervous system; LDLRs: LDL receptor family receptors; LCAT: lecithin:cholesterol:acyltransferase; LXR: liver X receptor; PL: phospholipids; PLTP: phospholipid transfer protein; RXR: retinoid X receptor; SR-BI: scavenger receptor BI; UC: unesterified cholesterol; 24-OHC: 24S-hydroxycholesterol; 27-OHC: 27-hydroxycholesterol

3. Lipoproteins and apolipoproteins BBB crossing

The emerging consistent relationship between plasma HDL-cholesterol (HDL-c) levels and neurodegenerative disorders (see section 4.1) raises the question of whether and how plasma cholesterol metabolism and transport could influence brain cholesterol homeostasis. Brain cholesterol metabolism and transport are isolated from the peripheral circulation by the BBB and the blood-cerebrospinal fluid barrier (BCSFB) [17, 62, 63]. Despite CNS can produce cholesterol by *de novo* synthesis, as mentioned above, a certain amount of cholesterol derived from plasma can be delivered to the brain and eventually influence the CNS homeostasis. A possible source of cholesterol in the brain are oxysterols, side-chain oxidized sterols whose physical properties allow to pass lipophilic phospholipid-containing membranes up to three orders of magnitude faster than cholesterol itself [64], so that they are transferred through the BBB and provide a flux of cholesterol-derived molecules in and out the CNS [65]. 27-hydroxycholesterol (27-OHC) is the major oxysterol present in the circulation, it is formed by almost all cells in the body and it's able to cross the BBB from the periphery to CNS [65]. On the opposite, brain cholesterol can be removed from the brain after conversion into 24S-hydroxycholesterol (24-OHC) and subsequent diffusion over the BBB [65] (Figure 1).

Another source of cholesterol for CNS is plasma HDL and their bound apolipoproteins, whose crossing through the BBB and BCSFB could promote a flux of cholesterol in and out the SNC. Plasma-derived apolipoproteins in the brain include apoA-I, apoA-II and the apoCs, and their still controversial crossing mechanisms are detailed below.

3.1. Apolipoprotein A-I

ApoA-I is the main structural protein of HDL in plasma; it is produced and secreted from the liver and the intestine and its positive function in the prevention of cardiovascular diseases has been confirmed in several studies [66]. It is known that apoA-I protein levels in CSF are second to apoE in abundance, but in comparison, *apoA-I* mRNA has not been detected in the brain [14, 67, 68]. Indeed astrocytes and microglia are not able to produce this apolipoprotein, consequently, brain apoA-I is believed to be plasma-derived [14, 16, 69, 70]. In order to clarify the source of brain apoA-

I, specific *apoA-I* knockout mice have been generated: the intestine-specific, the liver-specific and both intestine and liver-specific *apoA-I* knockout mice. The incisive decrease of apoA-I in CSF of both intestine- and liver-specific *apoA-I* knockout mice clearly show that brain apoA-I derives from the liver and the intestine via plasma HDL [71]. In addition, it has been demonstrated that the murine brain-specific deletion of ABCA1 increases levels of CSF apoA-I, suggesting a compensatory upregulation of the translocation of plasma apoA-I to satisfy the demand of apoA-I-HDL in the brain compartment [72].

Despite the known association between apoA-I and neurodegenerative diseases [73], the route by which apoA-I enters the CSF is still controversial [71]. Plasma-to-brain delivery of apoA-I is claimed to be handled by the BCSFB and the BBB which serves as a major portal for protein delivery to the brain [74]. Stukas et al. injected recombinant fluorescently tagged human apoA-I into mice, which rapidly localizes to the choroid plexus and accumulates in the brain, showing that human apoA-I is specifically bound, internalized, and transported across confluent monolayers of primary human choroid plexus epithelial cells and brain microvascular endothelial cells. Because *apoA-I* mRNA is undetectable in the murine brain, these results suggest that plasma apoA-I gains access to the CNS primarily by crossing the BBB via specific cellular mediated transport [75] (Figure 1). Possible mechanisms for apoA-I crossing of the BBB include a clathrin-independent and cholesterol-mediated endocytosis [33] and an SR-BI-mediated transcytosis [70]. To better understand the apoA-I-containing HDL crossing, Dal Magro et al. investigated *in vitro* the ability of apoA-I in different lipidated states to cross the BBB by using a transwell system made by immortalized human brain capillary endothelial cells [76]. The obtained results showed that apoA-I containing discoidal particles cross the BBB much better than spherical HDL particles [76]. These data suggest that apoA-I-containing lipoproteins may influence the pathogenesis of neurodegenerative disorders through an direct action, occurring after BBB crossing. In this evolving context, apoA-I has also been demonstrated to be able to bind the Aβ *in vitro* [76-78] and to reduce Aβ brain levels in AD animal models [79].

3.2. Apolipoprotein A-II

ApoA-II is the second most abundant apolipoprotein in plasma HDL and comprises 20% of HDL proteins [80]. In comparison to the well-known and established functions of apoA-I, physiological functions of apoA-II are poorly understood. ApoA-II is present in CSF, but its mRNA has not been detected in the CNS tissue. Thus plasma-to-brain delivery through the choroid plexus, similar to apoA-I, has been suggested for apoA-II [81]. Further experimental works on BBB crossing of this apolipoprotein will be crucial for understanding its origin and role in brain cholesterol homeostasis.

3.3. Apolipoprotein A-IV

ApoA-IV is a major protein component of TG-rich lipoproteins such as chylomicrons and VLDL and it is synthesized in the small intestine and hypothalamus [82]. ApoA-IV is a satiation protein and plays an important role in the control of food intake and ingestive behavior [83]. Its anorectic function supports its brain delivery from the peripheral circulation. However, the injection of a radio-labeled recombinant rat apoA-IV into mice did not lead to the detection of radioactive protein in the brain, suggesting that circulating apoA-IV is unable to cross the BBB [84], and that local production by neuronal cells is more likely.

3.4. ApoC peptides

ApoC-I, C-II and C-III are small proteins produced in the liver which play important roles in the regulation of TG metabolism [85]. In plasma, they are exchanged among lipoproteins and they exhibit isoforms *in vivo* [86-88]. Their role in brain cholesterol metabolism remains unclear. The genes encoding for *apoC-I* and *apoC-II* are located along with the gene for *apoE* and it has been shown that the gene for *apoε4*, one of the three apoE isoforms, influences the expression and processing of apoCs [89]. Furthermore, an *apoC-I* polymorphism has been shown to be associated with an increased risk of developing AD [90]. Lastly, lower levels of TG, apoE, and apoC-III, and higher apoC-III/apoE ratio in HDL have been described in apoε4 carriers, compared to apoε2 carriers [91].

ApoC-I mRNA has been found only in the marmoset brain [92]. Minimum amounts of *apoC-II* mRNA have been found in the adult human brain, while levels are slightly higher in children [32]. Conversely, the gene expression of *apoC-III* was below the limit of reliable detection at all ages [32]. However, apoC-II and apoC-III are detected in CSF at concentrations that are less than 5% of their plasma levels [14]. Crossing of the apoCs from plasma into CNS has been postulated [85] but further experimental studies are required.

4. Alterations of HDL and cholesterol metabolism in Alzheimer's disease

4.1. Plasma HDL

Several epidemiological evidence has suggested that HDLs are involved in the etiology and the progression of Alzheimer's disease (AD) (Table 1), although results are still controversial. The majority of the studies reported an inverse association between plasma HDL-c levels and the risk of dementia and AD [93-95], as well as cognitive functions [96-98] and the typical features associated with the disease, such as the presence of Aβ deposits, the hippocampal atrophy, or the gray and white matter volume changes [99-101]. The inverse relationship between plasma HDL-c and AD also

emerged from a recent meta-analysis, but only in the subgroup of subjects aged under 70 years [102]. Notably, Merched et al. suggested that higher plasma levels of apoA-I are directly correlated with an increased Mini-Mental State Examination score, a parameter used to evaluate cognitive function, and a lower risk of developing AD [103]. In contrast, other studies either failed to find a relationship [104, 105], or identified a positive correlation between HDL-c and AD severity [106]. Among the former, a population-based cohort study including more than 9000 individuals did not show an association of plasma HDL-c with incidence of dementia [107].

In addition to these controversies, the exact mechanisms by which plasma HDL may be involved in AD pathophysiology are still not completely understood, and several hypotheses have been suggested, including alterations of the vasoprotective functions of HDL exerted at the BBB, or systemic effects at the cerebrovascular lumen, thanks to the HDL anti-inflammatory, antioxidant and cholesterol efflux promoting capacities. Importantly, a direct effect of plasma HDL on CNS has also been suggested , given the ability of specific HDL subfractions or associated apolipoproteins to cross the BBB [108] (see section 3).

Plasma HDL of AD patients show several abnormalities, such as increased electronegativity, enrichment in apoC-III, and loss of sphingosine-1 phosphate (S1P) [109].This abnormal particle structure is associated with impaired cholesterol efflux capacity [109], with a specific reduction of the ABCA1-, SR-BI-, and ABCG1-mediated pathways [110, 111]. Consistently with the observed ABCA1-mediated cholesterol efflux impairment, a reduction of plasma small HDL particles, the best acceptor of cholesterol via this transporter [112], was reported in AD patients [113]. In addition, pro-oxidant [109] and compromised anti-inflammatory properties [111] have been detected in AD patients' HDL, partly explained by reduced activity of Lipoprotein-associated phospholipase A2, a molecule playing a pivotal role in redox processes in the CNS [114].

4.2. Brain HDL

Besides plasma HDL, a key role in cerebral cholesterol homeostasis is played by CNS HDL particles, as described in section 2. It is thus conceivable that any alteration of brain HDL may affect brain cholesterol homeostasis, leading to neuronal cholesterol depletion and thus impacting neurodegeneration. The main brain HDL alterations related to cholesterol transport and observed in AD are described in the following section and summarized in Table 1.

4.2.1. HDL biogenesis

As described above, the HDL-mediated brain cholesterol transport from astrocyte to neurons initiates with astrocyte-secreted lipid-free apoE which binds cholesterol and PL through the

interaction with specific membrane transporters, such as ABCA1 and ABCG1 (Figure 1). The relevance of ABCA1 in AD is highlighted by several findings, including the results of human genetic studies showing that loss-of-function mutations in *ABCA1* are associated with increased AD risk [115]. Supporting this evidence, the most powerful GWAS study to date identified *ABCA1* among genes associated with the risk of AD and AD-associated dementia [116]. Mechanistically, *ABCA1* deficiency is associated to lower brain apoE levels and lipidation, resulting in increased brain parenchyma Aβ deposition [48, 117, 118], while its overexpression leads to amyloid burden reduction [119], as observed in pre-clinical models.

