HDL and cholesterol handling in the brain

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Cholesterol is an essential component of both the peripheral nervous system and central nervous system (CNS) of mammals. Brain cholesterol is synthesized in situ by astrocytes and oligodendrocytes and is almost completely isolated from other pools of cholesterol in the body, but a small fraction can be taken up from the circulation as 27-hydroxycholesterol, or via the scavenger receptor class B type I. Glial cells synthesize native high-density lipoprotein (HDL)-like particles, which are remodelled by enzymes and lipid transfer proteins, presumably as it occurs in plasma. The major apolipoprotein constituent of HDL in the CNS is apolipoprotein E, which is produced by astrocytes and microglia. Apolipoprotein A-I, the major protein component of plasma HDL, is not synthesized in the CNS, but can enter and become a component of CNS lipoproteins. Low HDL-C levels have been shown to be associated with cognitive impairment and various neurodegenerative diseases. On the contrary, no clear association with brain disorders has been shown in genetic HDL defects, with the exception of Tangier disease. Mutations in a wide variety of lipid handling genes can result in human diseases, often with a neuronal phenotype caused by dysfunctional intracellular lipid trafficking.

1. Brain cholesterol

The brain is the most cholesterol-rich organ in the body and contains almost 25% of the total amount.1 The majority (70–80%) of this cholesterol is present in myelin, where it fulfils a critical insulating role.2 Brain cholesterol synthesis appears to be regulated by mechanisms similar to those observed outside the brain, with hydroxyl-methyl-glutaryl CoA reductase (HMGCoAR) being the most important regulatory enzyme. Brain cholesterol synthesis in both neurons and glial cells is highest during embryogenesis and childhood when myelination is maximal. In the adult, fully differentiated neurons progressively lose their cholesterol biosynthetic capability and rely on cholesterol-containing lipoproteins secreted by glial cells for ongoing needs for maintenance and repair of damaged membranes.4

The brain is largely separated from peripheral organs by multiple barrier systems. The core of the blood–brain barrier (BBB) are tight junctions formed by cerebrovascular endothelial cells that greatly restrict entry and egress of many blood components into the brain.5 A second barrier system, the blood–cerebrospinal fluid barrier (BCSFB), is formed by cuboidal epithelial cells of the choroid plexus as cerebral origin.9 Although cholesterol cannot cross the BBB and BCSFB, side-chain oxidized oxysterols easily traverse biological membranes and thus can also cross these barriers.3 24S-hydroxycholesterol (24S-OHC) is formed in the brain by CYP46A1, which is exclusively located in neuronal cells in the brain and in the retina, and can then flux 24S-OHC from the brain into the circulation.9 The plasma levels of 24S-OHC thus reflect the number of metabolically active neurons in the brain, and indeed its plasma levels are increased in neurodegenerative diseases.10 A second oxysterol, 27-hydroxycholesterol (27-OHC), has similar properties to 24S-OHC and is also able to pass the BBB.27-OHC is produced by all cells in the body by CYP27A1 and is quantitatively the most important oxysterol in the circulation. Production of 27-OHC in the brain is very low, and most of its presence in the brain and CSF reflects its extracerebral origin.9

A second possible mechanism for lipid movement between the brain and periphery is via the scavenger receptor class B type I (SR-BI), a multiligand receptor that promotes the bidirectional flux of cholesterol between lipoproteins and cellular membranes. SR-BI plays a major role in high-density lipoprotein (HDL) metabolism by mediating selective uptake of HDL cholesterol by hepatocytes.11 In the brain, SR-BI is present on the membrane of brain capillary endothelial cells, where it is reported to mediate the selective uptake of cholesterol from the periphery into the brain. This mechanism may be critical in the normal exchange of cholesterol between the brain and periphery. In addition, SR-BI can also mediate the uptake of HDL cholesterol by astrocytes and oligodendrocytes, which are the main astrocyte type and oligodendrocyte type in the brain, respectively.12

Keywords High-density lipoproteins • Apolipoprotein E • Central nervous system • Alzheimer disease • Parkinson disease

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plasma HDL and LDL. SR-BI can also allow the uptake of vitamin E that may play an important role in preventing oxidative stress and protecting brain cells against neurodegeneration.

