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Plasma Lipoproteins in Brain Inflammatory and Neurodegenerative Diseases

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1. Introduction

Functions of the central nervous system (CNS) are mainly performed by neurons and glial cells (astrocytes, oligodendrocytes and microglia). Microglia or microcytes have macrophage-like immune related functions; oligodendrocytes are the myelinating cells in the CNS; and astrocytes have diverse roles in synaptogenesis, neurotransmission, myelination and reactive mechanisms to injury. CNS tissue is separated from blood circulation by specialized cell barriers, the most extensive being the endothelium of the so-called blood-brain barrier (BBB).

Brain cholesterol and lipid homeostasis is largely independent of plasma lipoproteins because the BBB restricts the transport of these molecules. In consequence, lipoprotein fractions and compositions in the CNS are different from those in the blood, and consist mainly of high-density lipoproteins (HDL)-like particles. Glial cells (in particular astrocytes) are the main source of cholesterol and HDL-like particles in the CNS [1]. This specialized scenario is reflected on the analysis of cerebrospinal fluid (CSF). The CSF contains apolipoproteins similar to those of plasma, including apoE, apoA-I and A-II, apoC-I, C-II and C-III, apoJ and apoD, but not apoB; apoE and apo A-I are the most abundant. Importantly, while HDL-cholesterol and apoA-I in blood influence its levels in the CSF, this is not the case for apoE, apoJ and apoD, which are synthesized by glial cells [1-2]. In vitro studies have suggested apoA-I expression by brain endothelium and that plasma HDL (containing apoA-I) is transcytosed across the BBB [3]. In consequence, the implications of plasma lipoprotein metabolism in brain physiology and pathological states have been controversial. Nevertheless, many CNS disorders are associated with disturbances of the plasma lipoprotein profile and there is increasingly evidence for pathogenic and clinical relevance of these alterations.

In this chapter we do not pretend to make an exhaustive review on the vast literature related to this theme. Rather, we intend to incorporate some relevant studies in a comprehensive framework addressed to open new avenues of research. With this purpose, we will mainly focus on two frequent and disabling conditions, multiple sclerosis (MS) and Alzheimer disease (AD), and discuss the involvement of plasma lipoproteins in brain inflammatory and neurodegenerative mechanisms. With this approach we expect that useful insights may emerge regarding the contribution of plasma lipoproteins in CNS physiology and pathological states.

2. Multiple sclerosis

MS is a demyelinating inflammatory and neurodegenerative disease of the CNS with heterogeneous pathology (see below) and clinical outcomes. More than 80% of MS patients present initially with acute attacks (relapses) of neurological dysfunction (follow by variable degree of recovery and periods of “remission”), characterizing the relapsing-remitting phenotype (RR-MS). Most of these patients develop a disabling progressive course independently of eventual relapses (secondary progressive MS). A small percentage of patients (10-15%) presents initially with a progressive disease course (primary progressive MS). Patients with clinical isolated syndrome (CIS) have an isolated episode suggestive of MS. The investigation of CIS patients is of special theoretical and practical interest because of their increased risk to develop the disease.

A possible involvement of plasma lipoprotein in MS pathogenesis was suggested in 1953 by the work of Swank [4]. This author presented evidence for a favorable disease course in patients taking a diet poor in animal fat [5]. Sinclair, in 1956, called attention for the importance of a deficiency in polyunsaturated fatty acids and remarked similar epidemiological aspects of MS and cerebrovascular disease [6]. A landmark work, providing a clear potential involvement of plasma lipoproteins in disease was published by Shore *et al*, in 1987 [7]. These authors studied the animal model of MS, experimental autoimmune encephalomyelitis (EAE) and concluded that “*major changes in apoE-containing lipoproteins are undoubtedly significant in the altered immune function in EAE*”. Supporting this prediction, it was observed higher plasma apoE concentrations in MS patients during relapses in comparison to remission states and lower levels in patients under remission in comparison to normal controls [8-10]. Studying EAE induction in apoE-deficient female mice, Karussis in 2003, found that apoE deficiency might be connected with a defective neuronal repair mechanism and enhanced immune reactivity and worse course of the disease [11]. These results could indicate that plasma apoE may have an immunosuppressive role in MS [9]. In agreement with this concept, our group observed that lower levels of plasma apoE might promote immune reactivity in these patients [12].

In their work, Shore *et al* observed higher concentrations of total LDL and HDL cholesterol after onset of clinical symptoms. Giubilei *et al*, in 2002, studied plasma lipoproteins and magnetic resonance imaging (MRI) in patients with a first clinical episode suggestive of MS (CIS), supporting the findings in EAE [13]. These authors

observed high total and HDL-cholesterol in these patients and a significant correlation between disease activity (as assessed by MRI) and both total and LDL-cholesterol levels. Jamroz-Wisniewska *et al* found high total cholesterol levels in patients (RR and progressive forms) and also higher LDL-cholesterol in RR patients in remission and in progressive forms than in healthy subjects [14]. Serum paraoxonase 1 (a HDL associated enzyme) activity in relapses was significantly lower in RR patients in comparison to other MS groups. An epidemiological survey based on almost 9000 patients with MS found that the presence of hypercholesterolemia, among other vascular co-morbidities, increased the risk of a more rapid disabling progression of the disease [15]. Recently, Weinstock-Guttman *et al* studied the serum lipid profiles in association with clinical disability and MRI measures in 492 MS patients [16]. They found that worsening disability was associated with higher total and LDL cholesterol, and triglycerides. Higher HDL levels were associated with lower probability for the presence of acute inflammatory lesions (assessed by MRI). Other authors have found higher HDL-cholesterol (and total blood homocysteine) levels in MS patients during a phase of clinical inactivity in comparison to normal controls [17].

The possible influence of apoE allele polymorphism in MS susceptibility and disease severity has been addressed in many studies. Overall, literature does not suggest a role of apoE alleles as risk factor of developing MS [18-19]. An association of apoE polymorphism with disease severity in MS patients has been more controversial. Using MRI methodology, some studies have shown an association between the apoE4 isoform and more severe brain tissue destruction in these patients [20-22]. However, an influence of this isoform on the clinical course of the disease is not established and the interaction with potential confounders should be considered. For example, it was suggested that an influence of apoE polymorphism on the clinical course, and even the risk of MS, could particularly exist in women [23]. Our group has provided evidence for an influence of cigarette smoking in apoE4-carriers, in modulating the clinical severity of RR-MS patients [24]. Some studies have suggested an association of apoE4 allele and apoA1 promoter polymorphism with cognitive impairment in these patients, which may occur very early in the clinical course of the disease [25-26].

As mentioned above, MS is a heterogeneous clinical entity. RR-MS has a higher prevalence in women (which is increasing) and the course of the disease is in general more disabling in men. It is not unreasonable to hypothesize that gender-related and other genetic influences could implicate different impacts of lipoprotein metabolism in MS. Few studies have analyzed the influence of MS therapies in plasma lipoproteins of these patients. However, these studies could provide useful insights on the pathogenic role of this metabolism. Our group first suggested that interferon beta therapy changes this metabolism in RR-MS patients. In particular, we found that at 12 month of therapy, lower apoA1 and higher apoE levels were associated with the presence of relapses and/or progression of the disease [27]. Others authors have found that MS therapy is associated with a decrease of plasma total cholesterol [28-29]. Overall, the reviewed data strongly support a role of plasma lipoproteins metabolism in the pathophysiology of the disease, as discussed below.

