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Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders

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02 May 2026

BBA - Molecular and Cell Biology of Lipids

Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders

--Manuscript Draft--

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Article Type:	VSI: High density lipoproteins
Keywords:	High-density lipoproteins; cholesterol; Alzheimer's Disease; apolipoprotein E; apolipoprotein A-I; central nervous system
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Abstract:	<p>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).</p>
Response to Reviewers:	See enclosed point-by-point answers to reviewers.



UNIVERSITÀ DEGLI STUDI DI MILANO

DIPARTIMENTO DI SCIENZE FARMACOLOGICHE
E BIOMOLECOLARI - DiSFeB

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,

Laura Calabresi
Professor of Pharmacology

Manuscript No.: BBALIP-21-275

Title: Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders

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.

Units 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).

1 **Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders**

2 2

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1 **ABSTRACT**

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

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

15 *1.2.1. Heterogeneity of brain HDL*

16 Brain HDL particles are, as plasma HDL, heterogeneous in terms of density, size, and composition.
17 Brain HDL slightly differ from plasma HDL in terms of size and density, but the major difference is
18 the apolipoprotein composition. The major protein component of brain HDL is apolipoprotein E
19 (apoE), while apoA-I is the major protein component of plasma HDL. Notably, apoE is the major
20 apolipoprotein expressed, translated, and secreted from astrocytes, microglia, and pericytes in
21 different species [17-20]. Analysis of CSF lipoproteins by anti-apoE and anti-apoA-I immunoaffinity
22 columns showed particles predominantly containing apoE and largely spherical (13-20 nm) with few
23 disc-like particles, and particles containing apoA-I, spherical and smaller (10-18 nm) [16]. The apoE-
24 containing particles are the predominant HDL subclass; the second HDL subclass is composed of
25 apoA-I- and apoA-II-containing particles. The third class is characterized by apoE-containing large
26 particles (18-22 nm) which also contain apoD, apoA-IV and apoJ. Finally, small HDL-like particles
27 (10-12 nm) containing apoD, apoH, apoA-IV and apoJ have been described [15].
28

29 Plasma HDL sediment in the density region from 1.063 to 1.21 g/ml, range from 7 to 13 nm of
30 diameter and present majorly a spherical shape [21]. Brain HDL particles identified in human CSF
31 also mainly present a spherical shape but have a density of 1.063-1.12 g/ml and a wider diameter
32 range (10-22 nm) [15]. Very dense HDL (VHDL), with a density up to 1.25 g/mL, mostly of spherical
33 shape and with a diameter around 17 nm, have been also reported in human CSF [22, 23].
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35 Plasma HDLs have been described to contain 251 individual proteins as tracked by the HDL
36 Proteome Watch (<https://homepages.uc.edu/~davidswm/HDLproteome.html> accessed on 17th
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1 November 2021) [24]. As in plasma, proteins represent the major building block of HDL found in
2 CSF. The total CSF protein concentration ranges between 0.2% and 0.5% of the blood total protein
3 concentration [25]. A proteomic study highlighted more than 300 proteins in CSF from healthy
4 donors [26], and among them, only 10 apolipoproteins have been characterized in brain HDL [27,
5 28]. ApoE and apoA-I represent the majority of brain apolipoproteins [15]; others apolipoproteins
6 include apoJ, apoA-II, apoA-IV, apoD, apoC-II, apoC-III, apoC-IV, and apoH. ApoE is secreted in
7 the brain and cannot cross the BBB, as demonstrated in liver transplanted patients that presented in
8 plasma the donor apoE phenotype but preserved their birth phenotype in the CNS [29]. ApoE is
9 synthesized mainly by astrocytes, microglia, and oligodendrocytes. Neurons are not normally able to
10 produce apoE, except that in response to certain conditions such as brain injuries [30, 31]. The origin
11 of CSF apolipoproteins other than apoE remains still unknown. *ApoA-I* mRNA is not expressed by
12 human primary brain endothelial cells, suggesting a peripheral origin [32] and the ability to cross the
13 BBB with an endocytosis process [33] (for further details see section 3). ApoD has been reported to
14 be expressed in neuroglial, pia mater, and perivascular cells of human brain [34, 35] and apoJ is also
15 produced from astrocytes but secreted free of lipids [18, 36].

16 Lipids present in the CSF also contribute to the heterogeneity of brain HDL. The main lipids
17 carried by brain HDL are cholesteryl esters, phospholipids (PL), and sphingolipids [13]. Five major
18 lipid classes have been detected in CSF: free fatty acids, sphingolipids, glycerophospholipids,
19 glycerolipids, and sterol lipids [37]. A recent untargeted lipidomic analysis has identified up to 245
20 lipids in CSF; these include predominantly PL (lysophosphatidylcholines, phosphatidylcholines,
21 lysophosphatidylethanolamines, phosphatidylethanolamine, cyclic phosphatidic acids,
22 phosphatidylglycerols and phosphatidylinositols), ceramides, sphingomyelins, cholesteryl esters,
23 diacylglycerols and triacylglycerols [38]. Average PL concentration in CSF has been reported to be
24 0.55 ± 0.3 mg/dl [15], and phosphatidylcholine has been identified as the most represented PL (range
25 of about 42-54%), followed by sphingomyelin (19-20%), phosphatidylethanolamine (9-13%), and
26 minor concentrations of lysophosphatidylcholine, phosphatidylinositol, and phosphatidylserine [39,
27 40].

28 A biochemical characterization of human CSF also revealed the presence of amyloid β ($A\beta$)
29 associated to brain HDL [23], as occurs for plasma HDL [41]. This interaction is probably due to the
30 $A\beta$ amphiphilic structure [42]. In particular, $A\beta$ seems to be preferentially associated to large,
31 spherical HDL [23]. Interestingly, $A\beta$ seems to be secreted by cells already in association with
32 apolipoproteins and lipids [43]. In this context, its specific interaction with apoE is one of the key
33 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

1 (LCAT), a soluble protein that catalyzes the conversion of unesterified cholesterol and
2 phosphatidylcholine to cholesteryl esters and lysophosphatidylcholine on circulating lipoproteins
3 [53]. LCAT, besides liver and testes, is also synthesized in the brain, suggesting a crucial role of this
4 enzyme in the maturation of brain lipoproteins, although CSF LCAT concentration is very low and
5 approximately 5% of the plasma once [17]. The primary producers of active LCAT in the brain are
6 astrocytes, and astrocyte-derived LCAT is the only enzyme able to esterify cholesterol on nascent
7 discoidal particles in the brain [54]. ApoE is the major LCAT activator in the CNS and both ABCA1
8 and apoE are required to generate glial particles substrate for this enzyme [54]. Thanks to its
9 esterifying activity, LCAT promotes the maturation of glial-derived nascent discoidal apoE-
10 containing particles into mature spherical ones (Figure 1).

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

22 2.3. HDL-mediated delivery of cholesterol to neurons

23 Once reached the completed maturation, brain HDL particles can finally deliver cholesterol to
24 neurons through the interaction with specific lipoprotein receptors, including the low-density
25 lipoprotein receptor (LDLR), the very low-density lipoprotein receptor (VLDLR), the apoE receptor
26 2 (apoER2) and the low-density lipoprotein receptor-related protein 1 (LRP1) (Figure 1) [9, 57]. This
27 process seems essential for the supply of cholesterol to neurons to exploit their physiological
28 functions, such as synaptogenesis and repairing of damaged membranes. In fact, the deletion of the
29 *Ldlr* gene in mice significantly increases apoE levels in the brain parenchyma and CSF, as a clear
30 consequence of an impaired brain HDL internalization by neurons [58]. Similarly, conditional
31 deletion of the *Lrp1* gene in mouse forebrain neurons increases apoE levels [59], suggesting that both
32 receptors are involved in the internalization of HDL-apoE secreted by astrocytes. The apoE receptors
33 show different binding affinity to apoE and lipidated apoE; in particular, nascent lipoprotein particles
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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].