2. Lipoprotein synthesis and metabolism in the brain

Due to its accessibility, most investigations on the central nervous system (CNS) lipoproteins have been conducted on CSF, which is a clear, watery liquid that bathes the brain and spinal cord and is produced by the choroid plexus and, to a lesser extent, by ependymal cells that line the brain’s ventricles. CSF lipoproteins have a similar size and density to plasma HDL and they have been defined as ‘HDL-like particles’. These particles are characterized by a wide size range (10–22 nm) and various lipid–protein compositions, with a preponderance of 13–20 nm apoE/apoA-I-containing lipoproteins (Table 1). Other apolipoproteins found in CSF are apoJ, apoA-II, apoA-IV, apoD, and apoH. Although apoA-I is the most important constituent of plasma HDL, it is not synthesized in the CNS. It has been demonstrated that apoA-I found in CSF is derived from blood HDL. Small HDL particles may enter the CNS via SR-BI-mediated uptake and transcytosis, or pathways that remain to be identified. Generally speaking, most of the CSF lipoprotein component exists at concentrations roughly 1–10% of their levels in plasma. It is important to note, however, that while CSF is in communication with the interstitial fluid (ISF) of the brain parenchyma, these two fluids are not homogenous and CSF composition therefore cannot be assumed to be representative of ISF. Very little is known about lipoprotein composition in the ISF compared with CSF, as well as how plasma-derived CSF lipoproteins gain access to the brain.

2.1 Brain apolipoproteins

2.1.1 ApoE

The major apolipoprotein constituent of HDL-like particles in the CNS is apoE. The absence of apoE has a subtle impact on brain development as apoE knock-out (KO) mice show behavioural and neurological abnormalities, and impaired synapse and dendritic arborizations especially at later ages. Brain and CSF apoE content and lipidation are regulated by the ABCA1 transporter, as shown by the reduced apoE levels detected in CSF and in brain tissue from ABCA1-deficient mice. ApoE is a 34 kDa glycoprotein that in humans is expressed in three different isoforms, apoE2, E3, and E4. The three isoforms are determined by single amino acid substitutions at residue 158 and Arg112 (E2: Arg158Cys; E4: Arg112Cys). Under normal physiological conditions, neurons do not produce apoE and most of the CNS apoE is synthesized by astrocytes and microglia. The main function of apoE in the CNS is the lipid transport between neurons and glial cells, and apoE has key roles in the regulation of lipid metabolism in both normal and pathological conditions. Recent data suggest that apolipoproteins such as apoE and apoJ may be overexpressed after brain injury, acting as modulators of the inflammatory response.

Evidence is accumulating that distinct apoE isoforms have different molecular and functional properties. The apoE e4 allele is strongly associated with the sporadic late-onset Alzheimer disease (AD). The mechanisms responsible for this association are not entirely known. Early data suggested that apoE may play an important role in binding β-amyloid (Aβ), thus influencing its deposition in amyloid plaques. ApoE isoforms show different Aβ-binding capacity (E2 > E3 > E4) and this ability seems to be correlated with the efficiency in promoting Aβ clearance. Interestingly, apoE2 and E3 isoforms are more easily lipidated compared with E4, and the lipidation degree is positively associated with its affinity for soluble Aβ. However, a recent study using microdialysis to sample the soluble apoE and Aβ pools in brain ISF demonstrated that very little apoE associates with Aβ in vivo, and that the mechanism by which apoE affects Aβ clearance may be due to a competition between apoE and Aβ for the low-density lipoprotein receptor-related protein (LRP), which regulates egress of Aβ out of the brain.

2.1.2 ApoJ

Human apoJ is a 75–80 kDa glycoprotein found in all biological fluids and expressed in several tissues such as testis, prostate, and brain. Its function in plasma has not been completely clarified, but it is involved in many and various biological and pathological processes, including complement inhibition, apoptosis, and cancer. In the CNS, apoJ is mainly synthesized by astrocytes. As in the whole body, apoJ in the brain is believed to have several functions. ApoJ expression is up-regulated under conditions of neuronal damage including inflammation, neurodegeneration, and senescence. ApoJ also complexes with complement components modulating the defence mechanisms in stress conditions and may play a role in regulating Aβ clearance from the CNS as apoJ-containing lipoproteins can bind Aβ and promote its efflux through the BBB via the interaction with LRP-2.