2.1. Pathophysiological mechanisms

A major link between plasma lipoproteins and MS concerns the immune system. It is well known that immune reactivity interacts with adaptive alterations of lipoprotein metabolism [30-31]. Recent reports have showed that distinct metabolic programs are essential for survival and functional specialization of different lymphocyte cell populations. For example, lipid oxidation is essential for Treg generation while Th1 differentiation and cytokine production by differentiated Th1, Th2 and Th17 cells are suppressed by lipids and require glucose metabolism [32]. Although the immunopathogenesis of MS lesions (demyelinating plaques) is heterogeneous and may differ in different patients, an imbalance favoring a Th1 effector cell activation is generally accepted [33]. Therefore, it would not be unexpected if an abnormal lipid modulation of immune functions could contribute for MS pathogenesis. However, a primary role of lymphocytes (T cells and B cells) in mediating CNS injury in this disease (at least in all patients) is controversial [32]. Myeloid cells play a pivotal role in the regulation of infiltrating lymphocyte cell activities and are involved in myelin breakdown and axonal injury [33-34]. Macrophages of M1 phenotype are characterized by high production of pro-inflammatory mediators and are crucial in Th1 cell response, while M2 phenotypes are associated with tissue remodeling/repair and expression of anti-inflammatory molecules [35]. In MS lesions, myelin phagocytosis by myeloid cells induces a foamy appearance. Foamy macrophages are originated from resident myeloid cells (microglia) and infiltrating monocytes and are suggested to be of M2-type macrophages and to contribute to the resolution of brain inflammation [36-37].

Macrophage polarization is modulated by different factors. For example, the M2 antinflammatory phenotype is induced by HDLs and apoE [35, 38], and fatty acid and phospholipid synthesis is essential for phagocytic differentiation of human monocytes [39]. ApoE is one ligand for the LDL-receptor-related-protein-1 (LRP1). Quite interesting, LRP1 mediates the downregulation of microglial inflammatory activity by apoE [40] and is essential for phagocytosis of degraded myelin in mice with EAE [41]. Moreover, LRP1 is also expressed in neurons and astrocytes and regulates BBB permeability [42]. This scenario is consistent with a reduction of inflammatory infiltrates and clinical disability by apoE-derived peptides in EAE [43] and immunosuppressive and neuroprotective effects of plasma apoE in EAE [11] and MS patients [8-10, 12].

Among the transcriptional factors regulating macrophage polarization, peroxisome proliferator-activated receptor (PPAR) γ is known to promote M2 macrophages [35]. This is of potential interest in the context of preliminary evidence implicating PPARs in MS pathogenesis and as therapeutic targets for the disease [44-45].

In brain, apoE is associated with HDL-like particles, also containing the second major apolipoprotein, apoA-I. These apolipoproteins are primarily located on separated lipoproteins particles [1]. Although apoE in the brain is predominantly synthesized by glial cells, plasma HDL/apoA-I may cross the BBB and influence its levels in the brain [2]. HDL effects include an inhibition of cytokine-induced expression of adhesion molecules in endothelial cells, which could further depress brain parenchyma immune reactivity [46]. As

mentioned, higher levels of plasma HDL were found in CIS and RR-MS and were associated with a lower probability in development of acute inflammatory lesions in these patients [13, 16-17]. Recently, preliminary evidence from our group suggests that higher plasma HDL levels are associated with an increased intrathecal IgG synthesis in these patients [47]. Because low plasma HDL-cholesterol is associated with a predominance of pro-inflammatory phenotype of monocyte-derived macrophage [48], these findings suggest an immunosuppressive role of HDL in the development of MS lesions. This interpretation is further supported by the beneficial therapeutical effects of fingolimod in the disease [49].

Fingolimod (FTY720) is a structural analog of sphingosine, which down modulates sphingosine 1-phosphate (S1P) receptors. S1P is a major component of HDL, including in the CNS and induces an anti-inflammatory phenotype in macrophages. S1P receptors are widespread in CNS cells and a defect of sphingolipid and phospholipid metabolism is observed early in normal appearing white and grey matter in MS patients. Moreover, S1P is reduced in affected white matter and is increased in CSF of these patients [49]. Importantly, FTY720 treatment has been shown to have neuroprotective effects independent of immunomodulatory mechanisms [50]. These data suggest a protective role of endogenous HDL components not only in the genesis of acute inflammatory lesions but also in the neurodegenerative process of MS.

An involvement of oxidative stress in MS, including of lipid peroxidation has recently received much support [51]. Newcombe *et al*, in 1994, demonstrated for the first time the presence of oxidized LDL (ox-LDL) and their peroxidative end-products in early and actively demyelinating plaques in post-mortem MS brain [36]. They suggested that plasma LDL enters (through a damaged BBB) the parenchyma and is oxidatively modified in the lesions. More recent data supports an important involvement of oxidative damage including oxidized phospholipids in myelin and axon injury in MS [52]. Several studies have also demonstrated that measures of oxidative stress and lipid peroxidation are consistently increased in the blood of these patients [51]. Our group reported increased levels of serum oxLDL in RR-MS patients in remission in comparison to normal controls and higher levels during relapses [53]. These findings are consistent with a contribution of plasma ox-LDL in promotion BBB permeability and acute inflammatory CNS lesions in the disease. However, increased plasma lipid peroxidation or oxidative stress is probably not associated with disability progression in these patients [54]. The pathophysiology of acute lesions (MS plaques) and disability progression are indeed thought to be mediated by different mechanisms. In fact, it was suggested that low oxygen radical formation in peripheral leukocytes may be associated with a increased severity of the disease [55]. These findings indicate that the role of oxidative stress in MS is complex. An oral formulation of dimethylfumarate (BG-12) activates the Nrf2 antioxidant pathway and was recently observed to be of clinical benefit in RR-MS patients, possibly in disease progression also [56]. These recent promising results should stimulate future research to clarify the involvement of lipid peroxidation in the disease. It should be noted that this involvement further supports a role of plasma HDL in disease pathogenesis, as discussed above. Plasma HDL-associated α -tocopherol is transcytosed across the BBB and may have antioxidant as well as anti-inflammatory effects [3].

Ludewig and Laman (2004) remarked the similarities that may exist between the atherosclerotic plaque development and MS lesions and suggested: “*Systematic comparison of these two diseases involving foam cells in chronic lesions may prove fruitful*” [57]. As we have reviewed, recent research clearly supports this prediction. Moreover, patients with MS have several vascular abnormalities and a higher risk for ischemic stroke [58]. In 2003, our group first reported a pilot trial suggesting a benefit of statin monotherapy in the pathogenesis process (assessed by MRI) and clinical activity of RR-MS patients [59]. These beneficial effects were confirmed by Vollmer *et al* trial in 2004 [60] and in a long-term follow-up of our patients [61]. Very recently, beneficial effects of statin monotherapy were reported in patients with a first clinical episode (CIS) suggestive of MS [62-63]. A synthesis of some shared pathophysiological factors involved in MS and atherosclerosis is presented on Table 1. As we will discuss below, the presence of similar mechanisms involving plasma lipoprotein metabolism in the pathogenesis of atherosclerosis/ischemic and demyelinating lesions may be extensive to other chronic inflammatory and neurodegenerative pathologies.

Pathophysiology	Comment	References
<i>Lesions</i>		
Foam Cells Plaques	Macrophage lipid uptake in early lesion formation	[36-37]
<i>Lipoprotein Related</i>		
Total and LDL cholesterol	Promotion of lesion formation and/or progression	[13-16]
HDL-Cholesterol	Protective of lesion formation and/or progression	[13, 16-17, 47]
ApoA-I	Immunosuppressive and protective	[26-27]
ApoE	Immunosuppressive and protective	[8-10, 12]
Sphingosine-1-phosphate	Modulation of immune reactivity and lesion formation	[49-50]
Oxidative stress and oxLDL	Lipid peroxidation in lesion formation	[51-53]
Secretory phospholipase A ₂	Increased expression	[115]
<i>Immunopathogenesis</i>		
M ₂ -Macrophages	Anti-inflammatory, phagocytic cells in lesions	[37]
T-Cells	Promoting lesion formation	[33]
Inflammatory cytokines	Promoting lesion formation	[33]
Interleukin-10	Protective of lesion formation	[116]

Pathophysiology	Comment	References
Adipocytokines	Leptin and Adiponectin involvement in immune dysfunction	[117-118]
MMP-9	Upregulation associated with lesion formation	[42]
<i>Others</i>		
Statins	Pathological and clinical benefits	[59, 63]
PPARs	PPAR-gamma agonists protective	[45]
Estrogens	Protective of lesion formation and/or progression	[119]
Homocysteine	Increased levels associated with lesion formation	[17, 58]
Platelets	Increased adhesiveness and aggregation	[58, 120]
Smoking	Promotes lesion formation	[121]
Ischemic events	Increased risk associated with atherogenesis and MS pathogenesis	[58]

Table 1. Some pathogenic similarities between multiple sclerosis and atherosclerosis.