The ABCA7 transporter, closest homolog of ABCA1, has also been implicated in the modulation of cerebral lipid metabolism, with possible implications on AD pathogenesis. In fact, *ABCA7* $^{-/-}$ mice display cognitive impairment [120, 121], and human genetic studies found an association of ABCA7 with AD [122]. Interestingly, *in vitro* studies demonstrated that silencing *ABCA7* ended up in reduced apoE secretion and impaired exchange of both cholesterol and Aβ across the BBB [123]. Similarly, the transporter ABCG1 is responsible for lipid homeostasis in the brain [124], and it has been associated with AD risk in genetic studies [125], although the involvement in Aβ processing and deposition in the brain is still controversial [126-129]. As a result of ABC transporter's activity, apoE, as well as other CSF apolipoproteins, undergoes lipidation for the generation of nascent HDL particles. Importantly, the lipidation state of apoE appears to be isoform-dependent, with apoE4 being poorly lipidated compared to apoE2 and apoE3 [130, 131]. This difference relates to the lower efficiency of apoE4 to promote cholesterol efflux [132, 133], resulting in cholesterol-poor lipoprotein particles, and may provide an additional mechanism linking apoE4 to increased risk of late-onset AD. A reduced lipidation of apoE4 leads to the formation of small CSF lipoproteins, as identified in both homozygous and heterozygous *APOE4* carriers [130]. In addition, cholesterol efflux from apoE4 expressing astrocytes is reduced compared to efflux from apoE3 astrocytes [133], because of a hypothesized reduction in the apoE4-ABCA1 interaction, resulting in lower apoE lipidation. Mechanistically, apoE4 would induce the retention of ABCA1 in the intracellular compartment, leading to a lower ABCA1-mediated cholesterol efflux [134]. In parallel, a lower Aβ degradation capacity of apoE4 was observed as a consequence of reduced affinity for Aβ [135], reinforcing the importance of a proper apoE lipidation to promote Aβ degradation [136]. However, the impact of (poorly lipidated) apoE4 on Aβ is not only limited to degradation but it is the result of multiple effects such as increased synthesis, deposition, aggregation, and reduced clearance [44]. Altogether these observations make apoE-lipidation targeted approaches an interesting therapeutic opportunity, as discussed below (see section 5).

All the above data point to the importance of defective apoE function. Concerning the CSF apoE levels, a meta-analysis of 24 studies evaluating the potential association with AD did not evidence significant differences compared to controls in all studies analyzed, but lower apoE concentration was found in the subgroup of studies with the biggest sample size [137]. At the same manner, a more recent study did not report any difference between AD and controls in terms of CSF apoE levels [138].

Besides lipid transport, an important aspect that may differ among apoE isoforms in the context of AD is the antioxidative property. In this regard, CSF lipoproteins of AD patients have shown increased susceptibility to oxidation, reduced content of the antioxidant vitamin E and enhanced neurotoxicity [139-142]. The allele-specific antioxidant function of apoE may have an important role in the association of apoE4 with AD. ApoE4 has less antioxidant activity than the other isoforms, and it is less effective in protecting neurons from oxidative damage [143], and indeed oxidative stress has been shown to be increased in the brain of AD *APOE4* carriers [144]. Moreover, in human apoE4 targeted replacement mice, a reduction in the levels of the endogenous antioxidant thioredoxin-1 was observed [145], suggesting a direct effect of apoE4 on this enzyme. Other possible mechanisms may involve a reduced capacity of apoE4 to counteract the pro-oxidant effect of Aβ [143, 146], due to weaker interactions because of the absence of the two important Cys residues in the protein [147].

Beyond apoE, the involvement of apoA-I and apoJ in AD have been documented and extensively reviewed in [148]. Interestingly, a reduced CSF apoA-I level was observed in AD [149, 150], correlating with disease progression [151]. The relationship between neurocognitive decline and apoA-I has been confirmed in mouse models of AD in which cognitive deficit is prevented by *apoA-I* overexpression [152], while *apoA-I* deletion increases the severity of the disease [153]. In addition, the infusion of reconstitute HDL made with apoA-I and phosphatidylcholine in APP/PS1 mice, a model of AD, reduces soluble Aβ brain levels [79]. Conversely, other studies reported CSF apoA-I levels directly correlating with clinical progression toward AD or no changes between AD and controls in CSF apoA-I levels [154, 155]. Interestingly, a recent work reported that CSF apoA-I level cannot distinguish between AD and other forms of dementia including Parkinson's disease and frontotemporal dementia [156], thus suggesting a role of apoA-I in different neurodegenerative disorders. No changes were found between CSF apoJ concentration in patients with and without dementia, even in the AD subgroup of subjects, in a meta-analysis including 28 studies [157]. However, in the same work an increased apoJ was observed in AD brain tissues, suggesting a role in the development and progression of AD.

The role of the HDL generated as described above in guaranteeing the flux of cholesterol between astrocytes and neurons is supported by their capacity to efficiently act as extracellular acceptors of

cholesterol from cultured astrocytes [28]. Some evidence shows that this property is lost in AD patients, with potentially deleterious consequences on neuronal cholesterol supply [28, 154, 158]. Specifically, we and others have demonstrated that CSF from AD patients has a reduced ability to promote cholesterol efflux via the transporters ABCA1 and ABCG1 [154, 158], the former pathway being compromised since the early stages of the disease [158]. A reduction in ABCA1 CSF cholesterol efflux capacity was also observed in homozygous *APOE4* carriers [134]. It is worth mentioning that, in the work of Marchi et al, lower CSF cholesterol efflux in AD patients was not accompanied by changes in either CSF apoE or apoA-I levels, suggesting that the impairment in HDL cholesterol efflux promoting function is unlinked to particles concentrations, as occurs for plasma HDL in the context of atheroprotection [159]. A specific link between the CSF cholesterol efflux impairment and AD pathophysiology was furtherly demonstrated by the correlation found between efflux capacity and Aβ and p-tau levels, the CSF markers currently used for disease diagnosis [154].

4.2.2. HDL remodeling

Beyond modification of structure, composition and function, few studies have highlighted an altered brain HDL remodeling in AD. Demeester and colleagues demonstrated a 50% reduction of the LCAT enzyme activity in the CSF of AD patients, although the number of analyzed subjects was very limited [28]. Defective LCAT activity is also reflected by lower levels of 24-hydroxycholesteryl ester, products of LCAT activity, found in the CSF of AD patients compared to controls, and able to discriminate between MCI subjects converting or not to AD [160]. However, the deletion of *LCAT* did not affect apoE and Aβ levels in AD mice models, suggesting that LCAT-derived mature apoE-containing lipoproteins in the CNS are not influencing Aβ deposition [161].

The PLTP, a downstream transport protein in HDL remodeling, displayed a higher expression in AD brain tissues [162], but lower activity in the CFS of AD patients [163]. In addition, in Aβ-injected AD mice models, *PLTP* deficiency was associated with memory impairment [164-166]. Differently, in the J20 mouse model of AD, cognitive performance was not affected by *PLTP* deletion, while Aβ deposition was markedly reduced because of enhanced clearance [167] and apoE levels were lowered, in accordance to the strong interaction between Aβ and apoE, physiologically resulting in PLTP activation [168].

Some evidence suggests that also the remodeling protein CETP seems to be involved in AD pathogenesis. Indeed, some single-nucleotide polymorphisms (SNP) in the *CETP* gene are associated with a lower rate of memory decline and lower risk of incidence of dementia, including AD [169, 170], while other polymorphisms do not [171]. Interestingly, specific *CETP* polymorphisms are able to influence AD in an apoE-dependent manner [172] and a specific *CETP* variant demonstrated to

mitigate the deleterious effects of apoε4 on memory decline in older adults [173], clearly suggesting a mechanistic link. To the best of our knowledge, no data are available on the CSF CETP levels or activity in AD patients.

4.2.3. HDL-mediated delivery of cholesterol to neurons

After being remodeled, the cholesterol-enriched, mature HDL finally interact with the LDLR and other apoE-binding receptors to mediate neuronal cholesterol uptake. According to this hypothesis, several human studies have associated these receptors to AD risk [174-176], and deletion of these receptors in animal models influence cognitive functions or Aβ metabolism [177, 178], even though the mechanisms are still far from being completely understood [reviewed in [179] and [180]]. Among the several functions of these receptors is the promotion of Aβ clearance. LRP1, a member of the LDLR family whose expression is abundant at the BBB [181], plays a central role in maintaining Aβ homeostasis in the CNS, mediating the clearance of Aβ aggregates from the brain [182, 183]. This process in pericytes of the BBB seems to occur in an apoE isoform-dependent manner, being less efficient in the presence of apoE4 [184]. In line with this pivotal role, silencing of LRP1 led to increased Aβ plaques in the cerebral cortex and hippocampus and exacerbate cognitive deficit in APP/PS1 mice [185, 186]. Consistently, lower LRP-1 levels have been detected in pericytes and brain endothelial cells from AD human tissue samples [187]. Thus, targeting LRP1 and more in general the apoE-receptors may offer novel therapeutic opportunities for AD treatment, as also mentioned in section 5.

The apoE-receptors in the brain may be the target of the proprotein convertase subtilisin/kexin type 9 (PCSK9), very well known for its regulating effect on plasma lipids through the degradation of the hepatic LDLR [188]. In the context of the brain HDL-mediated cholesterol transport, the degrading activity of PCSK9 on brain lipoprotein receptors may translate in a reduced cholesterol uptake by neurons, with potentially deleterious consequences [189]. The PCSK9-dependent degradation of the apoE-receptors may also contribute to AD through an increase of Aβ deposition or reduced clearance [180, 190]. A pathogenetic role of PCSK9 was indeed highlighted by us and others, finding increased PCSK9 concentrations in the CSF of AD patients compared to non-AD individuals [191, 192]. Consistently, an increased PCSK9 expression was found in the frontal cortex from AD patients [193]. Interestingly, in aged healthy individuals with a parental history of AD, the CSF apoE levels strongly correlate with those of PCSK9 [193]. This is consistent with the PCSK9-induced degradation of the apoE-receptors, leading to increased apoE concentrations in the CSF. A peculiar link between apoE4 and PCSK9 has also emerged from our study, in which CSF PCSK9 was higher in the apoE4 isoform carriers compared to non-carriers [192]. In line with this observation,

individuals bearing the apoE4 isoform show a breakdown of the BBB [194], suggesting increased permeability and facilitated crossing of PCSK9, and possibly explaining higher concentration in the brain. Despite this evidence, genetic analyses evaluating the link between PCSK9 and AD has brought to inconsistent results. On one hand, an association between the presence of specific *PCSK9* SNPs and the risk of AD was observed, although evident only in the female subgroup of the analyzed cohort [193]. On the other hand, loss of function mutations of PCSK9 variants has not been linked to AD [195, 196], still leaving unresolved the involvement of PCSK9 in AD pathogenesis.

5. HDL-based therapies in AD

ApoE is the most abundant and well-characterized apolipoprotein in the brain, making it a good pharmacological target. However, as well described in a very recent review [197], completed or ongoing clinical trials studying apoE are still limited, highlighting the lack of therapies currently available directed at this target. ApoE mimetic peptides derived from the receptor-binding or lipid-binding regions of apoE have been developed and tested for neurological diseases including AD. CN-105, a 5 amino acid peptide derived from the polar face of the receptor-binding region of apoE [198], has been tested in a mouse model of AD (APP/PS1/APO-E4TR mice) and shown to be able to reduce amyloid pathology and spatial learning deficits when treatment started in young mice [199], underlying the importance of initiating treatment at the early stages of the disease for achieving beneficial effects. Importantly, CN-105 has advanced to clinical phase 2 for intracerebral hemorrhage (NCT03168581) and postoperative cognitive dysfunction (NCT03802396), raising the possibility of CN-105 as a novel therapeutic agent for AD. A second apoE mimetic peptide, COG1410 (12 amino acids derived from the apoE receptor binding region) exerted positive effects on neurological deficits in early brain injury after experimental subarachnoid hemorrhage [200] and reduced behavioral deficits, plaques and tangles in AD transgenic mice [201]. Recently, the peptide COG112 (34 amino acids) was shown to rescue BBB function following traumatic spinal cord injury in apoE-knockout mice [202]. In addition, both peptides have been shown to ameliorate Aβ levels, Aβ plaque burden, tau hyperphosphorylation, and neuroinflammation in AD animal models [203,] but they have not yet been tested in humans.