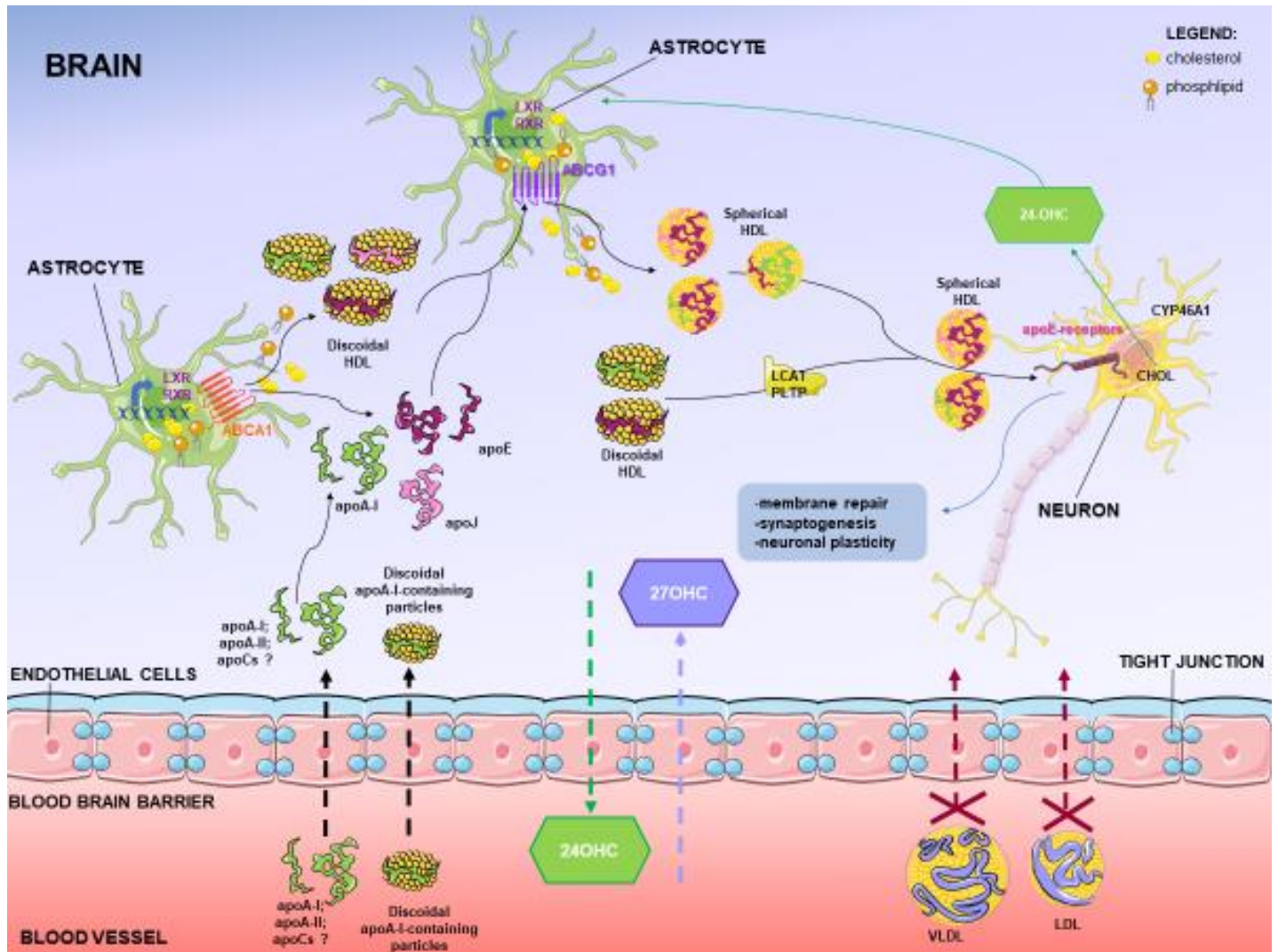


Fig. 1. Brain cholesterol transport in the CNS. In astrocytes, the ABCA1 transporter promotes the efflux of PL and UC to apoE, the major apolipoprotein in the CNS, thus leading to the formation of nascent discoidal lipoproteins. Among apolipoproteins, apoJ is also produced from astrocytes, while ApoA-I, 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.

1 ABCA1: ATP-binding cassette transporter A1, ABCG1: ATP-binding cassette transporter G1; apoA-I: apolipoprotein A-
2 I; apoA-II: apolipoprotein A-II; apoCs: apolipoprotein C; apoE: apolipoprotein E; BBB: blood-brain barrier; CETP:
3 cholesteryl ester transfer protein; CNS: central nervous system; LDLRs: LDL receptor family receptors; LCAT:
4 lecithin:cholesterol:acyltransferase; LXR: liver X receptor; PL: phospholipids; PLTP: phospholipid transfer protein;
5 RXR: retinoid X receptor; SR-BI: scavenger receptor BI; UC: unesterified cholesterol; 24-OHC: 24S-hydroxycholesterol;
6 27-OHC: 27-hydroxycholesterol

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11 12 **3. Lipoproteins and apolipoproteins BBB crossing**

13 The emerging consistent relationship between plasma HDL-cholesterol (HDL-c) levels and
14 15 neurodegenerative disorders (see section 4.1) raises the question of whether and how plasma
16 17 cholesterol metabolism and transport could influence brain cholesterol homeostasis. Brain cholesterol
18 19 metabolism and transport are isolated from the peripheral circulation by the BBB and the blood-
20 21 cerebrospinal fluid barrier (BCSFB) [17, 62, 63]. Despite CNS can produce cholesterol by *de novo*
22 23 synthesis, as mentioned above, a certain amount of cholesterol derived from plasma can be delivered
24 25 to the brain and eventually influence the CNS homeostasis. A possible source of cholesterol in the
26 27 brain are oxysterols, side-chain oxidized sterols whose physical properties allow to pass lipophilic
28 29 phospholipid-containing membranes up to three orders of magnitude faster than cholesterol itself
30 31 [64], so that they are transferred through the BBB and provide a flux of cholesterol-derived molecules
32 33 in and out the CNS [65]. 27-hydroxycholesterol (27-OHC) is the major oxysterol present in the
34 35 circulation, it is formed by almost all cells in the body and it's able to cross the BBB from the
36 37 periphery to CNS [65]. On the opposite, brain cholesterol can be removed from the brain after
38 39 conversion into 24S-hydroxycholesterol (24-OHC) and subsequent diffusion over the BBB [65]
40 (Figure 1).

41 42 Another source of cholesterol for CNS is plasma HDL and their bound apolipoproteins, whose
43 44 crossing through the BBB and BCSFB could promote a flux of cholesterol in and out the SNC.
45 46 Plasma-derived apolipoproteins in the brain include apoA-I, apoA-II and the apoCs, and their still
47 48 controversial crossing mechanisms are detailed below.
49

50 51 **3.1. Apolipoprotein A-I**

52 53 ApoA-I is the main structural protein of HDL in plasma; it is produced and secreted from the liver
54 55 and the intestine and its positive function in the prevention of cardiovascular diseases has been
56 57 confirmed in several studies [66]. It is known that apoA-I protein levels in CSF are second to apoE
58 59 in abundance, but in comparison, *apoA-I* mRNA has not been detected in the brain [14, 67, 68].
60 61 Indeed astrocytes and microglia are not able to produce this apolipoprotein, consequently, brain
62 63 apoA-I is believed to be plasma-derived [14, 16, 69, 70]. In order to clarify the source of brain apoA-
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1 I, specific *apoA-I* knockout mice have been generated: the intestine-specific, the liver-specific and
2 both intestine and liver-specific *apoA-I* knockout mice. The incisive decrease of apoA-I in CSF of
3 both intestine- and liver-specific *apoA-I* knockout mice clearly show that brain apoA-I derives from
4 the liver and the intestine via plasma HDL [71]. In addition, it has been demonstrated that the murine
5 brain-specific deletion of ABCA1 increases levels of CSF apoA-I, suggesting a compensatory
6 upregulation of the translocation of plasma apoA-I to satisfy the demand of apoA-I-HDL in the brain
7 compartment [72].