3. Alzheimer disease

Possession of the apoE4 allele is the major genetic risk factor for sporadic late-onset AD [64-65]. This observation led to a large body of research on cholesterol and lipid metabolism in patients and animal models of AD during the last two decades. However, the investigation of this metabolism in patients with clinical AD is not sufficient to clarify its role in the pathogenesis of the dementia. It is generally accepted that the pathogenic processes in AD begin many decades before the appearance of evident symptoms. More recently, a major focus of interest has been on longitudinal studies addressing the association between lipoprotein profiles and clinical evolution of cognitive normal subjects or patients with mild cognitive impairment (MCI). A large percentage of patients with the diagnosis of MCI by the 6th decade are known to develop AD later in life. Therefore prospective studies are crucial for development of efficient preventive or therapeutic measures.

Amyloid- β (A β) deposition in plaques (AP) (also known senile or neuritic plaques (NP)) and neurofibrillary tangles (NFT), characterized by hyperphosphorylated tau protein aggregates, are pathologic hallmarks of AD [66-67]. The association between plasma lipoprotein profiles and risk of development of clinical manifestations of dementia has been controversial. An association between high cholesterol levels in midlife and an increased

risk for dementia in old age has been suggested by several publications [68], but it was not confirmed by a recent large population study [69]. Instead, this study found that low cholesterol levels in late life were predictive of subsequent dementia. Supporting this conclusion, another study in elderly individuals found that low HDL-cholesterol and low total and Non-HDL cholesterol were associated with higher AD risk [70]. These authors suggested a protective effect of late life total cholesterol level on the risk for mild cognitive impairment and AD. Low HDL-cholesterol levels were also associated with decline of memory in middle-aged adults [71]. Within this framework, decreased plasma apoA-I levels have also been found in AD as well as in vascular dementia, and higher apoA-I levels associated with decreased risk of dementia [72-73]. Few studies have investigated the association of lipid profiles with AD-related pathology. A recent work has found that high total cholesterol, LDL-cholesterol and non-HDL-cholesterol levels were associated with risk of development of AP, but not NFT [74]. However, as we will discuss below, the genesis of pathological hallmarks of AD is not invariably associated with clinical manifestations of cognitive impairment and dementia.

The apoE4 allele is an established risk factor for the development of sporadic AD; it is associated with an early age at onset of dementia in an allele dose-dependent manner; and with increased A β burden. Moreover, in MCI it predicts conversion to AD. In contrast, apoE2 allele is associated with delayed age of onset of AD [66]. Recent data have provided evidence for an important role of apoE protein levels, independently of the genotype. In one study, middle-aged offspring with familial history of AD were found to have lower plasma apoE levels when compared with offspring without familial history of AD, independent of APOE genotype [75]. In other study, plasma apoE levels were found to be lower in patients with AD and decreased with A β load [76].

Overall the reviewed data strongly support a role of plasma lipoprotein metabolism in the pathogenesis of AD, as discussed in more detail below.

3.1. Pathophysiological mechanisms

As already mentioned, NP and NFT are the hallmarks of AD pathology. However, these aggregates are present in a variable extend in about 30% of cognitively normal elderly subjects. In AD, synaptic structural and functional alterations also occur early and are more pronounced than in normal ageing individuals. ApoE-containing lipoproteins, mainly derived from astrocytes, may influence these pathogenic processes in several ways. Cholesterol associated with these lipoproteins is necessary for neurons and to stimulate axonal growth and synaptogenesis. Lipidate-apoE contributes for clearing out A β from the brain, a process mediated by apoE receptors (especially LRP1) present in glial cells, neurons and in endothelium of the BBB. Pathways for A β clearance also include proteolytic degradation and oligomerization in the aggregates of amyloid plaques, mechanisms also modulated by apoE. For all these processes the isoform apoE4 (which is in general associated with less secreted production of the protein) is less efficient and promotes synaptic dysfunction, toxicity of soluble A β and NP deposits. Moreover, it is suggested that

apoE4 fragments induce mitochondrial dysfunction and neurotoxicity and that cholesterol levels may regulate A β production [65, 66]. Supporting this important role of apoE for AD and the harmful effects of A β on cognitive functions, cognitive performance in normal older adults was associated with A β load (PET), mainly in ϵ 4 carriers [77].

The above findings do not exclude the contribution of other apolipoproteins for A β pathology. For example, apoJ and apoD (see below) also modulate A β deposition, a deficiency of apoA-I promotes cognitive impairment and polymorphisms of all these apolipoproteins were associated with risk for AD [1]. Interestingly, increased plasma levels of apoJ (clusterin) are not present before the development of AD but are indeed associated with the severity and progression of the disease, supporting a neuroprotective role [78].

The link between a lipoprotein dysregulation and tau pathology (NFT deposition), in contrast, is not well understood. Beyond the involvement of cholesterol and apolipoproteins, AD is associated with disturbances of sphingolipids and phospholipid metabolism that may contribute for its pathogenesis [67]. Moreover, cognitive impairment and dementia, including AD, are frequently associated with markers of systemic and brain inflammatory activity [79], vascular atherogenic [80] and white-matter (myelin) pathology [81]. An underlying dysregulation of lipoprotein metabolism could be linked to all these pathogenic pathways.

The scenario briefly described above is clearly consistent with the observations that low plasma apoE may be associated with increased risk of AD and correlates with A β load, as assessed by PET [75-76]. As remarked, the last studies emphasized the importance of total apoE levels, independently of the genotype. Supporting this concept, it was recently reported in AD mouse models a stimulation of A β clearance and cognitive function by inducing apoE expression [82]. After apoE-mediated transport through the BBB, plasma A β transport is accomplished by triglyceride-rich lipoproteins (TRL) rich in apoE, for uptake in liver [83]. These findings are also consistent with the risk conferred by low plasma apoE levels. Low plasma apoE levels could also promote systemic immune reactivity and atherogenic pathology in these patients.

Although no relation exists between plasma and brain apoE levels, a strong correlation was found between HDL-cholesterol and apoA-I in serum and in CSF lipoproteins (which are HDL-like particles) [2]. This scenario could contribute to the risk of cognitive impairment and AD conferred by low plasma HDL-cholesterol and apoA-I levels [70-73]. On one hand, these deficiencies could be linked to an increased systemic inflammatory and oxidative status and promotion of atherogenesis. On the other hand, low HDL and apoA-I levels would provide less neurotrophic and immunosuppressive abilities to the brain [84]. If high total and LDL or non-HDL cholesterol in plasma cannot influence its levels in the brain, how could they be associated in some studies with an increased AD risk and A β load (NPs)? Experimental studies suggest that plasma cholesterol levels do not normally regulate production of brain A β [85]. One possibility resides in the fact that high non-HDL cholesterol in these patients may be associated with low HDL, apoE and apoA-I levels, a pro-inflammatory systemic status and increased atherogenic/ischemic pathology. Supporting this hypothesis, in animal models, cognitive impairment following high fat diet

consumption was associated with brain inflammation [86]. Among other markers of inflammation [79], serum levels of adipocytokines have been associated with cognitive impairment and progression of AD, as well as atherogenic/ischemic disease [87-88]. Metabolic syndrome [89] and insulin resistance and type 2 diabetes [90] are associated not only with higher risk of vascular disease but also with risk of dementia, including AD. All these conditions may promote the development of dementia also by affecting myelin integrity and white-matter connective functions.