Given that in brain apoE4 is less lipidated and less stable compared to apoE3 and apoE2 [204], increasing brain apoE levels and apoE lipidation has been proposed as a therapeutic approach, also to enhance the flux of cholesterol from astrocytes to neurons. In this respect, the role of the ABCA1 transporter has been reported as, by transferring cholesterol from cells onto lipid-poor apolipoproteins, it regulates apoE lipidation in the brain [205]. Indeed, it has been shown that nuclear receptor agonists, by upregulating *ABCA1* and *APOE* gene expression, increase apoE lipidation,

facilitate Aβ clearance, reduce amyloid deposition, and reverse memory deficit in an amyloid mouse model [119, 206]. In this context, the ABCA1 expression inducer bexarotene, approved by FDA for cutaneous T-cell lymphoma, has been tested in phase 1b proof-of-mechanism trial [207] in young (21–49 years) volunteers. Despite the poor penetration in the CNS, bexarotene was able to increase CSF apoE levels by 25%, although it had no effects on CSF Aβ levels. Moreover, in a proof of concept, double-blind, placebo-controlled clinical trial in 20 patients with moderate AD, bexarotene 150 mg twice daily for 4 weeks reduced Aβ PET burden and increased serum Aβ42 levels, but only in *Apo*ε4 non-carriers [208].

In the context of strategies to increase apoE levels, the old lipid-lowering drug probucol has also been tested in a pilot trial in mild-to-moderate sporadic AD; treatment with probucol could increase apoE levels in CSF and decreased both phosphorylated tau 181 and $A\beta_{1-42}$ concentrations in CSF [209]. Results from a phase 1/2 clinical trial (NCT02707458) are waited. Concerning apoE lipidation strategy, the introduction or generation of antibodies against the non-lipidated form of apoE4 could also reduce the related toxic effects. Liao et al. discovered an anti-human apoE antibody, anti-human apoE4 (HAE-4), that specifically recognizes human apoE4 and apoE3 and preferentially binds the non-lipidated, aggregated apoE. HAE-4 by preferentially bounding apoE aggregates reduced Aβ deposition and accumulation in the brain of APP/PS1-21/APOE4 mice [210].

Another potential therapeutic strategy consists in the modulation of the interaction between apoE and Aβ as this event is thought to stabilize toxic oligomeric and fibrillar Aβ species present within Aβ plaques [211]. This strategy has been tested in AD mouse models with both monoclonal anti-apoE antibodies and peptides, e.g. Aβ mimetics; the obtained results, extensively recently reviewed [197], resulted to be promising for being tested in future trials.

In light of previous studies suggesting that reduction of apoE levels through genetic manipulation can reduce Aβ pathology [212, 213], lowering brain apoE levels has also been considered as a possible therapy. This aim could be achieved by increasing the expression of apoE receptors [214], such as LRP1, thus favoring efflux of Aβ from the brain through the BBB [215], or through a more direct approach by silencing *apoE g*ene expression with specific antisense oligonucleotides [216].

Gene therapy represents an additional approach in neurodegenerative diseases. Preliminary data using the CRISPR-Cas9 editing technology to switch *apoE* alleles has been successfully tested in neurons and glial cells derived from human-induced pluripotent stem cells [217]. In humans, the effect of raising the expression of *apo*ε2 and increasing apoE2 levels in *Apo*ε4 carriers (or even *apo* ε3 homozygotes) through genetic switching *apoE4* to *apoE2* isoform has been tested in the first ongoing phase 1 clinical trial (NCT03634007). Preclinical data showed favorable effects of the transfer of human *apoE* alleles in mice after the administration of adeno-associated virus type-4, as

it increased expression of apoE2 mainly in choroid plexus and ependymal cells leading to an improvement of Aβ levels after Aβ plaque deposition [218]. This approach resulted in reduced soluble and insoluble Aβ levels, an enhanced plaque clearance, and a reduced efflux of Aβ40 from the brain to plasma through the BBB. Moreover, a slower plaque growth rate was observed in *apo*ε2 treated mice as compared to the *apo*ε4 treated mice [204].

Beyond apoE-directed therapies, apoA-I infusion and recombinant HDL represent additional potential therapies for AD [108]. Both overexpression and infusion of human apoA-I have been indeed shown to reduce neuroinflammation, inhibit cerebral amyloid angiopathy, and improve cognitive performance in transgenic mouse models [219]. Despite encouraging data have been obtained in animal models of AD with full-length apolipoproteins [219], whether this approach has any beneficial effect on human cognition has not been investigated yet. In addition, HDL-associated apolipoproteins, including apoA-I, demonstrated a limited penetrance across the BBB [15] while small, orally bioavailable peptides, have many advantages including the more efficient BBB crossing than full-length apolipoproteins. In this respect, the brain permeability of the apoA-I mimetic peptide 4F (18 amino acid peptide), estimated to be ~1000-fold greater than apoA-I, has been recently evaluated [220]. Further, in the same study, 4F treatment increased the brain efflux of Aβ and decreased its brain influx, as evaluated in mice and BBB cell monolayers. Consistently, the oral administration of 4F reduced Aβ deposition and improved cognitive functions in AD mice models [221], suggesting 4F as a potential therapeutic strategy to reduce brain amyloid accumulation in cerebral amyloid angiopathy and AD [220].

6. Cholesterol metabolism alterations in other neurodegenerative disorders

While cholesterol metabolism alterations in AD have been extensively studied, and encouraging treatments are under investigation, much less is known about its involvement in other neurodegenerative disorders. The available evidence demonstrating the relationship between HDL-c and Parkinson's disease, Huntington's disease, and frontotemporal dementia are described in the following section and summarized in Table 1.

6.1. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by tremor and bradykinesia and it affects about 1% of adults older than 60 years [222]. PD is attributed to selective loss of neurons in the substantia nigra, and its cause remains cryptic in most individuals [223]. Investigation on the relationship between plasma HDL-c and PD raised conflicting results. A recent meta-analysis suggests that elevated TG and total and LDL cholesterol levels may be protective in

the pathogenesis of PD, but no relationship with HDL-c has been highlighted [224]. Also in the large population-based AMORIS study, it has been found a consistent association between a higher level of total and LDL cholesterol, TG and apoB, but not HDL-c, with a lower risk of developing PD [225]. On the contrary, Cassani et al. found that HDL-c levels and the total/HDL cholesterol ratio were favorably associated with the duration of disease, contributing to cardiometabolic protection in PD [226], while Li et al. found that high HDL-c levels may be correlated with PD onset and progression [227]. Interestingly, it has been demonstrated that α-synuclein, the pathological protein hallmark of PD, is able to form HDL *in vitro*, but their presence and role *in vivo* remains to be demonstrated [228].

ApoA-I has also been suggested as a biomarker for PD risk in two different studies. In one study conducted in PD patients, lower plasma apoA-I levels correlated with an earlier PD onset [229, 230]; instead Whang et al. detected low levels of apoA-I in the prodromal stage of the disorder [229, 230]. The association between HDL-c and PD onset might be related to serum paraoxonase, an HDL-bound esterase which can protect HDL against oxidative stress [231]. Indeed, the genetic susceptibility to develop PD can be altered by a polymorphism in the *PON1* gene [232]. In addition, several studies reported the involvement of different apoE isoforms and susceptibility to PD [233-235]; specifically, the apoE4 isoform has been shown to be associated with an earlier onset of the disease and the development of dementia [236, 237].

Lipoproteins in CSF of PD patients have been poorly characterized yet. CSF apoJ and apoE have been found to be increased in CSF of PD patients [238]. In addition, α-synuclein seems to interact with apolipoproteins, offering a novel mechanism of uptake of this protein by neurons and diffusion in the brain [238]. Moreover, increased susceptibility to oxidation has been reported for CSF lipoproteins, as described in AD (see section 4.2.1) [239].

6.2. Huntington's disease

Huntington's disease (HD) is an inherited neurodegenerative disease characterized by progressive dementia, involuntary body movements, and psychiatric and cognitive abnormalities [240]. HD is caused by a dominant genetic mutation in the huntingtin (HTT), a ubiquitous protein with physiological beneficial activities for the brain and neurons, majorly located in the striatum and cortex [241]. Findings reported that the brain cholesterol precursor lathosterol and cholesterol levels are markedly reduced in HD mice and cholesterol reduction exacerbates with the progressive increase of CAG repetition in *huntingtin* gene in mice [242]. This disturbance seems to be associated with a specific action of mutant HTT on sterol-regulatory-element binding proteins (SREBPs) and on its target genes, whose decreased transcription resulted in reduced brain cholesterol levels [243]. Primary astrocytes bearing mutant HTT showed a decreased mRNA levels of *ABCA1* and *apoE*; as a

consequence, mutant astrocytes produce and secrete less apoE, and consistently apoE-HDL are smaller in CSF of mice expressing mutant HTT compared to CSF of WT mice, suggesting an impaired brain cholesterol transport *in vivo* [242]. In addition, the exposure of glial conditioned medium from HD astrocytes leads to less cholesterol in apoE-HDL, negatively affecting neurite outgrowth and neuronal synaptic properties [244], which are restored by exogenous cholesterol administration [244]. In accordance with the reduction of brain cholesterol biosynthesis, brain cholesterol turnover, measured as 24-OHC levels, was reduced in the brains of HD mice compared to controls [242]. Moreover, the PREDICT-HD study, a longitudinal, international, multi-site observational study in humans, revealed that plasma 24-OHC levels were reduced in HD patients compared to controls and correlate with markers of the disease progression [245]. These results suggested that modulation of brain cholesterol metabolism could represent a potential pharmacological strategy for HD, although HDL-enhancing approaches have not been investigated yet.

6.3. Frontotemporal dementia

Frontotemporal dementia (FTD) is a neurodegenerative disorder with progressive defects in behavior, language, and executive function [246]. The disorder is the third most common type of dementia and is predominantly diffused in patients younger than 65 years [247]. FTD can be diagnosed in three different clinical manifestations: the behavioral-variant FTD (bvFTD) is related to early behavioral and executive deficits, the non-fluent and the semantic-variant [246, 248].

Little data are available on the lipid profile in FTD patients. In bvFTD, the most common form of FTD, apoA-I and apoA-II levels have been found to be lower compared to controls [249]. Moreover, decreased serum HDL-c levels and HDL subclass alterations have been reported in C9orf72 repeat expansion carriers compared to sporadic FTD [250]. Finally, Ahmed et al. measured increased TG and insulin levels and decreased HDL-c levels in patients with FTD compared with controls, suggesting a potential role of cholesterol metabolism in FTD pathophysiology and progression [251].