2.1.3 ApoD

ApoD, a lipocalin family member, is a 29 kDa apolipoprotein. It is a component of plasma HDL and was found in the CNS where it presumably

<table>
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<th>Table 1 Characteristics of HDL in plasma and CNS</th>
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<td><strong>Plasma</strong></td>
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PL: phospholipids; UC: unesterified cholesterol; CE: cholesteryl esters.
functions as a lipid transporter and as an antioxidant factor. Its affinity for cholesterol is low compared with other apolipoproteins, but it binds other lipids such as arachidonic acid, progesterone, and pregnenolone. It is synthesized by astrocytes and oligodendrocytes and, as observed for apoJ and apoE, apoD mRNA and protein levels are markedly increased in neurodegenerative diseases and after neuronal injury.

2.2 Lipoprotein secretion and metabolism in the brain

The mechanism underlying the formation of nascent lipoproteins in the brain is not completely understood. Among glial cells, astrocytes are responsible for the synthesis of the majority of lipoproteins found in brain tissue and CSF (Figure 1). Cultured astrocytes synthesize discoidal lipoproteins (8–12 nm) containing phospholipids, unesterified cholesterol, and apoE or apoJ.

Several ATP-binding cassette (ABC) transporters, which are transmembrane proteins that utilize ATP hydrolysis to fuel transport of a variety of substances across biological membranes, are expressed in the CNS and are involved in apoE-containing lipoprotein secretion and lipidation (Figure 1). ABCA1 is expressed ubiquitously and interacts with lipid-free or poorly-lipidated apoE. ABCA1 in astrocytes is responsible for the secretion of newly lipidated nascent discoidal HDL-like particles. ABCA1 may also play a critical role in the removal of excess cholesterol from neurons, as shown in vitro using spherical reconstituted apoE-containing particles, as well as in microglia. A further incorporation of cholesterol into lipoproteins may be mediated by ABCG1 and ABCG4. ABCG1 in the CNS is expressed in microglia, oligodendrocytes, neurons, and astrocytes, whereas ABCG4 seems to be expressed preferentially in neurons. ABCA8 is expressed in several regions of the adult human brain with significantly higher expression in oligodendrocyte-enriched white matter compared with grey matter.

Most of the lipoproteins found in the CSF are spherical and have different sizes than nascent discoidal HDL secreted from astrocytes, supporting the hypothesis that brain lipoproteins undergo extensive modification after secretion from glial cells, analogous to plasma HDL maturation (Figure 1). Less is known about CNS lipoprotein maturation compared with plasma, but many remodelling enzymes and lipid transfer proteins are expressed in the brain. Lecithin:cholesterol acyltransferase (LCAT) is the only enzyme responsible for the production of cholesteryl and oxysterol esters in plasma and other fluids; it is

![Figure 1](https://academic.oup.com/cardiovascres/article-abstract/103/3/405/2931058) Production and interconversion of HDL particles in CNS and plasma. In brain parenchyma, ABCA1 transporter is expressed in neurons and astrocytes where it promotes the efflux of PL and UC to glia-derived apoE, thus leading to the formation of nascent lipoproteins. Moreover, discoidal apoA-I-containing HDL particles may enter the CNS via SR-BI-mediated uptake and other unknown mechanisms. Discoidal particles can further acquire PL and UC via ABCA1 and ABCG1. Maturation of discoidal particles into spherical lipoproteins likely involves the activity of LCAT, CETP, and PLTP, similar to what happens in plasma. Newly generated particles can be finally uptake by neurons or astrocytes through the binding of apoE to LDLR family receptors. ABCA1: ATP-binding cassette transporter A1, ABCG1: ATP-binding cassette transporter G1; BBB: blood–brain barrier; CETP: cholesteryl ester transfer protein; CNS: central nervous system; EL: endothelial lipase; HL: hepatic lipase; LDLRs: LDL receptor family receptors; LCAT: lecithin:cholesterol acyltransferase; PL: phospholipids; PLTP: phospholipid transfer protein; UC: unesterified cholesterol.
synthesized mainly in the liver, but it is also present in brain, where it is produced by astrocytes.\textsuperscript{44} LCAT catalyses the maturation of small nascent discoidal HDL into larger spherical HDL particles.\textsuperscript{22} In humans, LCAT is found in CSF at levels corresponding to \(\approx 5\%\) of that of plasma LCAT.\textsuperscript{22} The major activator of LCAT in the circulation is apolipoprotein A-I, which is found in the CSF at only 0.3% of its levels in plasma.\textsuperscript{2} ApoE may therefore act as a major activator of LCAT in the CNS.\textsuperscript{44} As astroglial-derived apoE-containing lipoproteins are LCAT substrates, LCAT likely plays a role in the maturation of apoE-containing particles in the brain. Cholesterol ester transfer protein (CETP) and phospholipid transfer protein (PLTP) also contribute to HDL remodelling in plasma. An active CETP enzyme has been identified in human CSF and in conditioned media from human neuroblastoma and neuroglioma cells, where it contributes to the transfer of lipids between lipoproteins.\textsuperscript{45} Whether a single-nucleotide polymorphism (SNP) in the CETP gene is associated with a lower rate of cognitive impairment is not clear, as some studies support an association but others do not.\textsuperscript{46–48} PLTP is expressed in cerebrovascular endothelial cells\textsuperscript{46} and PLTP deficiency has been associated with reduced BBB integrity and increased susceptibility to oxidative stress in animal models;\textsuperscript{50} moreover, high levels of PLTP have been detected in the CSF of AD subjects,\textsuperscript{51} providing additional support for dysregulation of brain lipid homeostasis in AD.