It should be noted that clinical overt cognitive impairment and dementia do not depend solely on the severity of neurodegenerative and vascular pathologies. Human brain is provided with potential compensatory or plastic mechanism, which may mitigate the clinical impact of ageing-associated pathologies [91-92]. This means that in old age, risk factors for dementia may not have the same significance they have in previous decades. Those factors may include high total and non-HDL cholesterol plasma levels, which may have a major impact in promoting atherogenesis/ischemic/inflammatory processes and AD-related pathology in middle-life, but not in neuroplastic mechanisms increasingly required with advancing age. Lower total and LDL cholesterol have indeed been associated with a poor prognosis in the ischemic stroke [93] and in elderly individuals, as observed above, this profile may increase the risk for overt dementia. Increased body mass index (BMI) in middle life appears to be a risk factor for latter development of cognitive decline and AD, but in late life the burden of cerebral amyloid and tau is associated with lower BMI in cognitively normal and MCI subjects [94-95]. These facts could contribute to the inconsistent results regarding the benefits of statins on prevention and treatment of AD, despite in vitro and animal studies demonstrating an effect in decreasing A β formation [96].

In Figure 1 are presented some of the suggested implications of lipoproteins in the pathogenesis of AD and MS.

4. Other brain disorders

Results concerning an association between high serum cholesterol levels and the risk for **Parkinson disease (PD)** have been conflicting. However, this possible association may not exist in older subjects (≥ 55 years). As for AD, low serum total and LDL-cholesterol levels may increase the risk of PD with advancing age [97-99]. In this context, it is intriguing that hyperlipidemia probably has also a protective role on the neurodegenerative process of **amyotrophic lateral sclerosis (ALS)** [100-101]. PD and ALS also involve inflammatory processes and it has been noted some convergence in the mechanisms underlying neurodegeneration in these disorders, in AD and MS. [102]. An abnormal brain cholesterol homeostasis may also contribute to the pathophysiology of **Huntington's disease** [103]. In what concerns PD, and in contrast to AD, an involvement of apoE genotypes is not clarified. Several studies reported no influence of apoE4 allele in the development of PD or in dementia associated with the disease, which is in contrast to its established role in AD pathogenesis [104]. However, apoE and LRP1 were found to be increased in brain from PD patients, suggesting an involvement in the deposition of α -sinuclein aggregates (Lewy bodies) typical of this disease [105].

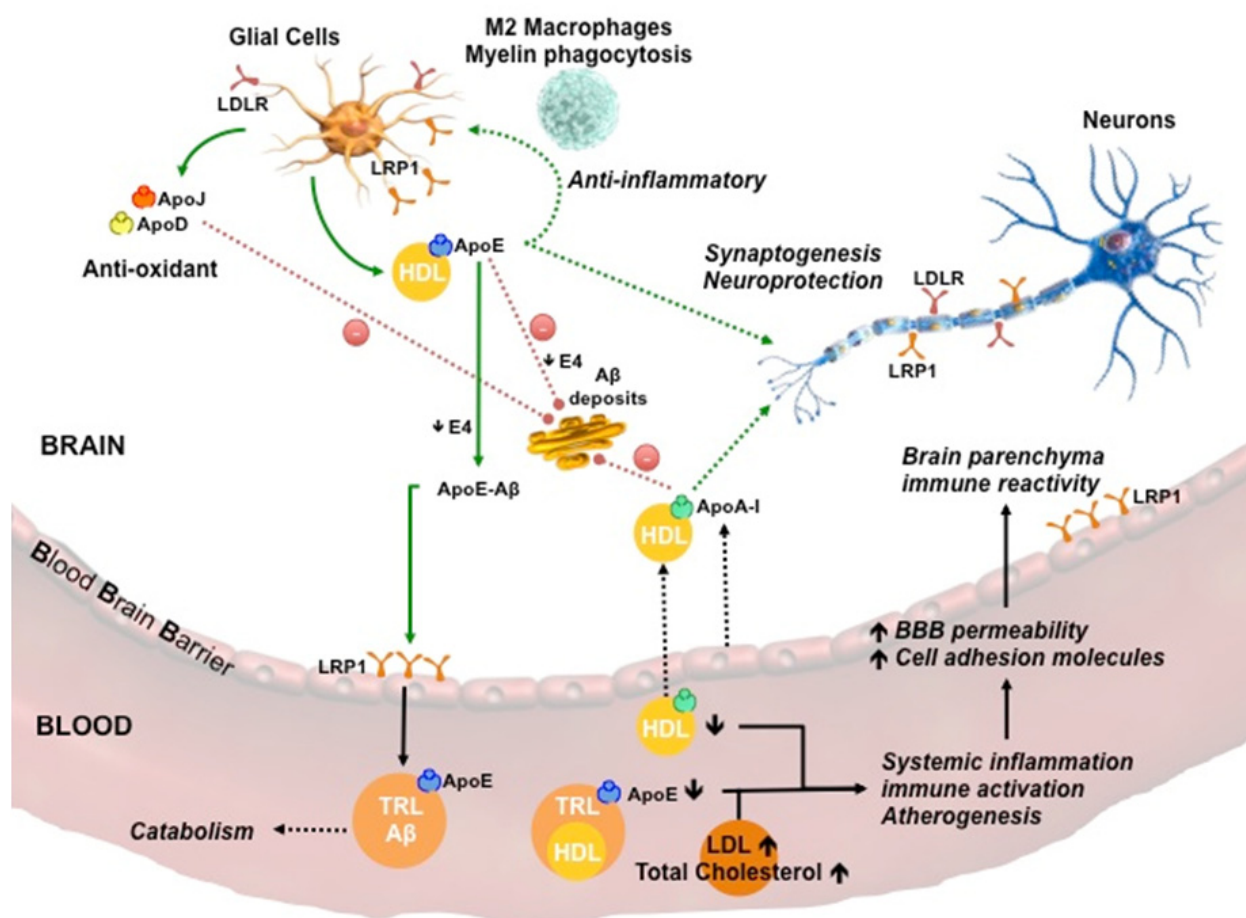


Figure 1. Some putative implications of lipoproteins for the pathogenesis of Multiple Sclerosis and Alzheimer disease (see text for interpretation).

As mentioned above, apolipoprotein D in the CNS is normally synthesized by glial cells (astrocytes and oligodendrocytes). Although present in the CSF in lower concentrations than apoE, A-I and J, some studies have suggested a possible neuroprotective role of apoD in neuropathological states [1,106]. ApoD is a member of the lipocalin family of proteins that are involved in the transport of small hydrophobic ligands. Among several proposed ligands (cholesterol, progesterone, pregnenolone, bilirubin), apoD can bind with high affinity arachidonic acid (AA). Inflammatory responses and oxidative stress associated with brain insults are known to mobilize AA from membranes. Therefore, apoD could have a neuroprotective role by controlling oxidative damage [106-107]. In fact, higher levels of apoD have been found in brain or CSF of AD and other neuropathologies [108]. Curiously, an increase of apoD has also been reported in plasma and certain brain regions of patients with **schizophrenia** and **bipolar disorder**. In these conditions, a disturbance of phospholipid metabolism has been proposed and apoD could represent a response addressed to stabilize membrane AA or bind free AA [106]. The fact that atypical antipsychotics such as clozapine up-regulate apoD expression supports neurotrophic effects of this protein [106]. It should be noted that other apolipoproteins have been implicated in these neuropsychiatric disorders, including apoE, and apoA-I [106, 109-110]. Interestingly, as observed for AD and MS, lower serum apoA-I levels were found in schizophrenia [110].