Table 1. Plasma and CSF HDL alterations in AD and other neurodegenerative disorders

Disease	Main HDL alterations	References
Alzheimer's disease (AD)	⇩ plasma HDL-c	[93-98, 102]
	⇩ plasma HDL cholesterol efflux capacity	[109, 110]
	⇩ CSF cholesterol efflux capacity	[154, 158]
	⇩ ABCA1in CNS	[48, 115-119]
	⇩ ABCA7 in CNS	[120-123]
	⇩ CSF apoA-I	[149-153]
	⇩ or ≈ CSF apoE	[137, 138]
	⇩ CSF LCAT activity	[28, 160]
	⇩ CSF PLTP activity	[163]
	⇧ CSF HDL susceptibility to oxidation	[139-142]
Parkinson's disease (PD)	⇩ apoA-I in plasma and CSF	[229, 230]
	⇧ apoE and apoJ in CSF	[238]
	⇧ CSF HDL susceptibility to oxidation	[239]
	Polymorphism in PON1alters genetic susceptibility to PD	[232]
	apoE4 is associated to an early onset	[233-235]
Huntington's disease (HD)	⇩ cholesterol production in CNS	[242]
	⇩ SREBP transcription	[243]
	⇩ apoE and ABCA1 mRNA levels in CSF	[242]
	⇩ 24-OHC in the brain	[242, 245]
Frontotemporal dementia (FTD)	⇩ plasma apoA-I and apoA-II	[249]
	⇩ plasma HDL-c	[251]

7. Conclusions and perspectives

Despite the long-lasting knowledge of the relevance of brain cholesterol homeostasis in physiological and pathological conditions, the characterization of cholesterol transport in the brain remains largely unknown. The obvious difficult accessibility has certainly hampered studies on CSF lipoproteins, which on the contrary have been extensively studied in circulation. CSF lipoproteins are very similar to plasma HDL but contain apoE, and not apoA-I, as the major apolipoprotein. Brain HDL undergo biogenesis and remodeling processes similar to that of plasma HDL, and defects in these pathways have been described in AD and other neurodegenerative disorders. More experimental studies on brain lipoproteins and apolipoproteins, and their movement between the periphery and the CNS in physiological and pathological conditions will be instrumental in clarifying disease etiopathogenesis and strategical to unravel potential novel pharmacological targets.

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Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders

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ABSTRACT

High-density lipoproteins (HDLs play a key role in cholesterol homeostasis maintenance in the central nervous system (CNS), by carrying newly synthesized cholesterol from astrocytes to neurons, to support their lipid-related physiological functions. As occurs for plasma HDLs, brain lipoproteins are assembled through the activity of membrane cholesterol transporters, undergo remodeling mediated by specific enzymes and transport proteins, and finally deliver cholesterol to neurons by a receptor-mediated internalization process. A growing number of evidences indicates a strong association between alterations of CNS cholesterol homeostasis and neurodegenerative disorders, in particular Alzheimer's disease (AD), and a possible role in this relationship may be played by defects in brain HDL metabolism. In the present review, we summarize and critically examine the current state of knowledge on major modifications of HDL and HDL-mediated brain cholesterol transport in AD, by taking into consideration the individual steps of this process. We also describe potential and encouraging HDL-based therapies that could represent new therapeutic strategies for AD treatment. Finally, we revise the main plasma and brain HDL modifications in other neurodegenerative disorders including Parkinson's disease (PD), Huntington's disease (HD), and frontotemporal dementia (FTD).

Keywords: High-density lipoproteins, cholesterol, Alzheimer's disease, apolipoprotein E, apolipoprotein A-I, central nervous system, neurodegenerative diseases

1. Cholesterol in the brain

1.1. Cholesterol role and regulation in the brain

The central nervous system (CNS) accounts for only 2% of the whole body weight but it contains approximately 25% of the total pool of cholesterol [1]. Most of the cholesterol (about 80%) exists in the adult brain in the form of myelin [2], produced by oligodendrocytes and surrounding axons. Besides, brain cholesterol is an important constituent of neuronal membranes. It is the major component of synaptic vesicles, whose formation, shape, and release properties are controlled by cholesterol content. In addition, on the postsynaptic side, cholesterol has an important role in the organization and the correct positioning of neurotransmitter receptors; therefore, a reduced amount of cholesterol at this level can impair neurotransmission and induce a loss of dendrite spines and synapses [3]. The brain relies on endogenous local cholesterol since the blood-brain barrier (BBB) strictly regulates the transport of lipoprotein-associated lipids to the brain and vice versa [4]. Differently from cholesterol, oxysterols can flux across the BBB [5], as discussed below (see section 3).

Findings on the ontogenesis and regulation of cholesterol turnover in the brain in mice revealed that the CNS grows rapidly during the first three weeks after birth and equalled about 5% of the total body weight. The brain cholesterol pool at this stage increases at a rate of 0.26 mg/day and the pool of total sterols of about 0.28 mg/day [6]. On the opposite, in adult mice, starting from week 13, the trend dramatically switches with a reduction in the size of the CNS to 1.7% of body weight and in the rate of cholesterol synthesis that drops to 0.035 mg/day [6]. Neuronal cells are able to synthesize cholesterol during the prenatal period but progressively lose this capacity in the postnatal period and become dependent on cholesterol produced from other cell types, mainly astrocytes [4, 7], which display 2-3 higher biosynthetic capacity compared to neurons in adulthood [8, 9]. However, cholesterol synthesis rate in neurons may not always be low, depending on the brain region, as well as on the neuronal cell type [1, 9].

Cholesterol is not uniformly distributed in biological membranes, but concentrated in lipid rafts, together with other lipids [4]. Lipid rafts are commonly defined as cholesterol- and sphingolipid-enriched membrane microdomains acting as a platform to modulate cell signaling and membrane fluidity, to regulate membrane trafficking of proteins and cellular processes, such as neurotransmission [10]. Since cholesterol is a key component of lipid rafts also in the CNS, its depletion and disruption could be relevant for age or disease-related cognitive impairment [11].

1.2. Brain lipoproteins

Brain cholesterol metabolism and transport are for the most part segregated from the peripheral circulation by the BBB and cholesterol transport is carried out by lipoproteins that have been identified in the brain [12]. In human plasma, four major lipoprotein classes have been described: chylomicrons, VLDL, LDL, and HDL. The role of circulating apolipoprotein B (apoB)-containing lipoproteins, including LDL, VLDL and chylomicrons, is to distribute cholesterol and triglycerides (TG) from the liver and gut to peripheral tissues. Since CNS does not use TG as an energy source, apoB-containing lipoproteins are not present in healthy brains and this leads to a transport system of lipids reliant exclusively on "HDL-like particles" (called HDL throughout the paper), which absolves all lipid transport duty in the brain [13, 14]. While plasma HDL have been extensively studied, cerebrospinal fluid (CSF) HDL are still poorly characterized, mainly because of their very low amount. Indeed, the main constituents of brain lipoproteins have been reported to be markedly lower than in plasma; CSF cholesterol content ranges between 0.1 and 0.6 mg/dl, and apoA-I concentrations between 0.1 and 0.4 mg/dl [15] [16].

1.2.1. Heterogeneity of brain HDL

Brain HDL particles are, as plasma HDL, heterogeneous in terms of density, size, and composition. Brain HDL slightly differ from plasma HDL in terms of size and density, but the major difference is the apolipoprotein composition. The major protein component of brain HDL is apolipoprotein E (apoE), while apoA-I is the major protein component of plasma HDL. Notably, apoE is the major apolipoprotein expressed, translated, and secreted from astrocytes, microglia, and pericytes in different species [17-20]. Analysis of CSF lipoproteins by anti-apoE and anti-apoA-I immunoaffinity columns showed particles predominantly containing apoE and largely spherical (13-20 nm) with few disc-like particles, and particles containing apoA-I, spherical and smaller (10-18 nm) [16]. The apoE-containing particles are the predominant HDL subclass; the second HDL subclass is composed of apoA-I- and apoA-II-containing particles. The third class is characterized by apoE-containing large particles (18-22 nm) which also contain apoD, apoA-IV and apoJ. Finally, small HDL-like particles (10-12 nm) containing apoD, apoH, apoA-IV and apoJ have been described [15].

Plasma HDL sediment in the density region from 1.063 to 1.21 g/ml, range from 7 to 13 nm of diameter and present majorly a spherical shape [21]. Brain HDL particles identified in human CSF also mainly present a spherical shape but have a density of 1.063-1.12 g/ml and a wider diameter range (10-22 nm) [15]. Very dense HDL (VHDL), with a density up to 1.25 g/mL, mostly of spherical shape and with a diameter around 17 nm, have been also reported in human CSF [22, 23].

Plasma HDLs have been described to contain 251 individual proteins as tracked by the HDL Proteome Watch (https://homepages.uc.edu/~davidswm/HDLproteome.html accessed on 17th

November 2021) [24]. As in plasma, proteins represent the major building block of HDL found in CSF. The total CSF protein concentration ranges between 0.2% and 0.5% of the blood total protein concentration [25]. A proteomic study highlighted more than 300 proteins in CSF from healthy donors [26], and among them, only 10 apolipoproteins have been characterized in brain HDL [27, 28]. ApoE and apoA-I represent the majority of brain apolipoproteins [15]; others apolipoproteins include apoJ, apoA-II, apoA-IV, apoD, apoC-II, apoC-III, apoC-IV, and apoH. ApoE is secreted in the brain and cannot cross the BBB, as demonstrated in liver transplanted patients that presented in plasma the donor apoE phenotype but preserved their birth phenotype in the CNS [29]. ApoE is synthesized mainly by astrocytes, microglia, and oligodendrocytes. Neurons are not normally able to produce apoE, except that in response to certain conditions such as brain injuries [30, 31]. The origin of CSF apolipoproteins other than apoE remains still unknown. *ApoA-I* mRNA is not expressed by human primary brain endothelial cells, suggesting a peripheral origin [32] and the ability to cross the BBB with an endocytosis process [33] (for further details see section 3). ApoD has been reported to be expressed in neuroglial, pia mater, and perivascular cells of human brain [34, 35] and apoJ is also produced from astrocytes but secreted free of lipids [18, 36].

Lipids present in the CSF also contribute to the heterogeneity of brain HDL. The main lipids carried by brain HDL are cholesteryl esters, phospholipids (PL), and sphingolipids [13]. Five major lipid classes have been detected in CSF: free fatty acids, sphingolipids, glycerophospholipids, glycerolipids, and sterol lipids [37]. A recent untargeted lipidomic analysis has identified up to 245 lipids in CSF; these include predominantly PL (lysophosfatidylcholines, phosphatidylcholines, lysophosphatatidylethanolamines, phosphatidylethanolamine, cyclic phosphatidic acids, phosphatidylglycerols and phosphatidylinositols), ceramides, sphingomyelins, cholesteryl esters, diacylglycerols and triacylglycerols [38]. Average PL concentration in CSFhas been reported to be 0.55 ± 0.3 mg/dl [15], and phosphatidylcholine has been identified as the most represented PL (range of about 42-54%), followed by sphingomyelin (19-20%), phosphatidylethanolamine (9-13%), and minor concentrations of lysophosphatidylcholine, phosphatidylinositol, and phosphatidylserine [39, 40].

A biochemical characterization of human CSF also revealed the presence of amyloid β (Aβ) associated to brain HDL [23], as occurs for plasma HDL [41]. This interaction is probably due to the Aβ amphiphilic structure [42]. In particular, Aβ seems to be preferentially associated to large, spherical HDL [23]. Interestingly, Aβ seems to be secreted by cells already in association with apolipoproteins and lipids [43]. In this context, its specific interaction with apoE is one of the key factors in AD pathophysiology (see section 4.2.1) [44, 45].

2. HDL and cholesterol metabolism in the brain

Brain HDL have a pivotal role to carry and supply adult neurons with cholesterol to guarantee their physiological functions [13]. These lipoproteins in the CSN undergo biogenesis, maturation, and remodeling processes similar to those observed for plasma HDL, as described in detail in the following section and summarized in Figure 1.

2.1. HDL biogenesis

Although the synthesis and metabolism of plasma lipoproteins are well characterized, little is known about lipoproteins within the CNS. Brain lipoprotein metabolism involves pathways that are independent of those of the peripheral compartment. As mentioned above, HDL identified in the human CSF display apoE as a major protein component [46]. ApoE in the brain is predominantly secreted from astrocytes by the ATP-binding cassette transporter A1 (ABCA1) in the form of nascent apoE-containing HDL of about 8-12 nm, mainly composed by PL and unesterified cholesterol [20] (Figure 1). Other apolipoproteins are present in brain HDL, and the apolipoprotein composition of HDL particles may influence their lipidation degree. For example, the apoJ containing particles are lipid-poor compared to those containing apoE [36, 47].

