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Peripheral cholesterol, metabolic disorders and Alzheimer's disease

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1. ABSTRACT

Strong correlations have been made between high levels of blood cholesterol and the risk to suffer Alzheimer's disease (AD). The question arises on how a peripheral event contributes to a disease that so severely affects the integrity and function of the Central Nervous System. Hypercholesterolemia has been also associated to peripheral metabolic disorders like diabetes, obesity or atherosclerosis that, in turn, predispose to AD. Here we review data, which point to alterations in blood cholesterol levels as a link between these metabolic disorders and AD. We describe and discuss common, cholesterol-related, molecular mechanisms and strategies to fight these conditions that, altogether, constitute a major cause of death in our societies.

2. INTRODUCTION

Alzheimer's disease (AD) is a Central Nervous System (CNS) pathology in which cognitive decline and the accumulation in the brain of the amyloid peptide and hyperphosphorylated tau protein are hallmarks (1). However, increasing evidence support the influence of the periphery in the late onset, non-familial forms of the disease, which represent the vast majority of the cases. The origin of the late onset AD is not known but it is now viewed as a multifactorial disorder in which genetic predisposition and environmental factors may play key pathological roles. In contrast, the early onset, familial forms of the disease are caused by mutations in genes encoding for the proteins amyloid precursor protein (APP) and presenilins (2). This observation together with the fact

that the pathological hallmarks, amyloid plaques and neurofibrillary tangles, respond to alterations in the postranslational modification of proteins prompted the attention to protein-based molecular mechanisms leading to disease. More recently, however, lipids are getting central stage in AD pathology. Among them cholesterol has attracted special attention. Increasing genetic, biochemical and clinical evidences support the involvement of brain and peripheral cholesterol in AD. Although still controversial, changes in cholesterol content in brain cell membranes have been related directly to alterations in the processing of APP or Tau phosphorylation (3,4,5,6,7). These findings could explain the potential role of alterations in CNS cholesterol in the disease and have been addressed in recent reviews (8,9,10). Still, a stronger link has been made between peripheral cholesterol levels and the risk to suffer AD. Because there is ample evidence for the independency of peripheral and central cholesterol metabolism (11), the question arises on how blood cholesterol contributes to one of the most common and devastating disorders affecting the CNS. Imbalances in peripheral cholesterol levels are associated to metabolic disorders that, in turn, have been significantly associated to AD risk. They may indeed be among the factors triggering the late onset forms of the disease. This review aims to present and discuss data that unveil cholesterol as a common link between these peripheral metabolic disorders and AD. We also revise the numerous efforts to develop strategies that may represent a treatment for all of them.

3. PERIPHERAL CHOLESTEROL AND AD

Two large retrospective studies reporting a reduction of AD incidence, in as much as 70%, in hypercholesterolemic patients treated with statins (12,13) fostered the idea of a link between high serum cholesterol levels and the disease. Statins are inhibitors of a key enzyme in cholesterol synthesis, HMG-CoA reductase, and efficiently reduce the levels of the circulating lipid (14). This link was also supported by numerous prospective studies analyzing the possible correlation of plasma levels of cholesterol and the risk to suffer AD. In a recent meta-analysis of eighteen of such studies, high total serum cholesterol levels in mid-life were consistently associated with increased risk of AD and dementia (15). These studies involved follow-ups ranged from 3 to 29 years, and included a total of 14,331 participants evaluated for AD.