Overall, these data emphasizes the relevance of plasma lipoprotein metabolism in brain physiology and the convergence of similar dysfunctions of this metabolism associated with several neuropathologies.

5. Conclusion

This review has addressed MS and AD as a strategy to explore the potential relevance of plasma lipoproteins in CNS inflammatory and neurodegenerative disorders. Despite quite different in their demographics, clinical and pathological characteristics, some similarities in their inflammatory and neurodegenerative components have been noted previously [102].

In MS as in AD, the genesis of brain pathology is thought to begin many years before the clinical overt disease. Despite the occurrence of widespread lesions, brain plastic compensatory mechanisms may maintain those disorders clinically silent, delay their symptoms or modify their clinical evolution. Molecular mechanisms underlying grey and white matter plasticity are of outstanding neurobiological and medical importance and are currently poorly understood [111]. This review suggests that an involvement of lipoprotein metabolism in brain plasticity mechanisms is highly plausible and deserves much future research.

Clinical signs of MS very rarely first appear in individuals after 60 years of age and sporadic AD rarely manifest before that age. However, it is remarkable that a profile of low HDL-cholesterol, apoE and apoA-I plasma levels and elevated total and non-HDL cholesterol may promote the risk or progression of disability in both disorders. As discussed, this profile could be associated with both the genesis of lesions in the CNS and the systemic immune-related or metabolic alterations implicated in their pathophysiology (Table 1, Figure 1). It is to note that disturbances in brain cholesterol transport (that may occur in MS, AD and other neuropathologies) can lead to alterations in cholesterol uptake from plasma to brain and decrease plasma HDL levels (112). In MS as in AD, this lipoprotein profile may promote foam cell plaque formations. In young individuals genetically susceptible to MS, this profile may promote the genesis of demyelinating plaques; instead with advanced age, atheroma plaques formation prevails, contributing to AD, in genetically susceptible subjects. Supporting this speculation, MS pathogenesis may share many lipoprotein-related and inflammatory mechanisms underlying atherogenesis (Table1). In addition, with aging, this lipoprotein profile could have a convergent impact for the maintenance of the typical CNS lesions occurring in MS and AD. In fact, advanced ageing may be associated with lower recruitment of anti-inflammatory and phagocytic macrophages and other blood-derived factors to the CNS [113]. This situation, on one hand, favors lower capacity of β -amyloid clearance, oligodendrocyte toxicity and myelin lesions, early present in incipient AD. On the other hand, it restricts remyelination capacities in MS, which are more accentuated with advancing ageing in these patients. The presence of age-related changes in blood circulation has recently been noted of possible relevance for MS and AD [114]. These relevant age-related changes should comprise circulating lipoprotein metabolism.

Despite the similarities of lipoproteins involvement in these two disorders, including the neuroprotective, immunosuppressive and vascular/ischemic protective functions of HDL-

cholesterol and associated apolipoproteins (Fig. 1), distinctive implications on their pathogenesis are expected. In MS, a participation of lymphocyte infiltration is certainly important while this is not the case for AD. For example, sphingosine-1-phosphate component of HDL could be special relevant for the immune dysfunction and the abnormal sphingosine metabolism associated with the genesis of demyelinating plaques and neurodegenerative processes in MS. In AD, triglyceride-rich plasma lipoproteins and apoE4 isoform are especially relevant in the clearance of A β and genesis of amyloid plaques. It should be emphasized that MS and AD are pathological and clinical heterogeneous diseases. For example, the immunopathogenesis of MS differ among patients even with similar clinical profiles and prominent atherosclerosis lesions are absent in some patients with AD. Therefore, the contribution of plasma lipoprotein metabolism for the pathogenesis of these disorders may be variable and this could explain discrepancies among some studies. Future work aimed to clarify the roles of plasma lipoproteins in these diseases should address clinical homogeneous patient populations, include concomitant pathological and immunological markers and consider potential environmental confounders. Ideally, laboratory data should be correlated with neuroimaging measures. Finally, MS and AD are clear examples of complex conditions for which multiple genetic risk factors for developing and progression are to be expected. Selected genetic typing of the study population is therefore convenient, because lipoprotein alterations may not have the same significance and the same therapeutical implications in different genetic backgrounds.

In sum, the available reviewed data suggest that plasma lipoproteins metabolism is a fruitful “window” to an improved understanding of MS and AD and other neurological diseases. Of outstanding interest, plasma lipoproteins may represent useful targets for discovering preventive and therapeutical strategies for these common disabling human conditions.

A very recent paper from Dr Lawrence Steinman group at Stanford University highlights the importance of lipids in the pathogenesis of MS and the therapeutic potential of lipid-based strategies for the disease (Science Transl Med 2012; 8 (137); E-pub 2012 6 Jun).

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6. References

- [1] Hayashi H (2011) Lipid Metabolism and Glial Lipoproteins in the Central Nervous System. *Biol. pharm. bull.* 34: 453-461.
- [2] Fagan AM, Younkin LH, Morris JC et al (2000) Differences in the A β 40/ A β 42 Ratio Associated with Cerebrospinal Fluid Lipoproteins as a Function of Apolipoprotein E Genotype. *Ann. neurol.* 48: 201-210.
- [3] Balazs Z, Panzenboeck u, Hammer A et al (2004) Uptake and Transport of High-Density Lipoproteins (HDL) and HDL-Associated α -Tocopherol by an *in vitro* Blood-Brain Barrier Model. *J. neurochem.* 89: 939-950.
- [4] Swank RL (1953) Treatment of Multiple Sclerosis with Low-Fat Diet. *Arch. neurol. psych.* 69: 91-103.
- [5] Swank RL (1970) Multiple Sclerosis. Twenty Years on Low-Fat Diet. *Arch. neurol.* 23: 460-474
- [6] Sinclair HM (1956) Deficiency of Essential Fatty Acids and Atherosclerosis, etcetera. *Lancet*, 270: 381-383.
- [7] Shore VG, Smith ME, Perret V et al (1987) Alterations in Plasma Lipoproteins and Apolipoproteins in Experimental Allergic Encephalomyelitis. *J. lipid res.* 28: 119-129.
- [8] Rifai N, Christenson RH, Gelman BB et al (1987) Changes in Cerebrospinal Fluid IgG and Apolipoprotein E Indices in Patients with Multiple Sclerosis during Demyelination and Remyelination. *Clin. chem.* 33: 1155-1157.
- [9] Gelman BB, Rifai N, Christenson RH, et al (1988) Cerebrospinal Fluid and Plasma Apolipoproteins in Patients with Multiple Sclerosis. *Ann. clin. lab. science.* 18: 46-52.
- [10] Carlsson J, Armstrong VW, Reiber H et al (1991) Clinical Relevance of the Quantification of Apolipoprotein E in Cerebrospinal Fluid. *Clin. chim. acta*, 196: 167-176.
- [11] Karussis D, Michaelson DM, Grigoriadis N et al (2003) Lack of Apolipoprotein-E Exacerbates Experimentally Allergic Encephalomyelitis. *Mult. scler.* 9: 476-480.
- [12] Sena A, Bendtzen K, Cascais MJ et al (2010) Influence of Apolipoprotein E Plasma Levels and Tobacco Smoking on the Induction of Neutralising Antibodies to Interferon-Beta. *J. neurol.* 257: 1703-1707.
- [13] Giubilei F, Antonioni G, Di Legge S et al (2002) Blood Cholesterol and MRI Activity in First Clinical Episode Suggestive of Multiple Sclerosis. *Acta neurol. scand.* 106: 109-112.
- [14] Jamroz-Wisniewska A, Beltowski J, Stemasiak Z et al (2009) Paraoxonase 1 Activity in Different Types of Multiple Sclerosis. *Mult.scler.* 15: 399-402.