After secretion, further synthesized cholesterol is assembled into HDL through the interaction with ABCA1 in caveolin-enriched domains, leading to the generation of discoidal particles [48, 49]. The presence in the CSF of particles mainly spherical and of different sizes indicates that nascent HDL undergo a maturation and remodeling process similar to what occurs for plasma HDL. Other ABC transporters, including ABCG1 and ABCG4, are able to promote further incorporation of cholesterol and PL in the nascent HDL [50] (Figure 1). Among these transporters, ABCG1 seems to be involved in HDL assembly at the interface between the brain and the circulation thus contributing to the generation of HDL at the BBB [51]. Another transporter sharing significant sequence similarity to ABCA1 is ABCA7, highly expressed in the brain. The physiological function of ABCA7 and its transport substrates are less known compared to those of ABCA1. It has been reported that, as for ABCA1, ABCA7 promotes the efflux of choline-containing phospholipids in the presence of apoE and apoA-I; however, differently from ABCA1, the efflux of cholesterol seems less relevant [52].

2.2. HDL remodeling

Shifting of brain HDL from discoidal to spherical particles is the result of the activity of remodeling proteins (Figure 1). HDL remodeling enzymes and lipid transfer proteins have been identified in the CNS, although little is known about the brain lipoproteins maturation process. One of the enzymes responsible for a key step in HDL maturation is the lecithin cholesterol acyltransferase

(LCAT), a soluble protein that catalyzes the conversion of unesterified cholesterol and phosphatidylcholine to cholesteryl esters and lysophosphatidylcholine on circulating lipoproteins [53]. LCAT, besides liver and testes, is also synthesized in the brain, suggesting a crucial role of this enzyme in the maturation of brain lipoproteins, although CSF LCAT concentration is very low and approximately 5% of the plasma once [17]. The primary producers of active LCAT in the brain are astrocytes, and astrocyte-derived LCAT is the only enzyme able to esterify cholesterol on nascent discoidal particles in the brain [54]. ApoE is the major LCAT activator in the CNS and both ABCA1 and apoE are required to generate glial particles substrate for this enzyme [54]. Thanks to its esterifying activity, LCAT promotes the maturation of glial-derived nascent discoidal apoE-containing particles into mature spherical ones (Figure 1).

As it occurs for plasma HDL, other two proteins seem to be involved in the remodeling of brain HDL: cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) [55, 56]. CETP has been detected in human CSF at a concentration of about 12% of that of plasma. CETP was also identified in the conditioned medium of human neuroblastoma and neuroglioma cells, clearly suggesting that this transfer protein is synthesized and secreted in the CNS, where it may contribute to the transport and redistribution of lipids [55]. However, other authors did not demonstrate any detectable CETP activity or mass in human CSF [28], leaving still open the question about the relevance of this protein in brain HDL remodeling. PLTP is also produced by neurons, astrocytes and microglia and its CSF levels represent about 15% of plasma concentration. It has been demonstrated that PLTP is highly expressed and secreted also by brain capillary endothelial cells and is actively involved in HDL biogenesis and remodeling at the BBB [56].

2.3. HDL-mediated delivery of cholesterol to neurons

Once reached the completed maturation, brain HDL particles can finally deliver cholesterol to neurons through the interaction with specific lipoprotein receptors, including the low-density lipoprotein receptor (LDLR), the very low-density lipoprotein receptor (VLDLR), the apoE receptor 2 (apoER2) and the low-density lipoprotein receptor-related protein 1 (LRP1) (Figure 1) [9, 57]. This process seems essential for the supply of cholesterol to neurons to exploit their physiological functions, such as synaptogenesis and repairing of damaged membranes. In fact, the deletion of the *Ldlr* gene in mice significantly increases apoE levels in the brain parenchyma and CSF, as a clear consequence of an impaired brain HDL internalization by neurons [58]. Similarly, conditional deletion of the *Lrp1* gene in mouse forebrain neurons increases apoE levels [59], suggesting that both receptors are involved in the internalization of HDL-apoE secreted by astrocytes. The apoE receptors show different binding affinity to apoE and lipidated apoE; in particular, nascent lipoprotein particles

secreted by astrocytes display a higher affinity for LDLR, whereas apoE-enriched lipoprotein particles and HDL isolated from CSF bind more strongly to LRP1 [60]. The other apoE receptors, VLDLR and apoER2, are structurally very similar to the LDLR and are also receptors for other ligands like the neuromodulatory signaling protein reelin, that plays a pivotal role in neurodevelopment and synaptic functions [61].

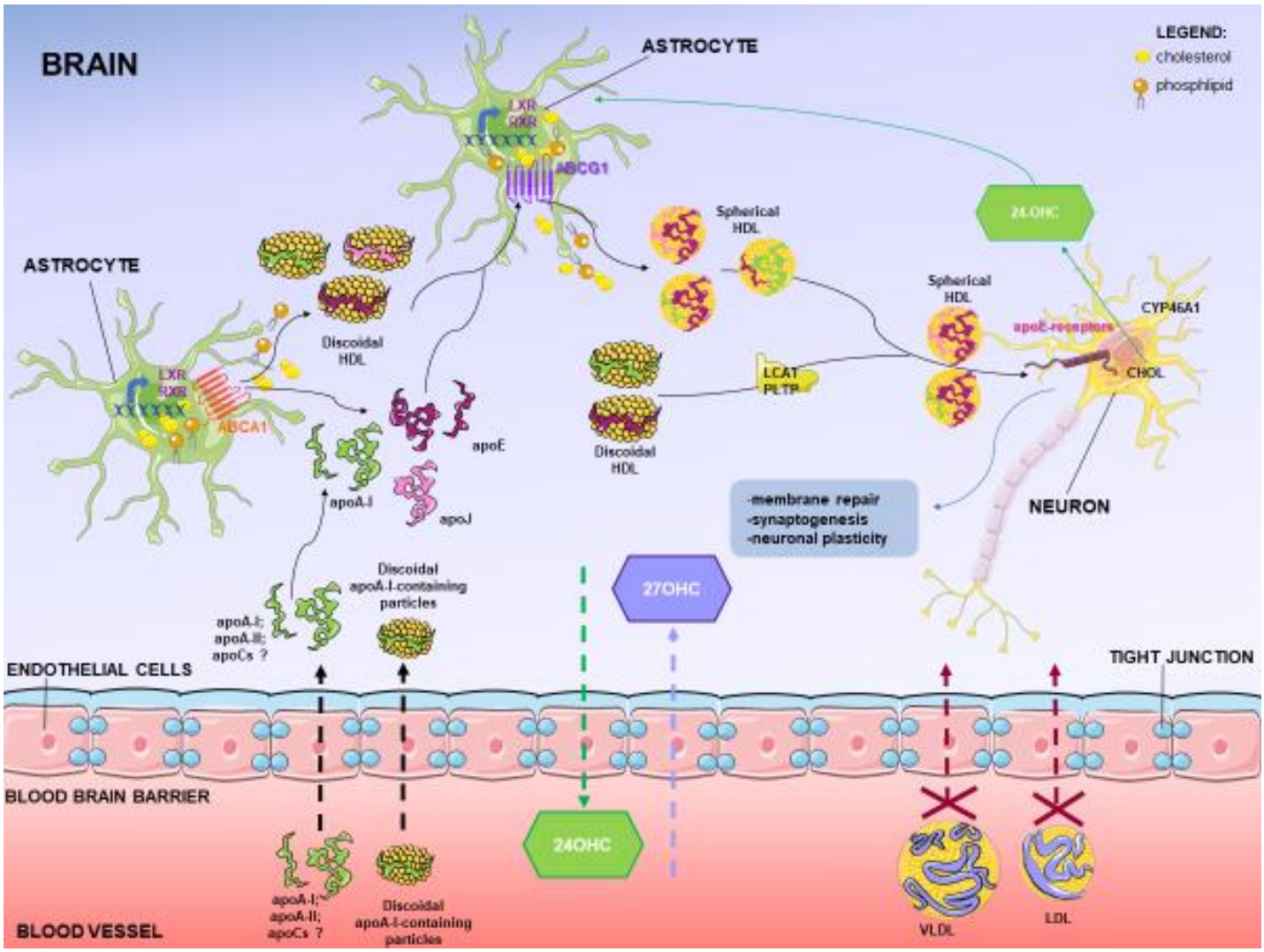

Fig. 1. Brain cholesterol transport in the CNS. In astrocytes, the ABCA1 transporter promotes the efflux of PL and UC to apoE, the major apolipoprotein in the CNS, thus leading to the formation of nascent discoidal lipoproteins. Among apolipoproteins, apoJ is also produced from astrocytes, while ApoA-I, apoA-II and apoCs are also present in the CNS, but differently from apoE are plasma-derived thanks to the ability to cross the BBB with an endocytosis process. In addition, discoidal apoA-I-containing particles may enter the CNS via SR-BI-mediated uptake and others unknown mechanisms. Discoidal particles can further acquire PL and UC via ABCA1 and ABCG1. Maturation of discoidal particles into spherical-HDL involves the activity of remodeling enzymes like LCAT, and lipid transfer proteins, such as PLTP. These newly generated lipoproteins can be finally uptaken by neurons through the binding of apoE to apoE-receptors belonging to the LDLR family. In neurons, cholesterol overload is handled by the conversion in oxysterols, mainly 24-hydroxycholesterol (OHC) that plays a significant regulatory role. 24-OHC is produced by CYP46A1 and it upregulates ABCA1 expression via activation of LXR. 24-OHC can also cross the BBB and be found in plasma. On the contrary, 27-OHC is produced by peripheral tissues but there is a net flux from circulation to the brain., through the BBB.

ABCA1: ATP-binding cassette transporter A1, ABCG1: ATP-binding cassette transporter G1; apoA-I: apolipoprotein A-I; apoA-II: apolipoprotein A-II; apoCs: apolipoprotein C; apoE: apolipoprotein E; BBB: blood-brain barrier; CETP: cholesteryl ester transfer protein; CNS: central nervous system; LDLRs: LDL receptor family receptors; LCAT: lecithin:cholesterol:acyltransferase; LXR: liver X receptor; PL: phospholipids; PLTP: phospholipid transfer protein; RXR: retinoid X receptor; SR-BI: scavenger receptor BI; UC: unesterified cholesterol; 24-OHC: 24S-hydroxycholesterol; 27-OHC: 27-hydroxycholesterol

3. Lipoproteins and apolipoproteins BBB crossing

The emerging consistent relationship between plasma HDL-cholesterol (HDL-c) levels and neurodegenerative disorders (see section 4.1) raises the question of whether and how plasma cholesterol metabolism and transport could influence brain cholesterol homeostasis. Brain cholesterol metabolism and transport are isolated from the peripheral circulation by the BBB and the blood-cerebrospinal fluid barrier (BCSFB) [17, 62, 63]. Despite CNS can produce cholesterol by *de novo* synthesis, as mentioned above, a certain amount of cholesterol derived from plasma can be delivered to the brain and eventually influence the CNS homeostasis. A possible source of cholesterol in the brain are oxysterols, side-chain oxidized sterols whose physical properties allow to pass lipophilic phospholipid-containing membranes up to three orders of magnitude faster than cholesterol itself [64], so that they are transferred through the BBB and provide a flux of cholesterol-derived molecules in and out the CNS [65]. 27-hydroxycholesterol (27-OHC) is the major oxysterol present in the circulation, it is formed by almost all cells in the body and it's able to cross the BBB from the periphery to CNS [65]. On the opposite, brain cholesterol can be removed from the brain after conversion into 24S-hydroxycholesterol (24-OHC) and subsequent diffusion over the BBB [65] (Figure 1).