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

3.2. Apolipoprotein A-II

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

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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

1 emerged from a recent meta-analysis, but only in the subgroup of subjects aged under 70 years [102].
2 Notably, Merched et al. suggested that higher plasma levels of apoA-I are directly correlated with an
3 increased Mini-Mental State Examination score, a parameter used to evaluate cognitive function, and
4 a lower risk of developing AD [103]. In contrast, other studies either failed to find a relationship [104,
5 105], or identified a positive correlation between HDL-c and AD severity [106]. Among the former,
6 a population-based cohort study including more than 9000 individuals did not show an association of
7 plasma HDL-c with incidence of dementia [107].

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

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

4.2. Brain HDL

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

4.2.1. HDL biogenesis

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

1 interaction with specific membrane transporters, such as ABCA1 and ABCG1 (Figure 1). The
2 relevance of ABCA1 in AD is highlighted by several findings, including the results of human genetic
3 studies showing that loss-of-function mutations in *ABCA1* are associated with increased AD risk
4 [115]. Supporting this evidence, the most powerful GWAS study to date identified *ABCA1* among
5 genes associated with the risk of AD and AD-associated dementia [116]. Mechanistically, *ABCA1*
6 deficiency is associated to lower brain apoE levels and lipidation, resulting in increased brain
7 parenchyma A β deposition [48, 117, 118], while its overexpression leads to amyloid burden reduction
8 [119], as observed in pre-clinical models.

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

1 All the above data point to the importance of defective apoE function. Concerning the CSF apoE
2 levels, a meta-analysis of 24 studies evaluating the potential association with AD did not evidence
3 significant differences compared to controls in all studies analyzed, but lower apoE concentration
4 was found in the subgroup of studies with the biggest sample size [137]. At the same manner, a more
5 recent study did not report any difference between AD and controls in terms of CSF apoE levels
6 [138].

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

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

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

1 cholesterol from cultured astrocytes [28]. Some evidence shows that this property is lost in AD
2 patients, with potentially deleterious consequences on neuronal cholesterol supply [28, 154, 158].
3 Specifically, we and others have demonstrated that CSF from AD patients has a reduced ability to
4 promote cholesterol efflux via the transporters ABCA1 and ABCG1 [154, 158], the former pathway
5 being compromised since the early stages of the disease [158]. A reduction in ABCA1 CSF
6 cholesterol efflux capacity was also observed in homozygous *APOE4* carriers [134]. It is worth
7 mentioning that, in the work of Marchi et al, lower CSF cholesterol efflux in AD patients was not
8 accompanied by changes in either CSF apoE or apoA-I levels, suggesting that the impairment in HDL
9 cholesterol efflux promoting function is unlinked to particles concentrations, as occurs for plasma
10 HDL in the context of atheroprotection [159]. A specific link between the CSF cholesterol efflux
11 impairment and AD pathophysiology was furtherly demonstrated by the correlation found between
12 efflux capacity and A β and p-tau levels, the CSF markers currently used for disease diagnosis [154].
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15 4.2.2. HDL remodeling

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

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

31 Some evidence suggests that also the remodeling protein CETP seems to be involved in AD
32 pathogenesis. Indeed, some single-nucleotide polymorphisms (SNP) in the *CETP* gene are associated
33 with a lower rate of memory decline and lower risk of incidence of dementia, including AD [169,
34 170], while other polymorphisms do not [171]. Interestingly, specific *CETP* polymorphisms are able
35 to influence AD in an apoE-dependent manner [172] and a specific *CETP* variant demonstrated to

1 mitigate the deleterious effects of apoE4 on memory decline in older adults [173], clearly suggesting
2 a mechanistic link. To the best of our knowledge, no data are available on the CSF CETP levels or
3 activity in AD patients.
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5 4.2.3. HDL-mediated delivery of cholesterol to neurons

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7 After being remodeled, the cholesterol-enriched, mature HDL finally interact with the LDLR and
8 other apoE-binding receptors to mediate neuronal cholesterol uptake. According to this hypothesis,
9 several human studies have associated these receptors to AD risk [174-176], and deletion of these
10 receptors in animal models influence cognitive functions or A β metabolism [177, 178], even though
11 the mechanisms are still far from being completely understood [reviewed in [179] and [180]]. Among
12 the several functions of these receptors is the promotion of A β clearance. LRP1, a member of the
13 LDLR family whose expression is abundant at the BBB [181], plays a central role in maintaining A β
14 homeostasis in the CNS, mediating the clearance of A β aggregates from the brain [182, 183]. This
15 process in pericytes of the BBB seems to occur in an apoE isoform-dependent manner, being less
16 efficient in the presence of apoE4 [184]. In line with this pivotal role, silencing of LRP1 led to
17 increased A β plaques in the cerebral cortex and hippocampus and exacerbate cognitive deficit in
18 APP/PS1 mice [185, 186]. Consistently, lower LRP-1 levels have been detected in pericytes and brain
19 endothelial cells from AD human tissue samples [187]. Thus, targeting LRP1 and more in general the
20 apoE-receptors may offer novel therapeutic opportunities for AD treatment, as also mentioned in
21 section 5.
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23 The apoE-receptors in the brain may be the target of the proprotein convertase subtilisin/kexin
24 type 9 (PCSK9), very well known for its regulating effect on plasma lipids through the degradation
25 of the hepatic LDLR [188]. In the context of the brain HDL-mediated cholesterol transport, the
26 degrading activity of PCSK9 on brain lipoprotein receptors may translate in a reduced cholesterol
27 uptake by neurons, with potentially deleterious consequences [189]. The PCSK9-dependent
28 degradation of the apoE-receptors may also contribute to AD through an increase of A β deposition
29 or reduced clearance [180, 190]. A pathogenetic role of PCSK9 was indeed highlighted by us and
30 others, finding increased PCSK9 concentrations in the CSF of AD patients compared to non-AD
31 individuals [191, 192]. Consistently, an increased PCSK9 expression was found in the frontal cortex
32 from AD patients [193]. Interestingly, in aged healthy individuals with a parental history of AD, the
33 CSF apoE levels strongly correlate with those of PCSK9 [193]. This is consistent with the PCSK9-
34 induced degradation of the apoE-receptors, leading to increased apoE concentrations in the CSF. A
35 peculiar link between apoE4 and PCSK9 has also emerged from our study, in which CSF PCSK9 was
36 higher in the apoE4 isoform carriers compared to non-carriers [192]. In line with this observation,
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1 individuals bearing the apoE4 isoform show a breakdown of the BBB [194], suggesting increased
2 permeability and facilitated crossing of PCSK9, and possibly explaining higher concentration in the
3 brain. Despite this evidence, genetic analyses evaluating the link between PCSK9 and AD has brought
4 to inconsistent results. On one hand, an association between the presence of specific *PCSK9* SNPs
5 and the risk of AD was observed, although evident only in the female subgroup of the analyzed cohort
6 [193]. On the other hand, loss of function mutations of PCSK9 variants has not been linked to AD
7 [195, 196], still leaving unresolved the involvement of PCSK9 in AD pathogenesis.

5. HDL-based therapies in AD

10 ApoE is the most abundant and well-characterized apolipoprotein in the brain, making it a good
11 pharmacological target. However, as well described in a very recent review [197], completed or
12 ongoing clinical trials studying apoE are still limited, highlighting the lack of therapies currently
13 available directed at this target. ApoE mimetic peptides derived from the receptor-binding or lipid-
14 binding regions of apoE have been developed and tested for neurological diseases including AD. CN-
15 105, a 5 amino acid peptide derived from the polar face of the receptor-binding region of apoE [198],
16 has been tested in a mouse model of AD (APP/PS1/APO-E4TR mice) and shown to be able to reduce
17 amyloid pathology and spatial learning deficits when treatment started in young mice [199],
18 underlying the importance of initiating treatment at the early stages of the disease for achieving
19 beneficial effects. Importantly, CN-105 has advanced to clinical phase 2 for intracerebral hemorrhage
20 (NCT03168581) and postoperative cognitive dysfunction (NCT03802396), raising the possibility of
21 CN-105 as a novel therapeutic agent for AD. A second apoE mimetic peptide, COG1410 (12 amino
22 acids derived from the apoE receptor binding region) exerted positive effects on neurological deficits
23 in early brain injury after experimental subarachnoid hemorrhage [200] and reduced behavioral
24 deficits, plaques and tangles in AD transgenic mice [201]. Recently, the peptide COG112 (34 amino
25 acids) was shown to rescue BBB function following traumatic spinal cord injury in apoE-knockout
26 mice [202]. In addition, both peptides have been shown to ameliorate A β levels, A β plaque burden,
27 tau hyperphosphorylation, and neuroinflammation in AD animal models [203,] but they have not yet
28 been tested in humans.