- [15] Marrie RA, Rudick R, Horwitz R et al (2010) Vascular Comorbidity is Associated with More Rapid Disability Progression in Multiple Sclerosis. *Neurology* 74: 1041-1047.
- [16] Weinstock-Guttman B, Zivadinov R, Mahfooz N et al (2011) Serum Lipid Profiles are Associated with Disability and MRI Outcomes in Multiple Sclerosis. *J. neuroinflammation* 8:127-133
- [17] Salemi G, Gueli MC, Vitale F, et al (2010) Blood Lipids, Homocysteine, Stress Factors, and Vitamins in Clinically Stable Multiple Sclerosis Patients. *Lipids in health and disease* 9:19-21.
- [18] Burwick RM, Ramsay PP, Haines JL et al (2006) ApoE Epsilon Variation in Multiple Sclerosis Susceptibility and Disease Severity. *Neurology* 66: 1373-1383.
- [19] Pinholt M, Frederiksen JL, Christiansen M (2006) The Association Between Apolipoprotein E and Multiple Sclerosis. *Eur. j. neur.* 13: 573-580.
- [20] Enzinger C, Ropele S, Strasser-Fuchs S et al (2003) Lower Levels of N-Acetylaspartate in Multiple Sclerosis Patients with the Apolipoprotein E ϵ 4 Allele. *Arch. neurol.* 60:65-70.
- [21] Enzinger C, Ropele S, Smith S et al (2004) Accelerated Evolution of Brain Atrophy and "Black Holes" in MS Patients with ApoE- ϵ 4. *Ann. neurol.* 55:563-569.
- [22] De Stefano N, Bartolozzi ML, Nacmias B et al (2004) Influence of Apolipoprotein E ϵ 4 Genotype on Brain Tissue Integrity in Relapsing-Remitting Multiple Sclerosis. *Arch. neurol.* 61: 536-540.
- [23] Kantarci OH, Hebrink DD, Achenbach SJ et al (2004) Association of ApoE Polymorphisms with Disease Severity in MS is Limited to Women. *Neurology* 62: 811-814.
- [24] Sena A, Couderc R, Ferret-Sena V et al (2009) Apolipoprotein E Polymorphisms Interacts with Cigarette Smoking in Progression of Multiple Sclerosis. *Eur. j. neur.* 16: 832-837.
- [25] Shi J, Zhao CB, Vollmer TL et al (2008) ApoE ϵ 4 Allele is Associated with Cognitive Impairment in Patients with Multiple Sclerosis. *Neurology*, 70: 185-190.
- [26] Koutsis G, Panas M, Giogkaraki E et al (2009) An ApoAI Promoter Polymorphism is Associated with Cognitive Performance in Patients with Multiple Sclerosis. *Mult. scler.* 15: 174-179.
- [27] Sena A, Pedrosa R, Ferret-Sena V et al (2000) Interferon β 1a Therapy Changes Lipoprotein Metabolism in Patients with Multiple Sclerosis. *Clin. chem. lab. med.* 38: 209-213.
- [28] Morra BV, Coppola G, Orefice G et al (2004) Interferon β Treatment Decreases Cholesterol Plasma Levels in Multiple Sclerosis Patients. *Neurology* 62: 829-830.
- [29] Coppola G, Lanzillo R, Florio C et al (2006) Long-Term Clinical Experience with Weekly Interferon β -1a in Relapsing Multiple Sclerosis. *Eur. j. neurol.* 13: 1014-1021.
- [30] Hansson GK (2007) Light Hits the Liver. *Science* 316: 206-207.
- [31] Glass CK, Saijo, K (2008) Oxysterols Hold T Cells in Check. *Nature* 455:40-41.
- [32] Michalek RD, Gerriets VA, Jacobs SR et al (2011) Cutting Edge: Distinct Glycolytic and Lipid Oxidative Metabolic Programs Are Essential for Effector and Regulatory CD4⁺ T Cells Subsets. *J. immunol.* 186: 3299-3303.

- [33] Henderson APD, Barnett MH, Parratt JDE et al (2009) Multiple Sclerosis – Distribution of Inflammatory Cells in Newly Forming Lesions. *Ann. neurol.* 66: 739-753.
- [34] Weber MS, Prod'homme T, Ypussef S. et al (2007) Type II Monocytes Modulate T Cell-Mediated Central Nervous System Autoimmune Disease. *Nat. med.* 13: 935-943.
- [35] Chinetti-Gbaguidi G, Staels B (2011) Macrophage Polarization in Metabolic Disorders: Functions and Regulation. *Curr. opin. lipidol.* 22: 365-372.
- [36] Newcombe J, Li H, Cuzner ML (1994) Low Density Lipoprotein Uptake by Macrophages in Multiple Sclerosis Plaques: Implications for Pathogenesis. *Neuropathol. appl. neurobiol.* 20: 152-162.
- [37] Boven LA, Van Mars M, Van Zwam M et al (2006) Myelin-Laden Macrophages Are Anti-Inflammatory with Foam Cells in Multiple Sclerosis. *Brain* 129: 517-526.
- [38] Baitsch D, Bock HH, Engel T et al (2011) Apolipoprotein E Induces Antiinflammatory Phenotype in Macrophages. *Arterioscler. thromb. vasc. biol.* 31: 1160-1168.
- [39] Ecker J, Liebisch G, Englmaier M et al (2010) Induction of Fatty Acids Synthesis is a Key Requirement for Phagocytic Differentiation of Human Monocytes. *Proc. natl. acad. sci. USA* 107: 7817-7822.
- [40] Pocivavsek A, Michailenko I, Strickland DK et al (2009), Microglial Low-Density Lipoprotein Receptor-Related Protein 1 Modulates c-Jun N-Terminal Kinase Activation. *J. neuroimmunol.* 214: 25-32.
- [41] Gaultier A, Wu X, Le Moan N et al (2008) Low-Density Lipoprotein Receptor-Related Protein 1 Is An Essential Receptor for Myelin Phagocytosis. *J. cell sci.* 122: 1155-1162.
- [42] Yepes M, Sandkvist M, Moore EG et al (2003) Tissue-Type Plasminogen Activator Opening of the Blood-Brain Barrier Via the LDL Receptor-Related Protein. *J. clin. invest.* 112:1533-1540.
- [43] Li F-Q, Sempowski GD, McKenna SE et al (2006) Apolipoprotein E-derived Peptides Ameliorate Clinical Disability and Inflammatory Infiltrates into the Spinal Cord in a Murine Model of Multiple Sclerosis. *J pharmacol. exp. ther.* 318: 956-965.
- [44] Sena A, Tavares A, Ferret-Sena V et al (2008) Peroxisome Proliferator-Activated Receptors (PPARs) in Relapsing-Remitting Multiple Sclerosis Patients. *Mult. scler.* 14: S244.
- [45] Shukla DK, Kaiser CC, Stebbins GT et al (2010) Effects of Poliglitzzone on Diffusion Tensor Imaging Indices in Multiple Sclerosis Patients. *Neuroscience Letters* 472: 153-156.
- [46] Cockerill GW, Rye KA, Gamble JR et al (1995) High-Density Lipoproteins Inhibit Cytokine-Induced Expression of Endothelial Cell Adhesion Molecules. *Arterioscler. thromb. vasc. biol.* 15: 1987-1994.
- [47] Nobrega C, Capela C, Gorjon A et al (2011) Plasma Lipoproteins and Intrathecal Immunoglobulin Synthesis in Multiple Sclerosis. *J. neurol.* 258 (Suppl 1): S202.
- [48] Sarov-Blat, L, Kiss RS, Haidar B et al (2007) Predominance of a Proinflammatory Phenotype in Monocyte-Derived Macrophages from Subjects with Low Plasma HDL-Cholesterol. *Arterioscler. thromb. vasc. biol.* 27: 1115-1122.