Another source of cholesterol for CNS is plasma HDL and their bound apolipoproteins, whose crossing through the BBB and BCSFB could promote a flux of cholesterol in and out the SNC. Plasma-derived apolipoproteins in the brain include apoA-I, apoA-II and the apoCs, and their still controversial crossing mechanisms are detailed below.

3.1. Apolipoprotein A-I

ApoA-I is the main structural protein of HDL in plasma; it is produced and secreted from the liver and the intestine and its positive function in the prevention of cardiovascular diseases has been confirmed in several studies [66]. It is known that apoA-I protein levels in CSF are second to apoE in abundance, but in comparison, *apoA-I* mRNA has not been detected in the brain [14, 67, 68]. Indeed astrocytes and microglia are not able to produce this apolipoprotein, consequently, brain apoA-I is believed to be plasma-derived [14, 16, 69, 70]. In order to clarify the source of brain apoA-

I, specific *apoA-I* knockout mice have been generated: the intestine-specific, the liver-specific and both intestine and liver-specific *apoA-I* knockout mice. The incisive decrease of apoA-I in CSF of both intestine- and liver-specific *apoA-I* knockout mice clearly show that brain apoA-I derives from the liver and the intestine via plasma HDL [71]. In addition, it has been demonstrated that the murine brain-specific deletion of ABCA1 increases levels of CSF apoA-I, suggesting a compensatory upregulation of the translocation of plasma apoA-I to satisfy the demand of apoA-I-HDL in the brain compartment [72].

Despite the known association between apoA-I and neurodegenerative diseases [73], the route by which apoA-I enters the CSF is still controversial [71]. Plasma-to-brain delivery of apoA-I is claimed to be handled by the BCSFB and the BBB which serves as a major portal for protein delivery to the brain [74]. Stukas et al. injected recombinant fluorescently tagged human apoA-I into mice, which rapidly localizes to the choroid plexus and accumulates in the brain, showing that human apoA-I is specifically bound, internalized, and transported across confluent monolayers of primary human choroid plexus epithelial cells and brain microvascular endothelial cells. Because *apoA-I* mRNA is undetectable in the murine brain, these results suggest that plasma apoA-I gains access to the CNS primarily by crossing the BBB via specific cellular mediated transport [75] (Figure 1). Possible mechanisms for apoA-I crossing of the BBB include a clathrin-independent and cholesterol-mediated endocytosis [33] and an SR-BI-mediated transcytosis [70]. To better understand the apoA-I-containing HDL crossing, Dal Magro et al. investigated *in vitro* the ability of apoA-I in different lipidated states to cross the BBB by using a transwell system made by immortalized human brain capillary endothelial cells [76]. The obtained results showed that apoA-I containing discoidal particles cross the BBB much better than spherical HDL particles [76]. These data suggest that apoA-I-containing lipoproteins may influence the pathogenesis of neurodegenerative disorders through an direct action, occurring after BBB crossing. In this evolving context, apoA-I has also been demonstrated to be able to bind the Aβ *in vitro* [76-78] and to reduce Aβ brain levels in AD animal models [79].

3.2. Apolipoprotein A-II

ApoA-II is the second most abundant apolipoprotein in plasma HDL and comprises 20% of HDL proteins [80]. In comparison to the well-known and established functions of apoA-I, physiological functions of apoA-II are poorly understood. ApoA-II is present in CSF, but its mRNA has not been detected in the CNS tissue. Thus plasma-to-brain delivery through the choroid plexus, similar to apoA-I, has been suggested for apoA-II [81]. Further experimental works on BBB crossing of this apolipoprotein will be crucial for understanding its origin and role in brain cholesterol homeostasis.

3.3. Apolipoprotein A-IV

ApoA-IV is a major protein component of TG-rich lipoproteins such as chylomicrons and VLDL and it is synthesized in the small intestine and hypothalamus [82]. ApoA-IV is a satiation protein and plays an important role in the control of food intake and ingestive behavior [83]. Its anorectic function supports its brain delivery from the peripheral circulation. However, the injection of a radio-labeled recombinant rat apoA-IV into mice did not lead to the detection of radioactive protein in the brain, suggesting that circulating apoA-IV is unable to cross the BBB [84], and that local production by neuronal cells is more likely.

3.4. ApoC peptides

ApoC-I, C-II and C-III are small proteins produced in the liver which play important roles in the regulation of TG metabolism [85]. In plasma, they are exchanged among lipoproteins and they exhibit isoforms *in vivo* [86-88]. Their role in brain cholesterol metabolism remains unclear. The genes encoding for *apoC-I* and *apoC-II* are located along with the gene for *apoE* and it has been shown that the gene for *apoε4*, one of the three apoE isoforms, influences the expression and processing of apoCs [89]. Furthermore, an *apoC-I* polymorphism has been shown to be associated with an increased risk of developing AD [90]. Lastly, lower levels of TG, apoE, and apoC-III, and higher apoC-III/apoE ratio in HDL have been described in apoε4 carriers, compared to apoε2 carriers [91].

ApoC-I mRNA has been found only in the marmoset brain [92]. Minimum amounts of *apoC-II* mRNA have been found in the adult human brain, while levels are slightly higher in children [32]. Conversely, the gene expression of *apoC-III* was below the limit of reliable detection at all ages [32]. However, apoC-II and apoC-III are detected in CSF at concentrations that are less than 5% of their plasma levels [14]. Crossing of the apoCs from plasma into CNS has been postulated [85] but further experimental studies are required.

4. Alterations of HDL and cholesterol metabolism in Alzheimer's disease

4.1. Plasma HDL

Several epidemiological evidence has suggested that HDLs are involved in the etiology and the progression of Alzheimer's disease (AD) (Table 1), although results are still controversial. The majority of the studies reported an inverse association between plasma HDL-c levels and the risk of dementia and AD [93-95], as well as cognitive functions [96-98] and the typical features associated with the disease, such as the presence of Aβ deposits, the hippocampal atrophy, or the gray and white matter volume changes [99-101]. The inverse relationship between plasma HDL-c and AD also

emerged from a recent meta-analysis, but only in the subgroup of subjects aged under 70 years [102]. Notably, Merched et al. suggested that higher plasma levels of apoA-I are directly correlated with an increased Mini-Mental State Examination score, a parameter used to evaluate cognitive function, and a lower risk of developing AD [103]. In contrast, other studies either failed to find a relationship [104, 105], or identified a positive correlation between HDL-c and AD severity [106]. Among the former, a population-based cohort study including more than 9000 individuals did not show an association of plasma HDL-c with incidence of dementia [107].

In addition to these controversies, the exact mechanisms by which plasma HDL may be involved in AD pathophysiology are still not completely understood, and several hypotheses have been suggested, including alterations of the vasoprotective functions of HDL exerted at the BBB, or systemic effects at the cerebrovascular lumen, thanks to the HDL anti-inflammatory, antioxidant and cholesterol efflux promoting capacities. Importantly, a direct effect of plasma HDL on CNS has also been suggested , given the ability of specific HDL subfractions or associated apolipoproteins to cross the BBB [108] (see section 3).

Plasma HDL of AD patients show several abnormalities, such as increased electronegativity, enrichment in apoC-III, and loss of sphingosine-1 phosphate (S1P) [109].This abnormal particle structure is associated with impaired cholesterol efflux capacity [109], with a specific reduction of the ABCA1-, SR-BI-, and ABCG1-mediated pathways [110, 111]. Consistently with the observed ABCA1-mediated cholesterol efflux impairment, a reduction of plasma small HDL particles, the best acceptor of cholesterol via this transporter [112], was reported in AD patients [113]. In addition, pro-oxidant [109] and compromised anti-inflammatory properties [111] have been detected in AD patients' HDL, partly explained by reduced activity of Lipoprotein-associated phospholipase A2, a molecule playing a pivotal role in redox processes in the CNS [114].

4.2. Brain HDL

Besides plasma HDL, a key role in cerebral cholesterol homeostasis is played by CNS HDL particles, as described in section 2. It is thus conceivable that any alteration of brain HDL may affect brain cholesterol homeostasis, leading to neuronal cholesterol depletion and thus impacting neurodegeneration. The main brain HDL alterations related to cholesterol transport and observed in AD are described in the following section and summarized in Table 1.

4.2.1. HDL biogenesis

As described above, the HDL-mediated brain cholesterol transport from astrocyte to neurons initiates with astrocyte-secreted lipid-free apoE which binds cholesterol and PL through the

interaction with specific membrane transporters, such as ABCA1 and ABCG1 (Figure 1). The relevance of ABCA1 in AD is highlighted by several findings, including the results of human genetic studies showing that loss-of-function mutations in *ABCA1* are associated with increased AD risk [115]. Supporting this evidence, the most powerful GWAS study to date identified *ABCA1* among genes associated with the risk of AD and AD-associated dementia [116]. Mechanistically, *ABCA1* deficiency is associated to lower brain apoE levels and lipidation, resulting in increased brain parenchyma Aβ deposition [48, 117, 118], while its overexpression leads to amyloid burden reduction [119], as observed in pre-clinical models.

The ABCA7 transporter, closest homolog of ABCA1, has also been implicated in the modulation of cerebral lipid metabolism, with possible implications on AD pathogenesis. In fact, *ABCA7* $^{-/-}$ mice display cognitive impairment [120, 121], and human genetic studies found an association of ABCA7 with AD [122]. Interestingly, *in vitro* studies demonstrated that silencing *ABCA7* ended up in reduced apoE secretion and impaired exchange of both cholesterol and Aβ across the BBB [123]. Similarly, the transporter ABCG1 is responsible for lipid homeostasis in the brain [124], and it has been associated with AD risk in genetic studies [125], although the involvement in Aβ processing and deposition in the brain is still controversial [126-129]. As a result of ABC transporter's activity, apoE, as well as other CSF apolipoproteins, undergoes lipidation for the generation of nascent HDL particles. Importantly, the lipidation state of apoE appears to be isoform-dependent, with apoE4 being poorly lipidated compared to apoE2 and apoE3 [130, 131]. This difference relates to the lower efficiency of apoE4 to promote cholesterol efflux [132, 133], resulting in cholesterol-poor lipoprotein particles, and may provide an additional mechanism linking apoE4 to increased risk of late-onset AD. A reduced lipidation of apoE4 leads to the formation of small CSF lipoproteins, as identified in both homozygous and heterozygous *APOE4* carriers [130]. In addition, cholesterol efflux from apoE4 expressing astrocytes is reduced compared to efflux from apoE3 astrocytes [133], because of a hypothesized reduction in the apoE4-ABCA1 interaction, resulting in lower apoE lipidation. Mechanistically, apoE4 would induce the retention of ABCA1 in the intracellular compartment, leading to a lower ABCA1-mediated cholesterol efflux [134]. In parallel, a lower Aβ degradation capacity of apoE4 was observed as a consequence of reduced affinity for Aβ [135], reinforcing the importance of a proper apoE lipidation to promote Aβ degradation [136]. However, the impact of (poorly lipidated) apoE4 on Aβ is not only limited to degradation but it is the result of multiple effects such as increased synthesis, deposition, aggregation, and reduced clearance [44]. Altogether these observations make apoE-lipidation targeted approaches an interesting therapeutic opportunity, as discussed below (see section 5).