Lipoprotein shape, size, and lipid and protein composition modulate the particles’ affinity for various lipoprotein receptors that can be differentially expressed on the various cell types in the CNS, and the presence of a particular receptor on a specific cell type determines where and how the lipid transfer will occur.

\subsection*{2.3 Lipoprotein receptors}

\subsubsection*{2.3.1 LRP1}

The LRP1 is a large endocytic receptor first isolated in the liver, but expressed in many tissues. It binds different ligands, including apoE-containing lipoproteins.\textsuperscript{52} In the brain, LRP1 has been found in both neurons and astrocytes, where it plays a major role in lipid homeostasis and intracellular signalling.\textsuperscript{53} LRP1 indeed interacts with the postsynaptic density protein PSD-95, a protein complex that regulates ion influx into neurons, thus modulating the neural response to excitatory molecules such as NMDA.\textsuperscript{54,55} LRP1 also plays key roles in the clearance of A\textsubscript{β} peptides.\textsuperscript{56} As deletion of the LRP1 gene leads to the embryonic death, most of the studies on LRP1 function in the brain are performed on cells or in conditional forebrain-specific KO mice. In these models, LRP1 deletion leads to a reduction in cholesterol and triglyceride levels.\textsuperscript{57} These lipid abnormalities are associated with age-dependent structural defects in cortex and hippocampus, including synapse and dendritic spine loss and neuronal cell degeneration.\textsuperscript{58} Moreover, mice showed an abnormal behavioural phenotype with motor dysfunction and memory deficit.\textsuperscript{58}

\subsubsection*{2.3.2 Low-density lipoprotein receptor}

The low-density lipoprotein receptor (LDLR) is the prototype member of the LDLR family that includes \(> 10\) receptors. It is localized on the outer cellular membrane of several peripheral cells and its quantitatively most relevant action is the internalization of apoB- and apoE-containing lipoproteins, thus removing cholesterol and cholesteryl esters from the circulation. The LDLR is expressed in brain capillary endothelial cells and astrocytes, where it is believed to play a role in cholesterol and A\textsubscript{β} clearance.\textsuperscript{59} LDLR KO mice show learning and memory deficits,\textsuperscript{59} and intriguingly, cholesterol supplementation worsens the cognitive function, which may be through the accumulation of oxidative products and increased oxidative stress.\textsuperscript{60,61}

\subsection*{2.3.3 VLDLR and ApoER2}

The very low-density lipoprotein receptor (VLDLR) and the apoE receptor 2 (apoER2) are structurally very similar to the LDLR. In the periphery, VLDLR and apoER2 bind triglyceride-rich apoE-containing particles such as VLDL and intermediate density lipoproteins, but they cannot bind LDL. In the brain, both receptors are involved in reelin signalling,\textsuperscript{62} which regulates the migration of neurons from glial fibres to the developing cortical plate. As a consequence, VLDLR/apolipoprotein E double KO mice show defects in the lamination of cerebral cortex.\textsuperscript{63} A selective deficiency of either VLDLR or apoER2 leads to a subtle phenotype consisting in contextual fear conditioning and long-term potentiation deficits.\textsuperscript{64} In humans, mutations in the VLDLR are the cause of rare neurodevelopmental and psychiatric disorders, such as autosomal recessive cerebellar ataxia with mental retardation (dysequilibrium syndrome) and cerebellar hypoplasia with quadrapedal locomotion.\textsuperscript{65}

\section*{3. Low HDL and mental disorders}

Despite the almost total inability of circulating lipoproteins to cross the BBB and CSF, experimental data suggest that small HDL particles can enter the brain through transcytosis or selective uptake.\textsuperscript{12} This possibility raises the question of whether changes in plasma HDL cholesterol levels could influence brain cholesterol homeostasis and function.