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

1 facilitate A β clearance, reduce amyloid deposition, and reverse memory deficit in an amyloid mouse
2 model [119, 206]. In this context, the ABCA1 expression inducer bexarotene, approved by FDA for
3 cutaneous T-cell lymphoma, has been tested in phase 1b proof-of-mechanism trial [207] in young
4 (21–49 years) volunteers. Despite the poor penetration in the CNS, bexarotene was able to increase
5 CSF apoE levels by 25%, although it had no effects on CSF A β levels. Moreover, in a proof of
6 concept, double-blind, placebo-controlled clinical trial in 20 patients with moderate AD, bexarotene
7 150 mg twice daily for 4 weeks reduced A β PET burden and increased serum A β 42 levels, but only
8 in *ApoE4* non-carriers [208].

9 In the context of strategies to increase apoE levels, the old lipid-lowering drug probucol has also
10 been tested in a pilot trial in mild-to-moderate sporadic AD; treatment with probucol could increase
11 apoE levels in CSF and decreased both phosphorylated tau 181 and A β ₁₋₄₂ concentrations in CSF
12 [209]. Results from a phase 1/2 clinical trial (NCT02707458) are awaited. Concerning apoE lipidation
13 strategy, the introduction or generation of antibodies against the non-lipidated form of apoE4 could
14 also reduce the related toxic effects. Liao et al. discovered an anti-human apoE antibody, anti-human
15 apoE4 (HAE-4), that specifically recognizes human apoE4 and apoE3 and preferentially binds the
16 non-lipidated, aggregated apoE. HAE-4 by preferentially bounding apoE aggregates reduced A β
17 deposition and accumulation in the brain of APP/PS1-21/APOE4 mice [210].

18 Another potential therapeutic strategy consists in the modulation of the interaction between apoE
19 and A β as this event is thought to stabilize toxic oligomeric and fibrillar A β species present within
20 A β plaques [211]. This strategy has been tested in AD mouse models with both monoclonal anti-
21 apoE antibodies and peptides, e.g. A β mimetics; the obtained results, extensively recently reviewed
22 [197], resulted to be promising for being tested in future trials.

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

28 Gene therapy represents an additional approach in neurodegenerative diseases. Preliminary data
29 using the CRISPR-Cas9 editing technology to switch *apoE* alleles has been successfully tested in
30 neurons and glial cells derived from human-induced pluripotent stem cells [217]. In humans, the
31 effect of raising the expression of *apoE2* and increasing apoE2 levels in *ApoE4* carriers (or even *apoE3*
32 homozygotes) through genetic switching *apoE4* to *apoE2* isoform has been tested in the first
33 ongoing phase 1 clinical trial (NCT03634007). Preclinical data showed favorable effects of the
34 transfer of human *apoE* alleles in mice after the administration of adeno-associated virus type-4, as

1 it increased expression of apoE2 mainly in choroid plexus and ependymal cells leading to an
2 improvement of A β levels after A β plaque deposition [218]. This approach resulted in reduced soluble
3 and insoluble A β levels, an enhanced plaque clearance, and a reduced efflux of A β 40 from the brain
4 to plasma through the BBB. Moreover, a slower plaque growth rate was observed in *apoE2* treated
5 mice as compared to the *apoE4* treated mice [204].
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9 Beyond apoE-directed therapies, apoA-I infusion and recombinant HDL represent additional
10 potential therapies for AD [108]. Both overexpression and infusion of human apoA-I have been
11 indeed shown to reduce neuroinflammation, inhibit cerebral amyloid angiopathy, and improve
12 cognitive performance in transgenic mouse models [219]. Despite encouraging data have been
13 obtained in animal models of AD with full-length apolipoproteins [219], whether this approach has
14 any beneficial effect on human cognition has not been investigated yet. In addition, HDL-associated
15 apolipoproteins, including apoA-I, demonstrated a limited penetrance across the BBB [15] while
16 small, orally bioavailable peptides, have many advantages including the more efficient BBB crossing
17 than full-length apolipoproteins. In this respect, the brain permeability of the apoA-I mimetic peptide
18 4F (18 amino acid peptide), estimated to be ~1000-fold greater than apoA-I, has been recently
19 evaluated [220]. Further, in the same study, 4F treatment increased the brain efflux of A β and
20 decreased its brain influx, as evaluated in mice and BBB cell monolayers. Consistently, the oral
21 administration of 4F reduced A β deposition and improved cognitive functions in AD mice models
22 [221], suggesting 4F as a potential therapeutic strategy to reduce brain amyloid accumulation in
23 cerebral amyloid angiopathy and AD [220].
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38 **6. Cholesterol metabolism alterations in other neurodegenerative disorders**

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40 While cholesterol metabolism alterations in AD have been extensively studied, and encouraging
41 treatments are under investigation, much less is known about its involvement in other
42 neurodegenerative disorders. The available evidence demonstrating the relationship between HDL-c
43 and Parkinson's disease, Huntington's disease, and frontotemporal dementia are described in the
44 following section and summarized in Table 1.
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49 *6.1. Parkinson's disease*

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51 Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by tremor and
52 bradykinesia and it affects about 1% of adults older than 60 years [222]. PD is attributed to selective
53 loss of neurons in the substantia nigra, and its cause remains cryptic in most individuals [223].
54 Investigation on the relationship between plasma HDL-c and PD raised conflicting results. A recent
55 meta-analysis suggests that elevated TG and total and LDL cholesterol levels may be protective in
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1 the pathogenesis of PD, but no relationship with HDL-c has been highlighted [224]. Also in the large
2 population-based AMORIS study, it has been found a consistent association between a higher level
3 of total and LDL cholesterol, TG and apoB, but not HDL-c, with a lower risk of developing PD [225].
4
5 On the contrary, Cassani et al. found that HDL-c levels and the total/HDL cholesterol ratio were
6 favorably associated with the duration of disease, contributing to cardiometabolic protection in PD
7 [226], while Li et al. found that high HDL-c levels may be correlated with PD onset and progression
8 [227]. Interestingly, it has been demonstrated that α -synuclein, the pathological protein hallmark of
9 PD, is able to form HDL *in vitro*, but their presence and role *in vivo* remains to be demonstrated [228].

10
11 ApoA-I has also been suggested as a biomarker for PD risk in two different studies. In one study
12 conducted in PD patients, lower plasma apoA-I levels correlated with an earlier PD onset [229, 230];
13 instead Whang et al. detected low levels of apoA-I in the prodromal stage of the disorder [229, 230].
14
15 The association between HDL-c and PD onset might be related to serum paraoxonase, an HDL-bound
16 esterase which can protect HDL against oxidative stress [231]. Indeed, the genetic susceptibility to
17 develop PD can be altered by a polymorphism in the *PON1* gene [232]. In addition, several studies
18 reported the involvement of different apoE isoforms and susceptibility to PD [233-235]; specifically,
19 the apoE4 isoform has been shown to be associated with an earlier onset of the disease and the
20 development of dementia [236, 237].

21
22 Lipoproteins in CSF of PD patients have been poorly characterized yet. CSF apoJ and apoE have
23 been found to be increased in CSF of PD patients [238]. In addition, α -synuclein seems to interact
24 with apolipoproteins, offering a novel mechanism of uptake of this protein by neurons and diffusion
25 in the brain [238]. Moreover, increased susceptibility to oxidation has been reported for CSF
26 lipoproteins, as described in AD (see section 4.2.1) [239].