All the above data point to the importance of defective apoE function. Concerning the CSF apoE levels, a meta-analysis of 24 studies evaluating the potential association with AD did not evidence significant differences compared to controls in all studies analyzed, but lower apoE concentration was found in the subgroup of studies with the biggest sample size [137]. At the same manner, a more recent study did not report any difference between AD and controls in terms of CSF apoE levels [138].

Besides lipid transport, an important aspect that may differ among apoE isoforms in the context of AD is the antioxidative property. In this regard, CSF lipoproteins of AD patients have shown increased susceptibility to oxidation, reduced content of the antioxidant vitamin E and enhanced neurotoxicity [139-142]. The allele-specific antioxidant function of apoE may have an important role in the association of apoE4 with AD. ApoE4 has less antioxidant activity than the other isoforms, and it is less effective in protecting neurons from oxidative damage [143], and indeed oxidative stress has been shown to be increased in the brain of AD *APOE4* carriers [144]. Moreover, in human apoE4 targeted replacement mice, a reduction in the levels of the endogenous antioxidant thioredoxin-1 was observed [145], suggesting a direct effect of apoE4 on this enzyme. Other possible mechanisms may involve a reduced capacity of apoE4 to counteract the pro-oxidant effect of Aβ [143, 146], due to weaker interactions because of the absence of the two important Cys residues in the protein [147].

Beyond apoE, the involvement of apoA-I and apoJ in AD have been documented and extensively reviewed in [148]. Interestingly, a reduced CSF apoA-I level was observed in AD [149, 150], correlating with disease progression [151]. The relationship between neurocognitive decline and apoA-I has been confirmed in mouse models of AD in which cognitive deficit is prevented by *apoA-I* overexpression [152], while *apoA-I* deletion increases the severity of the disease [153]. In addition, the infusion of reconstitute HDL made with apoA-I and phosphatidylcholine in APP/PS1 mice, a model of AD, reduces soluble Aβ brain levels [79]. Conversely, other studies reported CSF apoA-I levels directly correlating with clinical progression toward AD or no changes between AD and controls in CSF apoA-I levels [154, 155]. Interestingly, a recent work reported that CSF apoA-I level cannot distinguish between AD and other forms of dementia including Parkinson's disease and frontotemporal dementia [156], thus suggesting a role of apoA-I in different neurodegenerative disorders. No changes were found between CSF apoJ concentration in patients with and without dementia, even in the AD subgroup of subjects, in a meta-analysis including 28 studies [157]. However, in the same work an increased apoJ was observed in AD brain tissues, suggesting a role in the development and progression of AD.

The role of the HDL generated as described above in guaranteeing the flux of cholesterol between astrocytes and neurons is supported by their capacity to efficiently act as extracellular acceptors of

cholesterol from cultured astrocytes [28]. Some evidence shows that this property is lost in AD patients, with potentially deleterious consequences on neuronal cholesterol supply [28, 154, 158]. Specifically, we and others have demonstrated that CSF from AD patients has a reduced ability to promote cholesterol efflux via the transporters ABCA1 and ABCG1 [154, 158], the former pathway being compromised since the early stages of the disease [158]. A reduction in ABCA1 CSF cholesterol efflux capacity was also observed in homozygous *APOE4* carriers [134]. It is worth mentioning that, in the work of Marchi et al, lower CSF cholesterol efflux in AD patients was not accompanied by changes in either CSF apoE or apoA-I levels, suggesting that the impairment in HDL cholesterol efflux promoting function is unlinked to particles concentrations, as occurs for plasma HDL in the context of atheroprotection [159]. A specific link between the CSF cholesterol efflux impairment and AD pathophysiology was furtherly demonstrated by the correlation found between efflux capacity and Aβ and p-tau levels, the CSF markers currently used for disease diagnosis [154].

4.2.2. HDL remodeling

Beyond modification of structure, composition and function, few studies have highlighted an altered brain HDL remodeling in AD. Demeester and colleagues demonstrated a 50% reduction of the LCAT enzyme activity in the CSF of AD patients, although the number of analyzed subjects was very limited [28]. Defective LCAT activity is also reflected by lower levels of 24-hydroxycholesteryl ester, products of LCAT activity, found in the CSF of AD patients compared to controls, and able to discriminate between MCI subjects converting or not to AD [160]. However, the deletion of *LCAT* did not affect apoE and Aβ levels in AD mice models, suggesting that LCAT-derived mature apoE-containing lipoproteins in the CNS are not influencing Aβ deposition [161].

The PLTP, a downstream transport protein in HDL remodeling, displayed a higher expression in AD brain tissues [162], but lower activity in the CFS of AD patients [163]. In addition, in Aβ-injected AD mice models, *PLTP* deficiency was associated with memory impairment [164-166]. Differently, in the J20 mouse model of AD, cognitive performance was not affected by *PLTP* deletion, while Aβ deposition was markedly reduced because of enhanced clearance [167] and apoE levels were lowered, in accordance to the strong interaction between Aβ and apoE, physiologically resulting in PLTP activation [168].

Some evidence suggests that also the remodeling protein CETP seems to be involved in AD pathogenesis. Indeed, some single-nucleotide polymorphisms (SNP) in the *CETP* gene are associated with a lower rate of memory decline and lower risk of incidence of dementia, including AD [169, 170], while other polymorphisms do not [171]. Interestingly, specific *CETP* polymorphisms are able to influence AD in an apoE-dependent manner [172] and a specific *CETP* variant demonstrated to

mitigate the deleterious effects of apoε4 on memory decline in older adults [173], clearly suggesting a mechanistic link. To the best of our knowledge, no data are available on the CSF CETP levels or activity in AD patients.

4.2.3. HDL-mediated delivery of cholesterol to neurons

After being remodeled, the cholesterol-enriched, mature HDL finally interact with the LDLR and other apoE-binding receptors to mediate neuronal cholesterol uptake. According to this hypothesis, several human studies have associated these receptors to AD risk [174-176], and deletion of these receptors in animal models influence cognitive functions or Aβ metabolism [177, 178], even though the mechanisms are still far from being completely understood [reviewed in [179] and [180]]. Among the several functions of these receptors is the promotion of Aβ clearance. LRP1, a member of the LDLR family whose expression is abundant at the BBB [181], plays a central role in maintaining Aβ homeostasis in the CNS, mediating the clearance of Aβ aggregates from the brain [182, 183]. This process in pericytes of the BBB seems to occur in an apoE isoform-dependent manner, being less efficient in the presence of apoE4 [184]. In line with this pivotal role, silencing of LRP1 led to increased Aβ plaques in the cerebral cortex and hippocampus and exacerbate cognitive deficit in APP/PS1 mice [185, 186]. Consistently, lower LRP-1 levels have been detected in pericytes and brain endothelial cells from AD human tissue samples [187]. Thus, targeting LRP1 and more in general the apoE-receptors may offer novel therapeutic opportunities for AD treatment, as also mentioned in section 5.

The apoE-receptors in the brain may be the target of the proprotein convertase subtilisin/kexin type 9 (PCSK9), very well known for its regulating effect on plasma lipids through the degradation of the hepatic LDLR [188]. In the context of the brain HDL-mediated cholesterol transport, the degrading activity of PCSK9 on brain lipoprotein receptors may translate in a reduced cholesterol uptake by neurons, with potentially deleterious consequences [189]. The PCSK9-dependent degradation of the apoE-receptors may also contribute to AD through an increase of Aβ deposition or reduced clearance [180, 190]. A pathogenetic role of PCSK9 was indeed highlighted by us and others, finding increased PCSK9 concentrations in the CSF of AD patients compared to non-AD individuals [191, 192]. Consistently, an increased PCSK9 expression was found in the frontal cortex from AD patients [193]. Interestingly, in aged healthy individuals with a parental history of AD, the CSF apoE levels strongly correlate with those of PCSK9 [193]. This is consistent with the PCSK9-induced degradation of the apoE-receptors, leading to increased apoE concentrations in the CSF. A peculiar link between apoE4 and PCSK9 has also emerged from our study, in which CSF PCSK9 was higher in the apoE4 isoform carriers compared to non-carriers [192]. In line with this observation,

individuals bearing the apoE4 isoform show a breakdown of the BBB [194], suggesting increased permeability and facilitated crossing of PCSK9, and possibly explaining higher concentration in the brain. Despite this evidence, genetic analyses evaluating the link between PCSK9 and AD has brought to inconsistent results. On one hand, an association between the presence of specific *PCSK9* SNPs and the risk of AD was observed, although evident only in the female subgroup of the analyzed cohort [193]. On the other hand, loss of function mutations of PCSK9 variants has not been linked to AD [195, 196], still leaving unresolved the involvement of PCSK9 in AD pathogenesis.

5. HDL-based therapies in AD

ApoE is the most abundant and well-characterized apolipoprotein in the brain, making it a good pharmacological target. However, as well described in a very recent review [197], completed or ongoing clinical trials studying apoE are still limited, highlighting the lack of therapies currently available directed at this target. ApoE mimetic peptides derived from the receptor-binding or lipid-binding regions of apoE have been developed and tested for neurological diseases including AD. CN-105, a 5 amino acid peptide derived from the polar face of the receptor-binding region of apoE [198], has been tested in a mouse model of AD (APP/PS1/APO-E4TR mice) and shown to be able to reduce amyloid pathology and spatial learning deficits when treatment started in young mice [199], underlying the importance of initiating treatment at the early stages of the disease for achieving beneficial effects. Importantly, CN-105 has advanced to clinical phase 2 for intracerebral hemorrhage (NCT03168581) and postoperative cognitive dysfunction (NCT03802396), raising the possibility of CN-105 as a novel therapeutic agent for AD. A second apoE mimetic peptide, COG1410 (12 amino acids derived from the apoE receptor binding region) exerted positive effects on neurological deficits in early brain injury after experimental subarachnoid hemorrhage [200] and reduced behavioral deficits, plaques and tangles in AD transgenic mice [201]. Recently, the peptide COG112 (34 amino acids) was shown to rescue BBB function following traumatic spinal cord injury in apoE-knockout mice [202]. In addition, both peptides have been shown to ameliorate Aβ levels, Aβ plaque burden, tau hyperphosphorylation, and neuroinflammation in AD animal models [203,] but they have not yet been tested in humans.

Given that in brain apoE4 is less lipidated and less stable compared to apoE3 and apoE2 [204], increasing brain apoE levels and apoE lipidation has been proposed as a therapeutic approach, also to enhance the flux of cholesterol from astrocytes to neurons. In this respect, the role of the ABCA1 transporter has been reported as, by transferring cholesterol from cells onto lipid-poor apolipoproteins, it regulates apoE lipidation in the brain [205]. Indeed, it has been shown that nuclear receptor agonists, by upregulating *ABCA1* and *APOE* gene expression, increase apoE lipidation,

facilitate Aβ clearance, reduce amyloid deposition, and reverse memory deficit in an amyloid mouse model [119, 206]. In this context, the ABCA1 expression inducer bexarotene, approved by FDA for cutaneous T-cell lymphoma, has been tested in phase 1b proof-of-mechanism trial [207] in young (21–49 years) volunteers. Despite the poor penetration in the CNS, bexarotene was able to increase CSF apoE levels by 25%, although it had no effects on CSF Aβ levels. Moreover, in a proof of concept, double-blind, placebo-controlled clinical trial in 20 patients with moderate AD, bexarotene 150 mg twice daily for 4 weeks reduced Aβ PET burden and increased serum Aβ42 levels, but only in *Apo*ε4 non-carriers [208].