The relationship between HDL plasma levels and dementia has been the focus of considerable study. Although most of the studies were conducted in elderly subjects who have the presence of several dementia risk factors, low HDL-C levels are often associated with cognitive impairment.\textsuperscript{66–68} Data from the Whitehall II Study confirmed that, in middle-aged adults, low HDL-C was associated with impaired verbal memory and, interestingly, further reductions in HDL levels was associated with a consequent cognitive decline at 5-year follow up.\textsuperscript{69} In contrast, high HDL-C levels seem to reduce dementia risk.\textsuperscript{70} The mechanism underlying this association is not understood, but it may involve different pathogenic pathways. HDLL displays both antioxidant and anti-inflammatory properties\textsuperscript{71} that could affect the inflammatory response in the brain. HDL-mediated reverse cholesterol transport could also reduce atherosclerotic burden in brain vessels such as the Circle of Willis, thus limiting the developing of vascular dementia. HDL also has potent beneficial effects on endothelial function\textsuperscript{72} and as the brain contains \(>25\%\) of the body’s total vascular network, HDL may also affect cerebrovascular function that will in turn influence neuronal activity.\textsuperscript{73}

HDL plasma levels have also been associated with other neurodegenerative diseases such as multiple sclerosis (MS).\textsuperscript{74} Patients in the acute phase of MS have been reported to have lower HDL-C levels compared with those in the remission phase, and they show a higher probability of developing acute inflammatory lesions (assessed by MRI).\textsuperscript{74–76} The link between HDL and MS may reflect the ability of HDL to modulate the innate immune system.\textsuperscript{74,77} For example, HDL promotes the generation of M2 polarized macrophages that exhibit a reduced proinflammatory phenotype.\textsuperscript{77,78} Moreover, HDL inhibits cytokine-induced expression of adhesion molecules in endothelial cells.\textsuperscript{72} All these properties may contribute to the suppression of the immune system, thus preventing the relapses of MS. Abnormalities in HDL-C levels have been furthermore reported in patients with psychiatric disorders.\textsuperscript{79} Indeed, a reduction of CSF and serum apoA-I concentration was observed in schizophrenia patients\textsuperscript{80} and low HDL-C was observed in subjects affected by mood disorders.\textsuperscript{81}
3.1 Genetic HDL defects
Major causes of genetic HDL defects are mutations in three genes: APOA1, ABCA1, and LCAT.82

3.1.1 ApoA-I deficiency
Several mutations in the APOA-I gene have been associated with low HDL-C levels.83 These mutations are mainly located in the central region of apoA-I, which has been shown to be responsible for LCAT activation.84 Some A-I variants are instead associated with amyloidosis and are often located in the N-terminal region of the protein.85 This pathology develops through a progressive deposition of apoA-I fragments that accumulate in various organs including the peripheral nerves. There is no evidence of an association between apoA-I deficiency and AD in humans. In AD mice, apoA-I deficiency causes a marked decrease in total plasma cholesterol levels, but does not alter total or parenchymal Aβ deposition; however, it does increase cerebrovascular amyloid accumulation exacerbating the cognitive impairment.86

3.1.2 LCAT deficiency
LCAT deficiency syndromes are rare genetic disorders with an autosomal recessive mode of inheritance.16 Mutations in the LCAT gene lead to an impaired (fish-eye disease, FED) or completely defective cholesterol esterification (familial LCAT deficiency, FLD).86 Since LCAT is crucial in HDL particle maturation, in LCAT-deficient subjects HDL-C levels are very low. Main clinical manifestations in FLD cases include corneal opacity, anaemia, and renal disease that eventually progresses to end-stage renal disease.86 FED cases do not have clinical manifestations of the disease except for the corneal opacity.86 To date, no neurological or psychiatric characterization of LCAT-deficient subjects has been conducted, but a reduction in LCAT activity has been observed in CSF from AD patients.16