40 41 42 6.2. Huntington's disease

43
44 Huntington's disease (HD) is an inherited neurodegenerative disease characterized by progressive
45 dementia, involuntary body movements, and psychiatric and cognitive abnormalities [240]. HD is
46 caused by a dominant genetic mutation in the huntingtin (HTT), a ubiquitous protein with
47 physiological beneficial activities for the brain and neurons, majorly located in the striatum and cortex
48 [241]. Findings reported that the brain cholesterol precursor lathosterol and cholesterol levels are
49 markedly reduced in HD mice and cholesterol reduction exacerbates with the progressive increase of
50 CAG repetition in *huntingtin* gene in mice [242]. This disturbance seems to be associated with a
51 specific action of mutant HTT on sterol-regulatory-element binding proteins (SREBPs) and on its
52 target genes, whose decreased transcription resulted in reduced brain cholesterol levels [243]. Primary
53 astrocytes bearing mutant HTT showed a decreased mRNA levels of *ABCA1* and *apoE*; as a
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1 consequence, mutant astrocytes produce and secrete less apoE, and consistently apoE-HDL are
2 smaller in CSF of mice expressing mutant HTT compared to CSF of WT mice, suggesting an impaired
3 brain cholesterol transport *in vivo* [242]. In addition, the exposure of glial conditioned medium from
4 HD astrocytes leads to less cholesterol in apoE-HDL, negatively affecting neurite outgrowth and
5 neuronal synaptic properties [244], which are restored by exogenous cholesterol administration [244].
6
7 In accordance with the reduction of brain cholesterol biosynthesis, brain cholesterol turnover,
8 measured as 24-OHC levels, was reduced in the brains of HD mice compared to controls [242].
9 Moreover, the PREDICT-HD study, a longitudinal, international, multi-site observational study in
10 humans, revealed that plasma 24-OHC levels were reduced in HD patients compared to controls and
11 correlate with markers of the disease progression [245]. These results suggested that modulation of
12 brain cholesterol metabolism could represent a potential pharmacological strategy for HD, although
13 HDL-enhancing approaches have not been investigated yet.

14 6.3. Frontotemporal dementia

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

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

1 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 ↓↓ plasma HDL cholesterol efflux capacity ↓↓ CSF cholesterol efflux capacity ↓↓ ABCA1 in CNS ↓↓ ABCA7 in CNS ↓↓ CSF apoA-I ↓↓ or ≈ CSF apoE ↓↓ CSF LCAT activity ↓↓ CSF PLTP activity ↑↑ CSF HDL susceptibility to oxidation	[93-98, 102] [109, 110] [154, 158] [48, 115-119] [120-123] [149-153] [137, 138] [28, 160] [163] [139-142]
Parkinson's disease (PD)	↓↓ apoA-I in plasma and CSF ↑↑ apoE and apoJ in CSF ↑↑ CSF HDL susceptibility to oxidation Polymorphism in PON1 alters genetic susceptibility to PD apoE4 is associated to an early onset	[229, 230] [238] [239] [232] [233-235]
Huntington's disease (HD)	↓↓ cholesterol production in CNS ↓↓ SREBP transcription ↓↓ apoE and ABCA1 mRNA levels in CSF ↓↓ 24-OHC in the brain	[242] [243] [242] [242, 245]
Frontotemporal dementia (FTD)	↓↓ plasma apoA-I and apoA-II ↓↓ plasma HDL-c	[249] [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 strategic to unravel potential novel pharmacological targets.

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1 **Emerging role of HDL in brain cholesterol metabolism and neurodegenerative disorders**

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1 **ABSTRACT**

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

16

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

19

1 **1. Cholesterol in the brain**

2 *1.1. Cholesterol role and regulation in the brain*

3 The central nervous system (CNS) accounts for only 2% of the whole body weight but it contains
4 approximately 25% of the total pool of cholesterol [1]. Most of the cholesterol (about 80%) exists in
5 the adult brain in the form of myelin [2], produced by oligodendrocytes and surrounding axons.
6 Besides, brain cholesterol is an important constituent of neuronal membranes. It is the major
7 component of synaptic vesicles, whose formation, shape, and release properties are controlled by
8 cholesterol content. In addition, on the postsynaptic side, cholesterol has an important role in the
9 organization and the correct positioning of neurotransmitter receptors; therefore, a reduced amount
10 of cholesterol at this level can impair neurotransmission and induce a loss of dendrite spines and
11 synapses [3]. The brain relies on endogenous local cholesterol since the blood-brain barrier (BBB)
12 strictly regulates the transport of lipoprotein-associated lipids to the brain and vice versa [4].
13 Differently from cholesterol, oxysterols can flux across the BBB [5], as discussed below (see section
14 3).

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

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

32 33 *1.2. Brain lipoproteins*

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

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15 *1.2.1. Heterogeneity of brain HDL*

16 Brain HDL particles are, as plasma HDL, heterogeneous in terms of density, size, and composition.
17 Brain HDL slightly differ from plasma HDL in terms of size and density, but the major difference is
18 the apolipoprotein composition. The major protein component of brain HDL is apolipoprotein E
19 (apoE), while apoA-I is the major protein component of plasma HDL. Notably, apoE is the major
20 apolipoprotein expressed, translated, and secreted from astrocytes, microglia, and pericytes in
21 different species [17-20]. Analysis of CSF lipoproteins by anti-apoE and anti-apoA-I immunoaffinity
22 columns showed particles predominantly containing apoE and largely spherical (13-20 nm) with few
23 disc-like particles, and particles containing apoA-I, spherical and smaller (10-18 nm) [16]. The apoE-
24 containing particles are the predominant HDL subclass; the second HDL subclass is composed of
25 apoA-I- and apoA-II-containing particles. The third class is characterized by apoE-containing large
26 particles (18-22 nm) which also contain apoD, apoA-IV and apoJ. Finally, small HDL-like particles
27 (10-12 nm) containing apoD, apoH, apoA-IV and apoJ have been described [15].

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

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

1 November 2021) [24]. As in plasma, proteins represent the major building block of HDL found in
2 CSF. The total CSF protein concentration ranges between 0.2% and 0.5% of the blood total protein
3 concentration [25]. A proteomic study highlighted more than 300 proteins in CSF from healthy
4 donors [26], and among them, only 10 apolipoproteins have been characterized in brain HDL [27,
5 28]. ApoE and apoA-I represent the majority of brain apolipoproteins [15]; others apolipoproteins
6 include apoJ, apoA-II, apoA-IV, apoD, apoC-II, apoC-III, apoC-IV, and apoH. ApoE is secreted in
7 the brain and cannot cross the BBB, as demonstrated in liver transplanted patients that presented in
8 plasma the donor apoE phenotype but preserved their birth phenotype in the CNS [29]. ApoE is
9 synthesized mainly by astrocytes, microglia, and oligodendrocytes. Neurons are not normally able to
10 produce apoE, except that in response to certain conditions such as brain injuries [30, 31]. The origin
11 of CSF apolipoproteins other than apoE remains still unknown. *ApoA-I* mRNA is not expressed by
12 human primary brain endothelial cells, suggesting a peripheral origin [32] and the ability to cross the
13 BBB with an endocytosis process [33] (for further details see section 3). ApoD has been reported to
14 be expressed in neuroglial, pia mater, and perivascular cells of human brain [34, 35] and apoJ is also
15 produced from astrocytes but secreted free of lipids [18, 36].

16 Lipids present in the CSF also contribute to the heterogeneity of brain HDL. The main lipids
17 carried by brain HDL are cholesteryl esters, phospholipids (PL), and sphingolipids [13]. Five major
18 lipid classes have been detected in CSF: free fatty acids, sphingolipids, glycerophospholipids,
19 glycerolipids, and sterol lipids [37]. A recent untargeted lipidomic analysis has identified up to 245
20 lipids in CSF; these include predominantly PL (lysophosphatidylcholines, phosphatidylcholines,
21 lysophosphatidylethanolamines, phosphatidylethanolamine, cyclic phosphatidic acids,
22 phosphatidylglycerols and phosphatidylinositols), ceramides, sphingomyelins, cholesteryl esters,
23 diacylglycerols and triacylglycerols [38]. Average PL concentration in CSF has been reported to be
24 0.55 ± 0.3 mg/dl [15], and phosphatidylcholine has been identified as the most represented PL (range
25 of about 42-54%), followed by sphingomyelin (19-20%), phosphatidylethanolamine (9-13%), and
26 minor concentrations of lysophosphatidylcholine, phosphatidylinositol, and phosphatidylserine [39,
27 40].