Cholesterol is transported in the blood stream by lipoproteins. While low density lipoproteins (LDL) carry cholesterol from the liver to the cells, high density lipoproteins (HDL) collect cholesterol from tissues and bring it back to the liver for excretion in the bile in a process known as reverse cholesterol transport. Cholesterol associates with apolipoproteins in lipoprotein particles. Besides age, the inheritage of the E4 allele of the class E of apolipoproteins (apoE4) is the main established risk factor for late onset AD (16). Given the above, a more detailed analysis of the distribution of serum cholesterol in LDL and HDL particles in relation to the disease, and the association with ApoE genotypes appeared relevant. Such analysis had interesting outcome. While total and LDL serum cholesterol levels showed a direct correlation with AD risk, the level of HDL cholesterol in the serum of AD patients was lower than in controls and correlated inversely with the severity of dementia (17). Studies on the ApoE genotypes and LDL-cholesterol association showed the following progression: apoE2<apoE3<apoE4 (18,19,20). In contrast, HDL- cholesterol association showed an opposite tendency: highest in apoE2 carriers and lowest in those apoE4 (19,20). The latest seems to be dose dependent since apoE4/4 carriers showed lower HDL-cholesterol levels than those carrying a single e4 allele (21). The isoform-dependent apoE ability to release cholesterol from cells to generate HDL particles, which is lower for ApoE4 (22,23), has been proposed to explain these observations. Collectively, these results highlight the relevance of taking into account cholesterol association to lipoproteins rather than total cholesterol levels when trying to determine AD risk.

Despite the accumulating evidence supporting a link between serum cholesterol levels and AD, which points to the involvement of lipoproteins and ApoE, we are far from understanding the underlying molecular mechanisms. As stated in the introduction little, if any, relationship exists between serum and brain cholesterol (11). They show independent metabolism and, in fact, no significant correlation between cholesterol levels in the cerebro spinal fluid (CSF) and serum has been found (24,25). This makes unlikely that alterations of peripheral cholesterol levels influence those of the CNS leading to AD brain pathology. Most likely the effect is indirect. In agreement, longitudinal population-based studies, which assessed the incidence of dementia in relation to plasma cholesterol levels taking into account the effects of other vascular risk factors, suggested that the association between cholesterol and dementia depends on these factors (26). Among them, type 2 diabetes, obesity and atherosclerosis constitute main risk co-factors. In turn, evidences support a role for imbalances in serum cholesterol in the pathology of these disorders. Next we summarize and discuss data that point to cholesterol as a common link between these peripheral conditions and AD.

4. CHOLESTEROL, DIABETES AND AD

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by impaired glucose metabolism, increased oxidative stress, insulin resistance and amyloidogenesis. AD patients share these abnormalities (27). Several studies suggest that this is not an epiphenomenon, but rather these two diseases disrupt common molecular pathways. Supporting this view, a study performed in a community cohort revealed that greater than 80% of the AD patients analyzed had T2DM or showed abnormal blood glucose (28). Furthermore, it is widely accepted that T2DM increases significantly the risk to suffer AD, regardless of the age at which T2DM occurs (27). That peripheral cholesterol may be a common link in the pathogenesis of these two diseases is supported by the observation that, as in AD, T2DM generally occurs in the context of abundant LDL particles but low levels of plasma HDL (29). The latter are in addition an independent risk factor for the disease (30).

Peripheral insulin resistance and reduced insulin secretion by pancreatic islet β-cells are hallmarks of T2DM. The reasons for the β-cell dysfunction are not clear but seem to include the accumulation of cholesterol in the islets. Two key molecules in cholesterol homeostasis: the ATP-binding cassette transporter A1 (ABCA1) and the Sterol regulatory element-binding protein (SREBP-2), have been so far related to such accumulation.

ABCA1 is the major regulator of intracellular cholesterol efflux essential in the biogenesis of nascent HDL particles. A number of polymorphisms and mutations in ABCA1 have been associated with T2DM across multiple ethnic groups (31). ABCA1 inactivation (experimentally induced in mice or due to disruptive mutations in humans), leads to markedly impaired glucose tolerance and defective insulin secretion (32). The absence of ABCA1 in humans and animals also leads to nearly absent HDL cholesterol in serum (33) but abnormal accumulation of the lipid in islets (34). It seems that an optimal concentration of cholesterol is essential for the normal exocytosis of insulin granules and appropriate nutrient-stimulated insulin release. A model has emerged in which impaired ABCA1 function, which is directly influenced by serum cholesterol levels (35), leads to elevated islet cholesterol altering β-cell membrane composition and affecting the docking and fusion of insulin containing granules from the ready releasable pool (34,35).