- [49] Mehling M, Johnson TA, Antel J (2011) Clinical Immunology of the Sphingosine 1-Phosphate Receptor Modulator Fingolimod (FTY720) in Multiple Sclerosis. *Neurology*, 76 (Suppl 3): S20-S27.
- [50] Norimatsu Y, Ohmori T, Kimura A et al (2012) FTY720 Improves Functional Recovery after Spinal Cord Injury by Primarily Nonimmunomodulatory Mechanisms. *Am. J. pathol.* 180: 1625-1635.
- [51] Ferretti G, Bacchetti T (2011) Peroxidation of Lipoproteins in Multiple Sclerosis. *J. neurol. sci.* 311: 92-97
- [52] Haider L, Fisher MT, Frischer JM et al (2011) Oxidative Damage in Multiple Sclerosis Lesions. *Brain* 134: 1914-1924.
- [53] Sena A, Pedrosa R, Roque R et al (2006) Oxidised Low Density Lipoprotein in Serum of Relapsing-Remitting Multiple Sclerosis Patients. *Mult. scler.* 12 (Suppl 1): S168-S169.
- [54] Koch M, Mostert J, Arutjunyan AV et al (2007) Plasma Lipid Peroxidation and Progression of Disability in Multiple Sclerosis. *Eur. j. neurol.* 14: 529-533.
- [55] Mossberg N, Movitz C, Hellstrand K et al (2009) Oxygen Radical Production in Leukocytes and Disease Severity in Multiple Sclerosis. *J. immunol.* 213: 131-134.
- [56] Linker RA, Lee D-H, Ryan S et al (2011) Fumaric Acid Esters Exert Neuroprotective Effects in Neuroinflammation Via Activation of the Nrf2 Antioxidant Pathway. *Brain* 134: 678-692.
- [57] Ludewig B, Laman JD (2004) The In and Out of Monocytes in Atherosclerotic Plaques: Balancing Inflammation through Migration. *Proc. natl. acad. sci. USA* 101: 11529-11530.
- [58] D'haeseleer M, Cambron M, Vanopdenbosch L et al (2011) Vascular Aspects of Multiple Sclerosis. *Lancet neurol.* 10: 657-666.
- [59] Sena A, Pedrosa R, Morais MG (2003) Therapeutical Potential of Lovastatin in Multiple Sclerosis. *J. neurol.* 250: 754-755.
- [60] Vollmer T, Key L, Durkalski V et al (2004) Oral Simvastatin Treatment in Relapsing-Remitting Multiple Sclerosis. *Lancet*, 363: 1607-1608.
- [61] Sena A, Pedrosa R, Morais MG (2007) Beneficial Effect of Statins in Multiple Sclerosis: Is It Dose-Dependent? *Atherosclerosis*, 191: 462.
- [62] Tskiri A, Lakkenbach K, Fuglø D et al (2011) Simvastatin Improves Final Visual Outcome in Acute Optic Neuritis: a Randomized Study. *Mult. scler. j.* 18: 72-81.
- [63] Waubant E, Pelletier D, Mass M et al (2012) Randomized Controlled Trial of Atorvastatin in Clinically Isolated Syndrome. *Neurology* 78:1171-1178.
- [64] Strittmatter WJ, Saunders AM, Schmechel D et al (1993) Apolipoprotein E: High-Avidity Binding to β -Amyloid and Increased Frequency of Type 4 Allele in Late-Onset Alzheimer Disease. *Proc. natl. acad. sci. USA* 90: 1977-1981.
- [65] Corder EH, Saunders AM, Strittmatter WJ (1993) Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late-Onset Families. *Science* 261:921-931.
- [66] Bu G, (2009) Apolipoprotein E and its Receptors in Alzheimer's Disease: Pathways, Pathogenesis and Therapy. *Nat. rev. neuroscience* 10: 333-344.
- [67] Di Paolo G, Kim T-W (2011) Linking Lipids to Alzheimer's Disease. Cholesterol and Beyond. *Nat. rev. neuroscience* 12: 284-296.

- [68] Haan MN (2010) Midlife Cholesterol Level and Dementia 32 Years Later. Is There a Risk? *Neurology* 75: 1862-1863.
- [69] Mielke MM, Zandi PP, Shao H (2010) The 32-Year Relationship Between Cholesterol and Dementia from Midlife to Late Life. *Neurology* 75: 1888-1895.
- [70] Reitz C, Tang M-X, Schupf N et al (2010) Association of Higher Levels of High-Density Lipoprotein Cholesterol in Elderly Individuals and Lower Risk of Late-Onset Alzheimer Disease. *Arch. neurol.* 67: 1491-1497.
- [71] Singh-Manoux A, Gimeno D, Kivimaki M et al (2008) Low HDL Cholesterol Is a Risk Factor for Deficit and Decline in Memory in Midlife. The Whitehall II Study. *Arterioscler. thromb. vasc. biol.* 28: 1556-1562.
- [72] Merched A, Xia Y, Visvikis S et al (2000) The Relation Between Apolipoprotein AI and Dementia. The Honolulu-Asia Aging Study. *Am. j. epidemiol.* 165: 985-992.
- [73] Kutiyama M, Takahashi K, Yamano T et al (1994) Low Levels of Serum Apolipoprotein AI and AII in Senile Dementia. *Jpn j. psychiatry neurol.* 48: 589-593.
- [74] Matsuzaki T, Sasaki K, Hata J et al (2011) Association of Alzheimer Disease Pathology with Abnormal Lipid Metabolism. The Hisayama Study. *Neurology* 77: 1068-1075.
- [75] Van Vliet p, Westendorp RGJ, Eikelenboom P et al (2009) Parental History of Alzheimer Disease Associated with Lower Plasma Apolipoprotein E Levels. *Neurology* 73: 681-687.
- [76] Gupta VB, Laws SM, Villemagne VL et al (2011) Plasma Apolipoprotein E and Alzheimer Disease Risk. The AIBL Study of Aging. *Neurology* 76: 1091-1098.
- [77] Kantarci K, Lowe V, Przybelski SA et al (2012) ApoE Modifies the Association Between A β Load and Cognition in Cognitively Normal Older Adults. *Neurology* 78: 232-240.
- [78] Schrijvers EM, Koudstaal PJ, Hofman A et al (2011) Plasma Clusterin and the Risk of Alzheimer Disease. *Jama* 305: 1322-1326.
- [79] Holmes C, Cunningham C, Zotova E et al (2009) Systemic Inflammation and Disease Progression in Alzheimer Disease. *Neurology* 73: 768-774.
- [80] Iadecola C (2003) Atherosclerosis and Neurodegeneration. Unexpected Conspirators in Alzheimer's Dementia. *Arterioscler. thromb. vasc. biol.* 23: 1951-1953.
- [81] Desai MK, Mastrangelo MA, Ryan DA et al (2010) Early Oligodendrocyte/Myelin Pathology in Alzheimer's Disease Mice Constitutes a Novel Therapeutic Target. *Am. J. pathol.* 177: 1422-1435.
- [82] Cramer PE, Cirrito JR, Wesson DW et al (2012) ApoE-Directed Therapeutics Rapidly Clear β -Amyloid and Reverse Deficits in AD Mouse Models. *Science* 335: 1503-1506.
- [83] Takechi, R, Galloway S, Pallegage-Gamarallage MMS et al (2008) Chylomicron Amyloid-Beta in the Aetiology of Alzheimer's Disease. *Atherosclerosis (Suppl 9)* 19-25.
- [84] Kontush A, Chapman MJ (2008) HDL: Close to Our Memories? *Arterioscler. thromb. vasc. biol.* 28: 1418-1420.
- [85] Elder GA, Cho JY, English DF et al (2007) Elevated Plasma Cholesterol. Does Not Affect Brain A β in Mice Lacking the Low-Density Lipoprotein Receptor. *J. neurochem.* 102: 1220-1231.
- [86] Pistell PJ, Morrison CD, Gupta S et al (2010) Cognitive Impairment Following High Fat Diet Consumption Is Associated with Brain Inflammation. *J. immunol.* 191: 25-32.