28 A biochemical characterization of human CSF also revealed the presence of amyloid β ($A\beta$)
29 associated to brain HDL [23], as occurs for plasma HDL [41]. This interaction is probably due to the
30 $A\beta$ amphiphilic structure [42]. In particular, $A\beta$ seems to be preferentially associated to large,
31 spherical HDL [23]. Interestingly, $A\beta$ seems to be secreted by cells already in association with
32 apolipoproteins and lipids [43]. In this context, its specific interaction with apoE is one of the key
33 factors in AD pathophysiology (see section 4.2.1) [44, 45].

34

1 **2. HDL and cholesterol metabolism in the brain**

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

6 7 *2.1. HDL biogenesis*

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

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

29 30 *2.2. HDL remodeling*

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

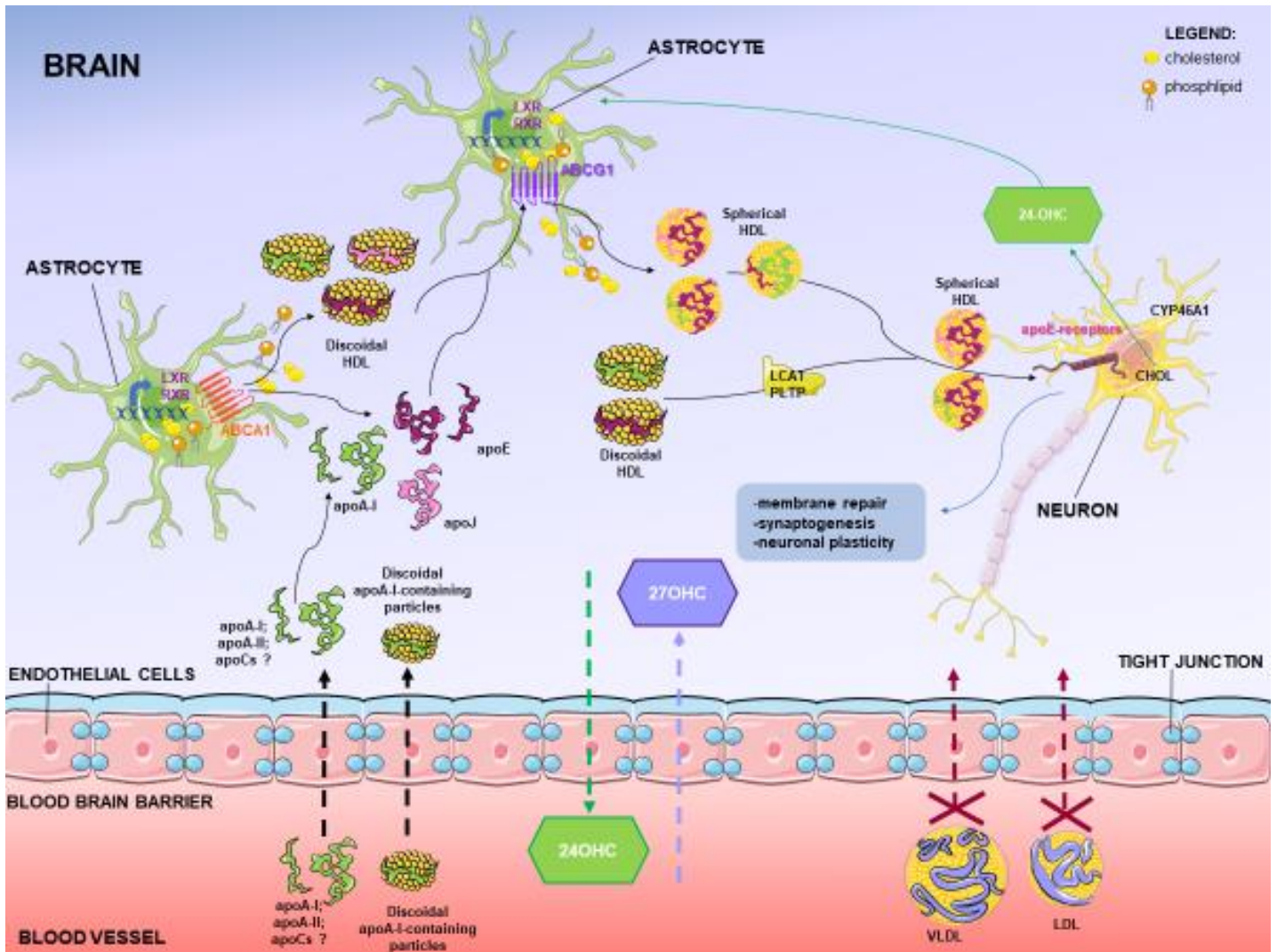
1 (LCAT), a soluble protein that catalyzes the conversion of unesterified cholesterol and
2 phosphatidylcholine to cholesteryl esters and lysophosphatidylcholine on circulating lipoproteins
3 [53]. LCAT, besides liver and testes, is also synthesized in the brain, suggesting a crucial role of this
4 enzyme in the maturation of brain lipoproteins, although CSF LCAT concentration is very low and
5 approximately 5% of the plasma once [17]. The primary producers of active LCAT in the brain are
6 astrocytes, and astrocyte-derived LCAT is the only enzyme able to esterify cholesterol on nascent
7 discoidal particles in the brain [54]. ApoE is the major LCAT activator in the CNS and both ABCA1
8 and apoE are required to generate glial particles substrate for this enzyme [54]. Thanks to its
9 esterifying activity, LCAT promotes the maturation of glial-derived nascent discoidal apoE-
10 containing particles into mature spherical ones (Figure 1).

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

22 23 *2.3. HDL-mediated delivery of cholesterol to neurons*

24 Once reached the completed maturation, brain HDL particles can finally deliver cholesterol to
25 neurons through the interaction with specific lipoprotein receptors, including the low-density
26 lipoprotein receptor (LDLR), the very low-density lipoprotein receptor (VLDLR), the apoE receptor
27 2 (apoER2) and the low-density lipoprotein receptor-related protein 1 (LRP1) (Figure 1) [9, 57]. This
28 process seems essential for the supply of cholesterol to neurons to exploit their physiological
29 functions, such as synaptogenesis and repairing of damaged membranes. In fact, the deletion of the
30 *Ldlr* gene in mice significantly increases apoE levels in the brain parenchyma and CSF, as a clear
31 consequence of an impaired brain HDL internalization by neurons [58]. Similarly, conditional
32 deletion of the *Lrp1* gene in mouse forebrain neurons increases apoE levels [59], suggesting that both
33 receptors are involved in the internalization of HDL-apoE secreted by astrocytes. The apoE receptors
34 show different binding affinity to apoE and lipidated apoE; in particular, nascent lipoprotein particles

1 secreted by astrocytes display a higher affinity for LDLR, whereas apoE-enriched lipoprotein
 2 particles and HDL isolated from CSF bind more strongly to LRP1 [60]. The other apoE receptors,
 3 VLDLR and apoER2, are structurally very similar to the LDLR and are also receptors for other
 4 ligands like the neuromodulatory signaling protein reelin, that plays a pivotal role in
 5 neurodevelopment and synaptic functions [61].
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 10 **Fig. 1. Brain cholesterol transport in the CNS.** In astrocytes, the ABCA1 transporter promotes the efflux of PL and
 11 UC to apoE, the major apolipoprotein in the CNS, thus leading to the formation of nascent discoidal lipoproteins. Among
 12 apolipoproteins, apoJ is also produced from astrocytes, while ApoA-I, apoA-II and apoCs are also present in the CNS,
 13 but differently from apoE are plasma-derived thanks to the ability to cross the BBB with an endocytosis process.
 14 In addition, discoidal apoA-I-containing particles may enter the CNS via SR-BI-mediated uptake and others unknown
 15 mechanisms. Discoidal particles can further acquire PL and UC via ABCA1 and ABCG1. Maturation of discoidal
 16 particles into spherical-HDL involves the activity of remodeling enzymes like LCAT, and lipid transfer proteins, such as
 17 PLTP. These newly generated lipoproteins can be finally uptaken by neurons through the binding of apoE to apoE-
 18 receptors belonging to the LDLR family. In neurons, cholesterol overload is handled by the conversion in oxysterols,
 19 mainly 24-hydroxycholesterol (OHC) that plays a significant regulatory role. 24-OHC is produced by CYP46A1 and it
 20 upregulates ABCA1 expression via activation of LXR. 24-OHC can also cross the BBB and be found in plasma. On the
 21 contrary, 27-OHC is produced by peripheral tissues but there is a net flux from circulation to the brain., through the BBB.