SREBP-2 is a membrane bound transcription factor critical for regulating cellular cholesterol synthesis. In the absence of cholesterol, SREBP-2 is transported from the endoplasmic reticulum to the Golgi where intramembrane proteolysis converts it into an active transcription factor that induces the expression of cholesterol-synthesis genes (36). The presence of cholesterol in cells has the opposite effect, retaining SREBP in the endoplasmic reticulum thus shutting off cholesterol synthesis. Transgenic overexpression of SREBP-2 in β-cells induced a significant elevation of esterified and total cholesterol in islets that was associated with impairment of glucose stimulated insulin secretion and marked impairment in glucose tolerance (37).

The aforementioned findings suggest that cholesterol-induced islet dysfunction can be caused by either decreasing cholesterol efflux from cells (as in the absence of ABCA1), or increasing cholesterol synthesis and uptake (as in the overexpression of SREBP2). Both pathways support the concept of cholesterol accumulation in islets contributing to decreased insulin secretion and propensity to diabetes. Interestingly, sequence variation of the ABCA1 (38,39) and SREBP family (40,41) genes have been linked to AD risk. Still, the question remains on how diabetes predisposes to AD.

Insulin exerts many important functions in the brain. It is involved in synaptic plasticity and long term potentiation (LTP), which are molecular bases for memory acquisition. Diabetic animal models showed impaired spatial learning and hippocampal LTP that was prevented by insulin treatment (42,43). Insulin was also shown to exert cognition-enhancing effects in experimental animals and humans (44). Hence, alterations of brain insulin levels occurring in T2DM could impair cognitive abilities and therefore increase AD risk. Hypercholesterolemia may contribute to such alterations. Evidence indicates that insulin accesses the brain from the circulation by crossing the blood-brain barrier (BBB), the integrity of which is influenced by hypercholesterolemia. The mechanisms underlying this influence are not clear and the proposed effects of high cholesterol levels on BBB are controversial pointing to either and enhancement or impairment of its permeability. ApoE (45) and tight junction proteins (46) are among the molecules that have been proposed to play a role in cholesterol-induced BBB anomalies, which may alter molecular transport into the brain. Interestingly, BBB dysfunction has been proposed to contribute to the pathogenesis of AD (47). On the other hand, the imbalance during the disease process between the two fundamental abnormalities involved in T2DM, insulin resistance and poor secretion, often leads to hyperinsulinemia. Paradoxically, increased blood insulin reduces its transport across the BBB, subsequently lowering the levels and activity of this hormone in the brain (48). This could compromise the aforementioned roles of insulin in cognition. That a similar scenario may take place in AD comes from the observations of high plasma insulin but reduced CSF insulin and brain insulin-signalling markers in AD patients (49).

Besides the impact in cognition, alterations of brain insulin levels seem to have a direct influence in the appearance of neurofibrillary tangles and amyloid plaques. Hence, reduced brain insulin signalling is associated with increased tau phosphorylation and experimentally induced diabetes exacerbates tau pathology in AD mouse models (50,51). Diabetic rats showed increased Aβ levels accompanied by decrease efflux of the peptide from the brain and decreased activity of Aβ degrading enzymes such as neprilysin (NEP), endothelin-converting enzyme 1 (ECE-1) and insulin degrading enzyme (IDE) (52).

Altogether these findings support a model in which low levels of insulin in the CNS of AD patients, which could be promoted by alterations in BBB permeability due to hypercholesterolemia and T2DM, favour cognitive impairment, tau phosphorylation and amyloid accumulation. In contrast, a series of results support the view that high insulin levels contribute to AD by enhancing extracellular accumulation of Aβ (53). In agreement, it was reported that insulin increases Aβ release by cultured neurons (54) and the infusion of insulin in human subjects led to a rapid increase in CSF Aβ levels (55). Moreover, it has been proposed that high amounts of insulin will compete with Aβ for their degrading enzyme IDE, therefore impairing the peptide clearance (54). Although evidence for high levels of insulin in the CSF of AD patients have not been reported all the above suggests that T2DM can favour AD by several ways. More work is required to clarify the mechanisms involved. Concurrence with genetic alterations (i.e. particular single nucleotide polymorphisms (SNPs)) or exposure to certain environmental factors may explain why not all T2DM-affected individuals develop AD.