3.1.3 ABCA1 deficiency
In humans, more than 100 mutations in ABCA1 gene have been identified, and they are related to a variable clinical phenotype.87 Functional mutations in both ABCA1 alleles cause Tangier disease (TD), characterized by very low or virtually absent HDL-C in plasma and by cholesterol esters accumulation in different tissues such as tonsils, spleen, liver, lymph nodes and, notably, peripheral nerves. The major neurological syndrome observed in TD patients is a peripheral neuropathy, which is caused by the accumulation of cholesterol esters in Schwann cells.88 Furthermore, TD patients have been reported to exhibit a syringomyelia-like syndrome, suggesting that the CNS may also be involved.88

The association between ABCA1 activity and AD is still controversial. In some isolated cases, subjects with rare ABCA1 mutations exhibited severe dementia and amyloid angiopathy. Investigations about the association of common SNPs in human ABCA1 gene and the risk of AD often led to conflicting results.

ABCA1-/- mice clearly show impaired apoA-I and apoE levels in plasma and brain tissue.89 Furthermore, CNS apolipoproteins in ABCA1-/- mice are less lipidsated and probably less functional in promoting Aβ clearance.89,90 This hypothesis is corroborated by experiments conducted on AD mice-overexpressing ABCA1, where a reduction of amyloid burden has been observed.91

4. Lipids and neurodegenerative disease
Mutations in a wide variety of lipid handling genes can result in human disease, often with a neuronal phenotype caused by dysfunctional intracellular lipid trafficking. For example, Smith–Lemli–Opitz syndrome (SLOS) is an autosomal recessive inborn error of cholesterol synthesis caused by a mutation in the enzyme 7-dehydrocholesterol reductase. SLOS is associated with a broad spectrum of effects, ranging from mild intellectual disability and behavioural problems to lethal malformations.92 The incidence of SLOS ranges between 1 in 10 000–60 000 persons.93 Gaucher’s disease, Niemann-Pick disease, Fabry’s disease, Farber’s disease, Tay-Sachs’s disease, Sandhoff’s disease, Krabbe disease, metachromatic leuokodystrophy, and Wolman’s disease are all examples of lipid storage diseases, which are inherited metabolic disorders in which the accumulation of various lipids leads to detrimental effects in many tissues including the CNS, the peripheral nervous system (PNS), liver, spleen, and bone marrow. That most lipid storage diseases can affect the nervous system indicates the narrow tolerance for dysfunctional lipid homeostasis in both the CNS and PNS. For the purposes of this review, however, we will focus our discussion on recent developments in understanding how lipid metabolism affects both common and rare neurodegenerative disease.

4.1 Alzheimer disease
AD is the most common form of dementia in the elderly and is characterized by progressive memory loss. Age is the largest risk factor, as in 8 persons over age 65 years and nearly 2 persons over age 85 years currently have AD. The most common genetic risk factor for late-onset AD is apoE. Inheritance of apoE4 increases AD risk and decreases AD age of onset in a gene-dose dependent manner,24,29 and accounts for ~25% of heritability. ABCA1 has been shown to play key roles in apoE lipiddation and Aβ clearance in AD.90,91,94

Several recent genome wide association studies have shown several other genes involved in lipid metabolism to potentially contribute to AD risk. The International Genomics of Alzheimer’s Project (http://www.alzforum.org/newsconference-coverage/pooled-gwas-reveals-new-alzheimers-genes-and-pathways, 1 April 2014) pooled genome-wide association study data from four separate studies in a first-stage meta-analysis and identified nearly 12 000 loci with potential association with AD. These candidates were then tested in a new analysis including 11 000 controls and 8500 new cases, from which 20 genes reached statistical significance. Pathway analysis revealed 11 loci to be involved in four broad functional domains: ubiquitination, endocytosis, immunity, and cholesterol metabolism. ApoE, apoJ, ABCA7, and SORL1 are among the notable lipid-related genes.