1 ABCA1: ATP-binding cassette transporter A1, ABCG1: ATP-binding cassette transporter G1; apoA-I: apolipoprotein A-
2 I; apoA-II: apolipoprotein A-II; apoCs: apolipoprotein C; apoE: apolipoprotein E; BBB: blood-brain barrier; CETP:
3 cholesteryl ester transfer protein; CNS: central nervous system; LDLRs: LDL receptor family receptors; LCAT:
4 lecithin:cholesterol:acyltransferase; LXR: liver X receptor; PL: phospholipids; PLTP: phospholipid transfer protein;
5 RXR: retinoid X receptor; SR-BI: scavenger receptor BI; UC: unesterified cholesterol; 24-OHC: 24S-hydroxycholesterol;
6 27-OHC: 27-hydroxycholesterol

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13 3. Lipoproteins and apolipoproteins BBB crossing

14 The emerging consistent relationship between plasma HDL-cholesterol (HDL-c) levels and
15 neurodegenerative disorders (see section 4.1) raises the question of whether and how plasma
16 cholesterol metabolism and transport could influence brain cholesterol homeostasis. Brain cholesterol
17 metabolism and transport are isolated from the peripheral circulation by the BBB and the blood-
18 cerebrospinal fluid barrier (BCSFB) [17, 62, 63]. Despite CNS can produce cholesterol by *de novo*
19 synthesis, as mentioned above, a certain amount of cholesterol derived from plasma can be delivered
20 to the brain and eventually influence the CNS homeostasis. A possible source of cholesterol in the
21 brain are oxysterols, side-chain oxidized sterols whose physical properties allow to pass lipophilic
22 phospholipid-containing membranes up to three orders of magnitude faster than cholesterol itself
23 [64], so that they are transferred through the BBB and provide a flux of cholesterol-derived molecules
24 in and out the CNS [65]. 27-hydroxycholesterol (27-OHC) is the major oxysterol present in the
25 circulation, it is formed by almost all cells in the body and it's able to cross the BBB from the
26 periphery to CNS [65]. On the opposite, brain cholesterol can be removed from the brain after
27 conversion into 24S-hydroxycholesterol (24-OHC) and subsequent diffusion over the BBB [65]
28 (Figure 1).

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

34 3.1. Apolipoprotein A-I

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

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

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

27

28 3.2. Apolipoprotein A-II

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

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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

1 emerged from a recent meta-analysis, but only in the subgroup of subjects aged under 70 years [102].
2 Notably, Merched et al. suggested that higher plasma levels of apoA-I are directly correlated with an
3 increased Mini-Mental State Examination score, a parameter used to evaluate cognitive function, and
4 a lower risk of developing AD [103]. In contrast, other studies either failed to find a relationship [104,
5 105], or identified a positive correlation between HDL-c and AD severity [106]. Among the former,
6 a population-based cohort study including more than 9000 individuals did not show an association of
7 plasma HDL-c with incidence of dementia [107].

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

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

24

25 *4.2. Brain HDL*

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

31

32 *4.2.1. HDL biogenesis*

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

1 interaction with specific membrane transporters, such as ABCA1 and ABCG1 (Figure 1). The
2 relevance of ABCA1 in AD is highlighted by several findings, including the results of human genetic
3 studies showing that loss-of-function mutations in *ABCA1* are associated with increased AD risk
4 [115]. Supporting this evidence, the most powerful GWAS study to date identified *ABCA1* among
5 genes associated with the risk of AD and AD-associated dementia [116]. Mechanistically, *ABCA1*
6 deficiency is associated to lower brain apoE levels and lipidation, resulting in increased brain
7 parenchyma A β deposition [48, 117, 118], while its overexpression leads to amyloid burden reduction
8 [119], as observed in pre-clinical models.

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

1 All the above data point to the importance of defective apoE function. Concerning the CSF apoE
2 levels, a meta-analysis of 24 studies evaluating the potential association with AD did not evidence
3 significant differences compared to controls in all studies analyzed, but lower apoE concentration
4 was found in the subgroup of studies with the biggest sample size [137]. At the same manner, a more
5 recent study did not report any difference between AD and controls in terms of CSF apoE levels
6 [138].

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

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

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

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

13

14 4.2.2. HDL remodeling

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

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

30 Some evidence suggests that also the remodeling protein CETP seems to be involved in AD
31 pathogenesis. Indeed, some single-nucleotide polymorphisms (SNP) in the *CETP* gene are associated
32 with a lower rate of memory decline and lower risk of incidence of dementia, including AD [169,
33 170], while other polymorphisms do not [171]. Interestingly, specific *CETP* polymorphisms are able
34 to influence AD in an apoE-dependent manner [172] and a specific *CETP* variant demonstrated to

1 mitigate the deleterious effects of apoE4 on memory decline in older adults [173], clearly suggesting
2 a mechanistic link. To the best of our knowledge, no data are available on the CSF CETP levels or
3 activity in AD patients.

4 5 4.2.3. HDL-mediated delivery of cholesterol to neurons

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

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

1 individuals bearing the apoE4 isoform show a breakdown of the BBB [194], suggesting increased
2 permeability and facilitated crossing of PCSK9, and possibly explaining higher concentration in the
3 brain. Despite this evidence, genetic analyses evaluating the link between PCSK9 and AD has brought
4 to inconsistent results. On one hand, an association between the presence of specific *PCSK9* SNPs
5 and the risk of AD was observed, although evident only in the female subgroup of the analyzed cohort
6 [193]. On the other hand, loss of function mutations of PCSK9 variants has not been linked to AD
7 [195, 196], still leaving unresolved the involvement of PCSK9 in AD pathogenesis.

8

9 **5. HDL-based therapies in AD**

10 ApoE is the most abundant and well-characterized apolipoprotein in the brain, making it a good
11 pharmacological target. However, as well described in a very recent review [197], completed or
12 ongoing clinical trials studying apoE are still limited, highlighting the lack of therapies currently
13 available directed at this target. ApoE mimetic peptides derived from the receptor-binding or lipid-
14 binding regions of apoE have been developed and tested for neurological diseases including AD. CN-
15 105, a 5 amino acid peptide derived from the polar face of the receptor-binding region of apoE [198],
16 has been tested in a mouse model of AD (APP/PS1/APO-E4TR mice) and shown to be able to reduce
17 amyloid pathology and spatial learning deficits when treatment started in young mice [199],
18 underlying the importance of initiating treatment at the early stages of the disease for achieving
19 beneficial effects. Importantly, CN-105 has advanced to clinical phase 2 for intracerebral hemorrhage
20 (NCT03168581) and postoperative cognitive dysfunction (NCT03802396), raising the possibility of
21 CN-105 as a novel therapeutic agent for AD. A second apoE mimetic peptide, COG1410 (12 amino
22 acids derived from the apoE receptor binding region) exerted positive effects on neurological deficits
23 in early brain injury after experimental subarachnoid hemorrhage [200] and reduced behavioral
24 deficits, plaques and tangles in AD transgenic mice [201]. Recently, the peptide COG112 (34 amino
25 acids) was shown to rescue BBB function following traumatic spinal cord injury in apoE-knockout
26 mice [202]. In addition, both peptides have been shown to ameliorate A β levels, A β plaque burden,
27 tau hyperphosphorylation, and neuroinflammation in AD animal models [203,] but they have not yet
28 been tested in humans.

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

1 facilitate A β clearance, reduce amyloid deposition, and reverse memory deficit in an amyloid mouse
2 model [119, 206]. In this context, the ABCA1 expression inducer bexarotene, approved by FDA for
3 cutaneous T-cell lymphoma, has been tested in phase 1b proof-of-mechanism trial [207] in young
4 (21–49 years) volunteers. Despite the poor penetration in the CNS, bexarotene was able to increase
5 CSF apoE levels by 25%, although it had no effects on CSF A β levels. Moreover, in a proof of
6 concept, double-blind, placebo-controlled clinical trial in 20 patients with moderate AD, bexarotene
7 150 mg twice daily for 4 weeks reduced A β PET burden and increased serum A β 42 levels, but only
8 in *ApoE4* non-carriers [208].