5. CHOLESTEROL, OBESITY AND AD

Obesity is characterized by the presence of excessive amount of adipose tissue. It is a physiological response to the environment and behaviour, in which energy intake exceeds energy output. The body mass index (BMI kg/m2) is used for its assessment.

Although less clear than for T2DM growing evidence suggests an association between obesity in middle age and risk of dementia later in life (56,57,58). In addition, a direct link between BMI and plasma Aβ levels has been reported (59). Obesity is commonly associated with insulin resistance (60), hyperinsulinemia and T2DM (61,62,63). The risk of development of diabetes is clearly higher as the degree of overweight increases (64). Regarding the link between obesity and AD several mechanisms may explain it. As occurs with T2DM, obesity shares with AD a common profile of altered blood cholesterol distribution. In fact, the levels of HDL cholesterol are lower in obese than in lean subjects (61,65) while total and LDL cholesterol can be elevated (61,66,67). Moreover, increasing BMI correlates with LDL particle levels (68). On the other hand, high food intake and weight gain are associated and may be causally related to reduced insulin delivery into the CNS (69). As mentioned before insulin deficits will have deleterious effects on cognition. Yet, low brain leptin levels may be another mechanism by which obesity could lead to brain dysfunction. Together with insulin, leptin is an adiposity signal for the long-term regulation of body weight by the brain and its ablation is sufficient to cause obesity (70). Both, insulin and leptin, dynamically regulate each other. Loss of leptin restraint in insulin secretion leads to hyperinsulinemia, insulin resistance and β-cell loss therefore contributing to T2DM (71). Although there is some evidence that leptin can be synthesized in the brain (72), it is believed that the majority of leptin in the CNS is derived from peripheral white adipose tissue (73). Insulin promotes the transport of leptin across the BBB (74). The reduced transport to the brain of the former observed in obesity (75) may thus explain, at least in part, the decreased transport of leptin across the BBB also reported in obese humans and rodents (76).

As for insulin, important roles in the brain have been assigned for leptin. It seems to participate in cognition facilitating LTP and synaptic plasticity in the hippocampus, and improving memory function in animal models of aging and AD (77,78,79). Moreover, this hormone appears to influence a number of features defining AD. Indeed, it has been shown to reduce the amount of extracellular Aβ, both in cell culture and animal models, as well as to reduce tau phosphorylation in neuronal cells and to improve memory in AD animal models (80,81). Interestingly, leptin reduces amyloid accumulation and Tau phosphorylation induced by hydroxysterols (82). Accumulating data suggests that AD patients bear low plasma leptin levels and a negative correlation between circulating leptin concentrations and severity of dementia has been observed (83). Likewise, high circulating levels of leptin correlate with a reduced incidence of dementia and AD (84).

The above findings support a model in which hypercholesterolemia contributes to brain dysfunction by reducing transport into the brain of insulin and leptin, which play a role in the physiology of neural transmission.

6. CHOLESTEROL, ATHEROSCLEROSIS AND AD

Atherosclerosis is a condition in which an artery wall thickens as the result of a build-up of fatty materials. A chronic inflammatory response in the walls of arteries occurs in this syndrome, in large part due to the accumulation of macrophage white blood cells. Several studies have identified atherosclerosis as a risk factor for AD (85,86,87) and a strong association with the presence of amyloid plaques has been found (86). It has been shown that an atherogenic diet exacerbates cerebral β-amyloidosis and impairs learning capacities in AD animal models (88). These results suggest that synergistic mechanisms may be involved in the pathogenesis of atherosclerosis and AD. This may also apply for atherosclerosis and T2DM, since insulin resistance and hyperinsulinemia profoundly accelerate the development of the former. It is calculated that as much as 80% of people with T2DM will die from concurrent cardiovascular complications of atherosclerosis (89).