In addition to the requisite parenchymal amyloid plaques and neurofibrillary tangles that define AD, most of the AD patients also have significant accumulation of aggregation of Aβ within cerebrovascular smooth muscle cells that lead to inflammation, oxidative stress, impaired vasorelaxation and disruption of BBB integrity.95 As capillary loss in the brains of AD subjects can be extensive, increasing attention is being directed to understanding how metabolic factors such as hypertension, cardiovascular disease, Type II diabetes mellitus, and dyslipidaemia have established detrimental effects on blood vessels and also increase the relative risk for AD. Intriguingly, many of these co-morbidities are characterized by low and/or dysfunctional HDL.73
4.2 Huntington disease

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder that selectively targets medium spiny neurons of the caudate and putamen, leading to chorea, progressive cognitive decline, psychiatric problems, and progression to death 15–20 years after clinical onset.96,97 HD is caused by expansion of a trinucleotide repeat of CAG encoding glutamine in the amino terminus of the huntingtin (htt) gene product. HD commonly manifests between age 35–45 years and is inversely related to CAG repeat length. In the normal population, the CAG repeat length is <26, and repeats length of over 40 copies are fully penetrant. Htt is ubiquitously expressed in all tissue and has several reported roles including vesicle transport, endocytosis, transcriptional regulation protein trafficking, postsynaptic signalling, and regulation of apoptosis.98

Mutant htt affects maturation and translocation of sterol regulatory element-binding protein-2 (SREBP-2), a basic helix-loop-helix transcription factor that co-ordinates the expression of many genes involved in cholesterol metabolism.99–101 In cells with low cholesterol levels, SREBP-2 is activated by proteolytic cleavage that releases it from its tethered position at the nuclear envelope and endoplasmic reticulum and allows nuclear entry. Binding to SREBP-2 specific sterol regulatory element DNA sequences induces synthesis of enzymes involved in sterol biosynthesis. In turn, sterols inhibit the cleavage of SREBP-2, thus creating a negative feedback loop to constrain cellular cholesterol levels within a narrow homeostatic range.100 Expanded mutant htt interferes with SREBP-2 maturation and nuclear translocation, thereby reducing expression of several genes in the cholesterol biosynthetic pathways including HMGCoaR, Cyp51, and DHCR7.101–103 In cellular models expressing mutant htt including primary striatal neurons, a reduced ability to respond to cholesterol depletion compromises survival, and primary astrocytes expressing mutant htt secrete less lipidated apoE.101,104 Several HD mouse models show reduced amounts of cholesterol precursors and cholesterol metabolites including 24-OHC in proportion to CAG repeat length, further supporting a relationship between the severity of htt mutations and deficits in cholesterol metabolism.102,104 HD patients also have 24-OHC levels that are reduced proportionally to disease progression, suggesting that disease is associated with a progressive failure of CNS cholesterol metabolism.105,106 Additionally, interference with peroxisome proliferator gamma (PPARγ) co-activator alpha 1 alpha (PGC1α) expression leads to reduced myelin-binding protein expression in oligodendrocytes,107 potently exacerbating the potential for axonal damage. Wild-type htt binds nuclear receptors with established roles in lipid homeostasis including liver X receptor, PPARγ, and Vitamin D receptor, and it is hypothesized that CAG expansion interferes with the ability of htt to interact with these receptors.108 Taken together, htt appears to play a role in cholesterol metabolism and dysregulation of this essential function in the presence of CAG expansion may contribute to HD onset and progression.

4.3 Parkinson disease

Parkinson disease (PD) is the second most common neurodegenerative disease after AD, and like AD, aging is the largest risk factor for PD.109 PD affects ~1% of persons over age 60 years and ~4% of persons over 80 years. PD involves the selective loss of dopamine-producing cells in the substantia nigra, thereby disrupting communication between the substantia nigra and striatum. Thus, the clinical presentation of PD includes motor signs such as tremor, bradykinesia, stiffness, postural instability, and a shuffling gait. Depression, anxiety, and dementia are also common in PD patients. At the neuropathological level, PD brains show accumulation of the presynaptic protein α-synuclein in neuronal perikarya (Lewy bodies) or neuronal processes (Lewy neurites) and may also exhibit accumulation of the microtubule-binding protein tau.110