9 In the context of strategies to increase apoE levels, the old lipid-lowering drug probucol has also
10 been tested in a pilot trial in mild-to-moderate sporadic AD; treatment with probucol could increase
11 apoE levels in CSF and decreased both phosphorylated tau 181 and A β ₁₋₄₂ concentrations in CSF
12 [209]. Results from a phase 1/2 clinical trial (NCT02707458) are awaited. Concerning apoE lipidation
13 strategy, the introduction or generation of antibodies against the non-lipidated form of apoE4 could
14 also reduce the related toxic effects. Liao et al. discovered an anti-human apoE antibody, anti-human
15 apoE4 (HAE-4), that specifically recognizes human apoE4 and apoE3 and preferentially binds the
16 non-lipidated, aggregated apoE. HAE-4 by preferentially bounding apoE aggregates reduced A β
17 deposition and accumulation in the brain of APP/PS1-21/APOE4 mice [210].

18 Another potential therapeutic strategy consists in the modulation of the interaction between apoE
19 and A β as this event is thought to stabilize toxic oligomeric and fibrillar A β species present within
20 A β plaques [211]. This strategy has been tested in AD mouse models with both monoclonal anti-
21 apoE antibodies and peptides, e.g. A β mimetics; the obtained results, extensively recently reviewed
22 [197], resulted to be promising for being tested in future trials.

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

28 Gene therapy represents an additional approach in neurodegenerative diseases. Preliminary data
29 using the CRISPR-Cas9 editing technology to switch *apoE* alleles has been successfully tested in
30 neurons and glial cells derived from human-induced pluripotent stem cells [217]. In humans, the
31 effect of raising the expression of *apoE2* and increasing apoE2 levels in *ApoE4* carriers (or even *apoE3*
32 homozygotes) through genetic switching *apoE4* to *apoE2* isoform has been tested in the first
33 ongoing phase 1 clinical trial (NCT03634007). Preclinical data showed favorable effects of the
34 transfer of human *apoE* alleles in mice after the administration of adeno-associated virus type-4, as

1 it increased expression of apoE2 mainly in choroid plexus and ependymal cells leading to an
2 improvement of A β levels after A β plaque deposition [218]. This approach resulted in reduced soluble
3 and insoluble A β levels, an enhanced plaque clearance, and a reduced efflux of A β 40 from the brain
4 to plasma through the BBB. Moreover, a slower plaque growth rate was observed in *apoE2* treated
5 mice as compared to the *apoE4* treated mice [204].

6 Beyond apoE-directed therapies, apoA-I infusion and recombinant HDL represent additional
7 potential therapies for AD [108]. Both overexpression and infusion of human apoA-I have been
8 indeed shown to reduce neuroinflammation, inhibit cerebral amyloid angiopathy, and improve
9 cognitive performance in transgenic mouse models [219]. Despite encouraging data have been
10 obtained in animal models of AD with full-length apolipoproteins [219], whether this approach has
11 any beneficial effect on human cognition has not been investigated yet. In addition, HDL-associated
12 apolipoproteins, including apoA-I, demonstrated a limited penetrance across the BBB [15] while
13 small, orally bioavailable peptides, have many advantages including the more efficient BBB crossing
14 than full-length apolipoproteins. In this respect, the brain permeability of the apoA-I mimetic peptide
15 4F (18 amino acid peptide), estimated to be ~1000-fold greater than apoA-I, has been recently
16 evaluated [220]. Further, in the same study, 4F treatment increased the brain efflux of A β and
17 decreased its brain influx, as evaluated in mice and BBB cell monolayers. Consistently, the oral
18 administration of 4F reduced A β deposition and improved cognitive functions in AD mice models
19 [221], suggesting 4F as a potential therapeutic strategy to reduce brain amyloid accumulation in
20 cerebral amyloid angiopathy and AD [220].

21

22 **6. Cholesterol metabolism alterations in other neurodegenerative disorders**

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

28

29 *6.1. Parkinson's disease*

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

1 the pathogenesis of PD, but no relationship with HDL-c has been highlighted [224]. Also in the large
2 population-based AMORIS study, it has been found a consistent association between a higher level
3 of total and LDL cholesterol, TG and apoB, but not HDL-c, with a lower risk of developing PD [225].
4 On the contrary, Cassani et al. found that HDL-c levels and the total/HDL cholesterol ratio were
5 favorably associated with the duration of disease, contributing to cardiometabolic protection in PD
6 [226], while Li et al. found that high HDL-c levels may be correlated with PD onset and progression
7 [227]. Interestingly, it has been demonstrated that α -synuclein, the pathological protein hallmark of
8 PD, is able to form HDL *in vitro*, but their presence and role *in vivo* remains to be demonstrated [228].

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

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

23

24 6.2. Huntington's disease

25 Huntington's disease (HD) is an inherited neurodegenerative disease characterized by progressive
26 dementia, involuntary body movements, and psychiatric and cognitive abnormalities [240]. HD is
27 caused by a dominant genetic mutation in the huntingtin (HTT), a ubiquitous protein with
28 physiological beneficial activities for the brain and neurons, majorly located in the striatum and cortex
29 [241]. Findings reported that the brain cholesterol precursor lathosterol and cholesterol levels are
30 markedly reduced in HD mice and cholesterol reduction exacerbates with the progressive increase of
31 CAG repetition in *huntingtin* gene in mice [242]. This disturbance seems to be associated with a
32 specific action of mutant HTT on sterol-regulatory-element binding proteins (SREBPs) and on its
33 target genes, whose decreased transcription resulted in reduced brain cholesterol levels [243]. Primary
34 astrocytes bearing mutant HTT showed a decreased mRNA levels of *ABCA1* and *apoE*; as a

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

13

14 6.3. Frontotemporal dementia

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

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

26

1 Table 1. Plasma and CSF HDL alterations in AD and other neurodegenerative disorders
 2

Disease	Main HDL alterations	References
Alzheimer's disease (AD)	↓↓ plasma HDL-c ↓↓ plasma HDL cholesterol efflux capacity ↓↓ CSF cholesterol efflux capacity ↓↓ ABCA1 in CNS ↓↓ ABCA7 in CNS ↓↓ CSF apoA-I ↓↓ or ≈ CSF apoE ↓↓ CSF LCAT activity ↓↓ CSF PLTP activity ↑↑ CSF HDL susceptibility to oxidation	[93-98, 102] [109, 110] [154, 158] [48, 115-119] [120-123] [149-153] [137, 138] [28, 160] [163] [139-142]
Parkinson's disease (PD)	↓↓ apoA-I in plasma and CSF ↑↑ apoE and apoJ in CSF ↑↑ CSF HDL susceptibility to oxidation Polymorphism in PON1 alters genetic susceptibility to PD apoE4 is associated to an early onset	[229, 230] [238] [239] [232] [233-235]
Huntington's disease (HD)	↓↓ cholesterol production in CNS ↓↓ SREBP transcription ↓↓ apoE and ABCA1 mRNA levels in CSF ↓↓ 24-OHC in the brain	[242] [243] [242] [242, 245]
Frontotemporal dementia (FTD)	↓↓ plasma apoA-I and apoA-II ↓↓ plasma HDL-c	[249] [251]

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1 **7. Conclusions and perspectives**

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

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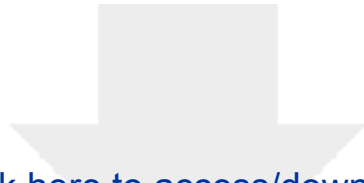
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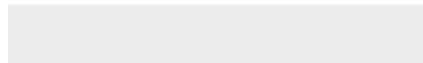
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CRediT author statement

Marta Turri: Writing-Original draft preparation. Cinzia Marchi: Writing-Original draft preparation. Maria Pia Adorni: Writing-Original draft preparation, Reviewing and Editing; Laura Calabresi: Conceptualization, Writing- Reviewing and Editing. Francesca Zimetti: Conceptualization, Writing- Reviewing and Editing.