- [87] Lieb W, Beiser AS, Vasan RS et al (2009) Association of Plasma Leptin Levels with Incident Alzheimer Disease and MRI Measures of Brain Aging. *Jama* 302: 2565-2572.
- [88] Une K, Takei A, Tomita N et al (2010) Adiponectin in Plasma and Cerebrospinal Fluid in MCI and Alzheimer's Disease. *Eur. j. neurol.* 18: 1006-1009.
- [89] Yaffe K, Weston AL, Blackwell T et al (2009) The Metabolic Syndrome and Development of Cognitive Impairment Among Older Women. *Arch. neurol.* 66: 324-328.
- [90] Craft S (2009) The Role of Metabolic Disorders in Alzheimer Disease and Vascular Dementia. *Arch. neurol.* 66: 300-305.
- [91] Brayne C, Ince PG, Keage H et al (2010) Education, the Brain and Dementia: Neuroprotection or Compensation? *Brain* 133: 2210-2216.
- [92] Belleville S, Clément F, Mellah S et al (2011) Training-Related Brain Plasticity in Subjects at Risk of Development Alzheimer's Disease. *Brain* 134: 1623-1634.
- [93] Cuadrado-Godia E, Jiménez-Conde J, Ois A et al (2009) Sex Differences in the Prognostic Value of the Lipid Profile After the First Ischemic Stroke. *J. neurol.* 256: 989-995.
- [94] Hughes TF, Borenstein AR, Schofield E et al (2009) Association Between Late-Life Body Mass Index and Dementia. The Kame Project. *Neurology* 72: 1741-1746.
- [95] Vidoni ED, Townley RA, Honea RA et al (2011) Alzheimer Disease Biomarkers Are Associated with Body Mass Index. *Neurology* 77: 1913-1920.
- [96] Shepardson NE, Shankar GM, Selkoe DJ (2011) Cholesterol Level and Statin Use in Alzheimer Disease. I. Review of Epidemiological and Preclinical Studies. *Arch. neurol.* 68: 1239-1244.
- [97] De Lau LML, Koudstaal PJ, Hofman A et al (2006) Serum Cholesterol Levels and the Risk of Parkinson's Disease. *Am. j. epidemiol.* 164: 998-1002.
- [98] Huang X, Chen H, Miller WC et al (2007) Lower Low-Density Lipoprotein Cholesterol Levels Are Associated with Parkinson's Disease. *Mov. disord.* 22: 377-381.
- [99] Hu G, Antikainen R, Jousilahti P et al (2008) Total Cholesterol and the Risk of Parkinson Disease. *Neurology* 70: 1972-1979.
- [100] Dupuis L, Corcia P, Fergani A et al (2008) Dyslipidemia Is a Protective Factor in Amyotrophic Lateral Sclerosis. *Neurology* 70: 1004-1009.
- [101] Chiò A, Calvo A, Ilardi A et al (2009) Lower Serum Lipids Are Related to Respiratory Impairment in Patients with ALS. *Neurology* 73: 1681-1685.
- [102] Glass CK, Saijo K, Winner B et al (2010) Mechanisms Underlying Inflammation in Neurodegeneration. *Cell* 140: 918-934.
- [103] Valenza M, Cattaneo E (2011) Emerging Roles for Cholesterol in Huntington's Disease. *Trends in neurosci.* 34: 474-486.
- [104] Whitehead AS, Bertrand S, Finnan F et al (1996) Frequency of the Apolipoprotein E ϵ 4 Allele in a Case-Control Study of Early Onset Parkinson's Disease. *J. neurol. neurosurg. psychiatry* (1996) 61: 347-351.
- [105] Wilhelmus MMM, Bol JGJM, Rozemuller AJM et al (2011) Apolipoprotein E and LRP1 Increase Early in Parkinson's Disease Pathogenesis. *Am. J. pathol.* 179: 2152-2156.

- [106] Thomas EA, Sutcliffe JG (2002) The Neurobiology of Apolipoproteins in Psychiatric Disorders. *Mol. Neurobiol.* 26: 369-388.
- [107] Muffat J, Walker DW, Benzer S (2008) Human ApoD, an Up-Regulated in Neurodegenerative Diseases, Extends Lifespan and Increases Stress Resistance in *Drosophila*. *Proc. natl. acad. sci. USA* 105: 7088-7093.
- [108] Terrise L, Poirier J, Bertrand P et al (1998) Increased Levels of Apolipoprotein D in Cerebrospinal Fluid and Hippocampus of Alzheimer's Patients. *J. neurochem.* 71: 1643-1650.
- [109] Digney A, Keriakous D, Scarr E et al (2005) Differential Changes in Apolipoprotein E in Schizophrenia and Bipolar I Disorder. *Biol. Psychiatry* 57: 711-715.
- [110] Huang JT-J, Wang L, Prabakaran S et al (2008) Independent Protein-Profilig Studies Show a Decrease in Apolipoprotein AI Levels in Schizophrenia CSF, Brain and Peripheral Tissues. *Mol. psychiatry* 13: 1118-1128.
- [111] Zatorre RJ, Fields RD, Johansen-Berg H et al (2012) Plasticity in Gray and White: Neuroimaging Changes in Brain Structure During Learning. *Nat. rev. neurosci.* 15: 528-536.
- [112] Karasinska JM, Rinninger F, Lütjohann et al (2009) Specific Loss of Brain ABCA1 Increases Brain Cholesterol Uptake and Influences Neuronal Structure and Function, *J. neurosci.*, 29: 3579-3589.
- [113] Ruckh JM, Zhao J-W, Shadrach JL et al (2012) Rejuvenation of Regeneration in the Aging Central Nervous System. *Cell stem cell* 10: 96-103.
- [114] Redmond SA, Chan JR (2012) Revitalizing Remyelination—the Answer Is Circulating. *Science* 336: 161-162.
- [115] Cunningham TJ, Yao L, Oettinger M et al (2006) Secreted Phospholipase A2 Activity in Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis. *J. neuroinflammation* 3: 26-33.
- [116] Hesse D, Krakauer M, Lund H et al (2011) Disease Protection and Interleukin-10 Induction by Endogenous Interferon- β in Multiple Sclerosis? *Eur. j. neurol.* 18: 266-272.
- [117] Matarese G, Procaccini C, De Rosa V, (2008) The Intricate Interface Between Immune and Metabolic Regulation: a Role for Leptin in the Pathogenesis of Multiple Sclerosis? *J. leukoc. biol.* 84: 893-899.
- [118] Hietaharju A, Kuusisto H, Nieminen R et al (2010) Elevated Cerebrospinal Fluid Adiponectin and Adipsin Levels in Patients with Multiple Sclerosis: a Finnish Co-Twin Study. *Eur. j. neurol.* 17: 332-334.
- [119] Sena A, Couderc R, Vasconcelos JC et al (2012) Oral Contraceptive Use and Clinical Outcomes in Patients with Multiple Sclerosis. *J. neurol. sci.* 317(1-2): 47-51.
- [120] Neu IS, Prosiegel M, Pfaffenrath V (1982) Platelet Aggregation and Multiple Sclerosis. *Acta neurol. scandinav.* 66:497-504.
- [121] Hawkes CH, (2007) Smoking is a Risk Factor for Multiple Sclerosis: a metanalysis. *Mult. scler.* 13: 610-615.