In the context of strategies to increase apoE levels, the old lipid-lowering drug probucol has also been tested in a pilot trial in mild-to-moderate sporadic AD; treatment with probucol could increase apoE levels in CSF and decreased both phosphorylated tau 181 and $A\beta_{1\text{-}42}$ concentrations in CSF [209]. Results from a phase 1/2 clinical trial (NCT02707458) are waited. Concerning apoE lipidation strategy, the introduction or generation of antibodies against the non-lipidated form of apoE4 could also reduce the related toxic effects. Liao et al. discovered an anti-human apoE antibody, anti-human apoE4 (HAE-4), that specifically recognizes human apoE4 and apoE3 and preferentially binds the non-lipidated, aggregated apoE. HAE-4 by preferentially bounding apoE aggregates reduced Aβ deposition and accumulation in the brain of APP/PS1-21/APOE4 mice [210].

Another potential therapeutic strategy consists in the modulation of the interaction between apoE and Aβ as this event is thought to stabilize toxic oligomeric and fibrillar Aβ species present within Aβ plaques [211]. This strategy has been tested in AD mouse models with both monoclonal anti-apoE antibodies and peptides, e.g. Aβ mimetics; the obtained results, extensively recently reviewed [197], resulted to be promising for being tested in future trials.

In light of previous studies suggesting that reduction of apoE levels through genetic manipulation can reduce Aβ pathology [212, 213], lowering brain apoE levels has also been considered as a possible therapy. This aim could be achieved by increasing the expression of apoE receptors [214], such as LRP1, thus favoring efflux of Aβ from the brain through the BBB [215], or through a more direct approach by silencing *apoE g*ene expression with specific antisense oligonucleotides [216].

Gene therapy represents an additional approach in neurodegenerative diseases. Preliminary data using the CRISPR-Cas9 editing technology to switch *apoE* alleles has been successfully tested in neurons and glial cells derived from human-induced pluripotent stem cells [217]. In humans, the effect of raising the expression of *apo*ε2 and increasing apoE2 levels in *Apo*ε4 carriers (or even *apo* ε3 homozygotes) through genetic switching *apoE4* to *apoE2* isoform has been tested in the first ongoing phase 1 clinical trial (NCT03634007). Preclinical data showed favorable effects of the transfer of human *apoE* alleles in mice after the administration of adeno-associated virus type-4, as

it increased expression of apoE2 mainly in choroid plexus and ependymal cells leading to an improvement of Aβ levels after Aβ plaque deposition [218]. This approach resulted in reduced soluble and insoluble Aβ levels, an enhanced plaque clearance, and a reduced efflux of Aβ40 from the brain to plasma through the BBB. Moreover, a slower plaque growth rate was observed in *apo*ε2 treated mice as compared to the *apo*ε4 treated mice [204].

Beyond apoE-directed therapies, apoA-I infusion and recombinant HDL represent additional potential therapies for AD [108]. Both overexpression and infusion of human apoA-I have been indeed shown to reduce neuroinflammation, inhibit cerebral amyloid angiopathy, and improve cognitive performance in transgenic mouse models [219]. Despite encouraging data have been obtained in animal models of AD with full-length apolipoproteins [219], whether this approach has any beneficial effect on human cognition has not been investigated yet. In addition, HDL-associated apolipoproteins, including apoA-I, demonstrated a limited penetrance across the BBB [15] while small, orally bioavailable peptides, have many advantages including the more efficient BBB crossing than full-length apolipoproteins. In this respect, the brain permeability of the apoA-I mimetic peptide 4F (18 amino acid peptide), estimated to be ~1000-fold greater than apoA-I, has been recently evaluated [220]. Further, in the same study, 4F treatment increased the brain efflux of Aβ and decreased its brain influx, as evaluated in mice and BBB cell monolayers. Consistently, the oral administration of 4F reduced Aβ deposition and improved cognitive functions in AD mice models [221], suggesting 4F as a potential therapeutic strategy to reduce brain amyloid accumulation in cerebral amyloid angiopathy and AD [220].

6. Cholesterol metabolism alterations in other neurodegenerative disorders

While cholesterol metabolism alterations in AD have been extensively studied, and encouraging treatments are under investigation, much less is known about its involvement in other neurodegenerative disorders. The available evidence demonstrating the relationship between HDL-c and Parkinson's disease, Huntington's disease, and frontotemporal dementia are described in the following section and summarized in Table 1.

6.1. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by tremor and bradykinesia and it affects about 1% of adults older than 60 years [222]. PD is attributed to selective loss of neurons in the substantia nigra, and its cause remains cryptic in most individuals [223]. Investigation on the relationship between plasma HDL-c and PD raised conflicting results. A recent meta-analysis suggests that elevated TG and total and LDL cholesterol levels may be protective in

the pathogenesis of PD, but no relationship with HDL-c has been highlighted [224]. Also in the large population-based AMORIS study, it has been found a consistent association between a higher level of total and LDL cholesterol, TG and apoB, but not HDL-c, with a lower risk of developing PD [225]. On the contrary, Cassani et al. found that HDL-c levels and the total/HDL cholesterol ratio were favorably associated with the duration of disease, contributing to cardiometabolic protection in PD [226], while Li et al. found that high HDL-c levels may be correlated with PD onset and progression [227]. Interestingly, it has been demonstrated that α-synuclein, the pathological protein hallmark of PD, is able to form HDL *in vitro*, but their presence and role *in vivo* remains to be demonstrated [228].

ApoA-I has also been suggested as a biomarker for PD risk in two different studies. In one study conducted in PD patients, lower plasma apoA-I levels correlated with an earlier PD onset [229, 230]; instead Whang et al. detected low levels of apoA-I in the prodromal stage of the disorder [229, 230]. The association between HDL-c and PD onset might be related to serum paraoxonase, an HDL-bound esterase which can protect HDL against oxidative stress [231]. Indeed, the genetic susceptibility to develop PD can be altered by a polymorphism in the *PON1* gene [232]. In addition, several studies reported the involvement of different apoE isoforms and susceptibility to PD [233-235]; specifically, the apoE4 isoform has been shown to be associated with an earlier onset of the disease and the development of dementia [236, 237].

Lipoproteins in CSF of PD patients have been poorly characterized yet. CSF apoJ and apoE have been found to be increased in CSF of PD patients [238]. In addition, α-synuclein seems to interact with apolipoproteins, offering a novel mechanism of uptake of this protein by neurons and diffusion in the brain [238]. Moreover, increased susceptibility to oxidation has been reported for CSF lipoproteins, as described in AD (see section 4.2.1) [239].

6.2. Huntington's disease

Huntington's disease (HD) is an inherited neurodegenerative disease characterized by progressive dementia, involuntary body movements, and psychiatric and cognitive abnormalities [240]. HD is caused by a dominant genetic mutation in the huntingtin (HTT), a ubiquitous protein with physiological beneficial activities for the brain and neurons, majorly located in the striatum and cortex [241]. Findings reported that the brain cholesterol precursor lathosterol and cholesterol levels are markedly reduced in HD mice and cholesterol reduction exacerbates with the progressive increase of CAG repetition in *huntingtin* gene in mice [242]. This disturbance seems to be associated with a specific action of mutant HTT on sterol-regulatory-element binding proteins (SREBPs) and on its target genes, whose decreased transcription resulted in reduced brain cholesterol levels [243]. Primary astrocytes bearing mutant HTT showed a decreased mRNA levels of *ABCA1* and *apoE*; as a

consequence, mutant astrocytes produce and secrete less apoE, and consistently apoE-HDL are smaller in CSF of mice expressing mutant HTT compared to CSF of WT mice, suggesting an impaired brain cholesterol transport *in vivo* [242]. In addition, the exposure of glial conditioned medium from HD astrocytes leads to less cholesterol in apoE-HDL, negatively affecting neurite outgrowth and neuronal synaptic properties [244], which are restored by exogenous cholesterol administration [244]. In accordance with the reduction of brain cholesterol biosynthesis, brain cholesterol turnover, measured as 24-OHC levels, was reduced in the brains of HD mice compared to controls [242]. Moreover, the PREDICT-HD study, a longitudinal, international, multi-site observational study in humans, revealed that plasma 24-OHC levels were reduced in HD patients compared to controls and correlate with markers of the disease progression [245]. These results suggested that modulation of brain cholesterol metabolism could represent a potential pharmacological strategy for HD, although HDL-enhancing approaches have not been investigated yet.

6.3. Frontotemporal dementia

Frontotemporal dementia (FTD) is a neurodegenerative disorder with progressive defects in behavior, language, and executive function [246]. The disorder is the third most common type of dementia and is predominantly diffused in patients younger than 65 years [247]. FTD can be diagnosed in three different clinical manifestations: the behavioral-variant FTD (bvFTD) is related to early behavioral and executive deficits, the non-fluent and the semantic-variant [246, 248].

Little data are available on the lipid profile in FTD patients. In bvFTD, the most common form of FTD, apoA-I and apoA-II levels have been found to be lower compared to controls [249]. Moreover, decreased serum HDL-c levels and HDL subclass alterations have been reported in C9orf72 repeat expansion carriers compared to sporadic FTD [250]. Finally, Ahmed et al. measured increased TG and insulin levels and decreased HDL-c levels in patients with FTD compared with controls, suggesting a potential role of cholesterol metabolism in FTD pathophysiology and progression [251].

Table 1. Plasma and CSF HDL alterations in AD and other neurodegenerative disorders

Disease	Main HDL alterations	References
Alzheimer's disease (AD)	⇩ plasma HDL-c	[93-98, 102]
	⇩ plasma HDL cholesterol efflux capacity	[109, 110]
	⇩ CSF cholesterol efflux capacity	[154, 158]
	⇩ ABCA1in CNS	[48, 115-119]
	⇩ ABCA7 in CNS	[120-123]
	⇩ CSF apoA-I	[149-153]
	⇩ or ≈ CSF apoE	[137, 138]
	⇩ CSF LCAT activity	[28, 160]
	⇩ CSF PLTP activity	[163]
	⇧ CSF HDL susceptibility to oxidation	[139-142]
Parkinson's disease (PD)	⇩ apoA-I in plasma and CSF	[229, 230]
	⇧ apoE and apoJ in CSF	[238]
	⇧ CSF HDL susceptibility to oxidation	[239]
	Polymorphism in PON1alters genetic susceptibility to PD	[232]
	apoE4 is associated to an early onset	[233-235]
Huntington's disease (HD)	⇩ cholesterol production in CNS	[242]
	⇩ SREBP transcription	[243]
	⇩ apoE and ABCA1 mRNA levels in CSF	[242]
	⇩ 24-OHC in the brain	[242, 245]
Frontotemporal dementia (FTD)	⇩ plasma apoA-I and apoA-II	[249]
	⇩ plasma HDL-c	[251]

7. Conclusions and perspectives

Despite the long-lasting knowledge of the relevance of brain cholesterol homeostasis in physiological and pathological conditions, the characterization of cholesterol transport in the brain remains largely unknown. The obvious difficult accessibility has certainly hampered studies on CSF lipoproteins, which on the contrary have been extensively studied in circulation. CSF lipoproteins are very similar to plasma HDL but contain apoE, and not apoA-I, as the major apolipoprotein. Brain HDL undergo biogenesis and remodeling processes similar to that of plasma HDL, and defects in these pathways have been described in AD and other neurodegenerative disorders. More experimental studies on brain lipoproteins and apolipoproteins, and their movement between the periphery and the CNS in physiological and pathological conditions will be instrumental in clarifying disease etiopathogenesis and strategical to unravel potential novel pharmacological targets.

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