Mutations in several genes including SNCA (α-synuclein), PARK2 (PD autosomal recessive, juvenile 2), PARK7 (PD autosomal recessive, early onset 7), PINK 1 (PTEN-induces putative kinase), and LRRK2 (leucine-rich repeat kinase 2) have been associated with PD, and a sequence of pathological events whereby deficits in synaptic exocytosis and endocytosis, endosomal trafficking, lysosome-mediated autophagy, and mitochondrial maintenance has been hypothesized to increase susceptibility to PD.111 The most frequently occurring mutations associated with PD risk are within GBA1 gene, which encodes lysosomal β-glucocerebrosidase, an enzyme that hydrolyses the beta-glucosidic linkage in glucocerebrosides to produce the bioactive lipid ceramide. Approximately 5–10% of PD patients have heterozygous GBA1 mutations, which closely mimic idiopathic PD but may present at a younger age and is more frequently complicated by cognitive dysfunction.112 Homozygous GBA1 mutations cause Gaucher disease, a lipid storage disorder characterized by accumulation of glucocerebroside within macrophages.113 How mutant GBA contributes to the pathogenesis of PD remains unknown and both loss of function and toxic gain of function by abnormal β-glucocerebrosidase may be important. However, both in vitro and in vivo evidence support a direct relationship between reduced glucocerebrosidase expression and α-synuclein accumulation in neurons. In cell and animal studies, decreased wild-type glucocerebrosidase leads to α-synuclein accumulation, and increased α-synuclein inhibits glucocerebrosidase function.114–116 In post-mortem brain tissue from symptomatic PD patients with GBA1 mutations, glucocerebrosidase and α-synuclein co-localize in Lewy bodies.117,118 A recent study of PD autopsy samples from patients with and without GBA mutations showed that glucocerebrosidase protein levels and enzyme activity were selectively reduced in the early stages of PD in brain regions with increased α-synuclein levels albeit limited inclusions, whereas GBA1 messenger RNA expression was non-selectively reduced in PD.119 The selective loss of lysosomal glucocerebrosidase was directly related to increased α-synuclein, decreased ceramide, and reduced lysosomal chaperone-mediated autophagy.

4.4 Multiple system atrophy

Cytoplasmic aggregation of α-synuclein can also occur in oligodendrocytes and lead to multiple system atrophy (MSA), a progressive neurodegenerative disease characterized by parkinsonism, ataxia, and autonomic failure.120 MSA affects approximately 4 in 100 000 persons, mostly after age 65 years with an average lifespan of 7–9 years after diagnosis. Oligodendrocytes are the CNS cells responsible for producing myelin, the cholesterol, and sphingolipid-rich membrane that ensheath and insulate axons. In addition to its structural importance, myelin is also known to have a considerable capacity to undergo oxidative phosphorylation, which is hypothesized to generate ATP for use by axons.121 Therefore, decreased myelin function could contribute to axonal degeneration by several mechanisms. In vitro studies show that α-synuclein associates with lipid droplets and phospholipid bilayers, and this association triggers a conformation shift from its normally unfolded random coil state to a stable α-helix conformation.122 In MSA, case–control studies of α-synuclein solubility in autopsy samples have shown increases in SDS-soluble membrane-associated α-synuclein in affected regions that can be associated with decreased or unchanged α-synuclein levels in the soluble cytosolic fraction.123–125 Additionally, a comparative
study of PD and MSA brain tissue revealed distinct patterns of α-synuclein solubility between the disease groups, with MSA tissue showing a broader regional involvement and markedly more membrane-associated α-synuclein accumulation in the MSA substantia nigra compared with PD. Recent studies also suggest that a member of the ABC transporter family, ABCA8, may have key roles in myelin formation and pathology. ABCA8 is expressed in several regions of the adult human brain with significantly higher expression in oligodendrogliocyte-enriched white matter compared with grey matter. Additionally, ABCA8 expression is increased during aging, presumably correlated with age-associated myelinulation. In vitro, ABCA8 significantly stimulates sphingomyelin production in a human oligodendrogliocyte cell line. ABCA1 may therefore be a critical regulator of oligodendrogliocyte lipid metabolism. Intriguingly, ABCA8 mRNA expression is significantly increased in MSA brains compared with controls, both in affected grey matter and in affected white matter underlying the motor cortex with no significant change in an unaffected region, strongly supporting a potential role for upregulation of ABCA8 in the MSA disease process.

5. Conclusions and perspectives

ApoloE, but not apoaI-I, is produced in the CNS and incorporated in HDL particles, which are fundamental for supplying cholesterol to neurons. ApoA-I circulating with plasma HDL can enter the brain, be incorporated in CNS HDL particles, and then contribute to the protective roles of HDL in the CNS. HDL in plasma may also have effects on cerebrovascular endothelial cell function without necessarily crossing the BBB. Much remains to be learned about lipoprotein metabolism in the brain and the relationship between plasma and CNS lipoproteins. Genetic HDL disorders represent a valid tool to possibly clarify some of the open issues.

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