Cholesterol is a central player in this pathology. Low HDL levels and a preponderance of LDL particles characterize atherosclerosis and are the major cause of its incidence in obese and T2DM patients (90). As mentioned before similar serum lipid profile is present in AD patients. A growing bulk of evidence suggests that oxysterols, which are cholesterol oxidation derivatives, make a significant contribution to the vascular remodelling that occurs in atherosclerosis and are consistently found within the characteristic lesions of this disease, both in experimental animals and in humans (91). Oxysterols have been involved in key steps of the atherogenic process: endothelial cell dysfunction, adhesion of circulating blood cells, foam cell formation and vascular cell apoptosis. Moreover, oxysterols have been demonstrated to be at least one or two orders of magnitude more reactive than unoxidized cholesterol in exerting pro-inflammatory and pro-apoptotic effects. Thus, a pathological level of cholesterol oxidation in the vasculature has been proposed as the molecular link between hypercholesterolemia and the formation of atherosclerotic lesions (91). Supporting this view, the anti-atherogenic properties of HDLs include not only the promotion of cellular cholesterol efflux and reverse cholesterol transport but also their antioxidant effects (92).

A strong lipid load promotes macrophage activation, which is a hallmark in atherosclerosis and in insulin resistance. These cells can handle such load by differentiating into foam cell macrophages, which take up and accumulate oxidized LDL and promote cholesterol efflux or storage in lipid droplets (93). However, prolonged lipid exposure results in failure of these lipid-handling mechanisms leading to lipotoxicity and cellular damage

(94,95). The action of ABCA1 and acyl-CoA-cholesterol acyltransferase (ACAT) can modulate these effects. ABCA1 favours the endocytosis of modified lipoproteins that are hydrolyzed in degradative organelles to yield free cholesterol, which is subsequently targeted to the plasma membrane and directed towards reverse cholesterol transport. Consistently, ABCA1 mutations or deficiency lead to atherosclerosis in humans and animals (96,97). ACAT esterifies free cholesterol that has been targeted to the ER producing cholesterol esters. Foam cells accumulate very high levels of these esters, which indeed characterize atherosclerotic lesions, and manage to maintain low free cholesterol levels. However, in the advanced stages of plaque development there is a progressive increase in the conversion of cholesterol ester into free cholesterol leading to toxicity due to the capacity of the later to modify membrane fluidity and induce apoptosis (98).

As with diabetes or obesity the question arises on how atherosclerosis may contribute to AD. Besides the negative effect that atherosclerosis of brain vessels have in cognition (99,100) peripheral atherosclerosis could also contribute to AD further reducing cerebral blood flow. Evidences point to neuronal energy crisis, due to chronic brain hypoperfusion, as responsible for protein synthesis defects that result in dysfunction and AD neurodegenerative lesions (101,102). In agreement, chronic brain hypoperfusion established in rats and AD mice models by carotid artery occlusion resulted in upregulation of BACE1, increased Aβ fibrils, accelerated Aβ deposition, and cognitive impairment (103,104).

7. PERIPHERAL CHOLESTEROL AS THERAPEUTICAL TARGET FOR METABOLIC DISORDERS AND AD

The research described above identified a number of molecules that could play roles in the pathology of metabolic disorders and AD having in common their involvement in peripheral cholesterol regulation. These are now envisioned as possible therapeutical targets. Studies have been already performed to test the benefits of their modulation, *in vitro* and *in vivo,* in experimental animals and in humans. These are summarized next.

7.1. Reducing LDL cholesterol levels

From the findings here reviewed it derives that total serum cholesterol and LDL levels are consistently increased in diabetic, obese, atherosclerotic and AD patients and that high levels in mid life elevate the risk to suffer these disorders. Hence, the use of strategies to lower LDL levels appears suitable for their prevention. Statin therapy is most efficient in achieving this goal. These inhibitors of HMG CoA reductase not only reduce cholesterol synthesis but also increase the number of surface LDL receptors enhancing the rate of clearance of LDL cholesterol from the plasma (105). Statins have already shown beneficial effects for the treatment or prevention of the metabolic disorders here considered. The benefits of statin therapy in T2DM have been confirmed and extended such that it is now proposed that the overwhelming majority of diabetic patients should be considered for this therapy (106). Clinical trials assessing the effects of statins on atherosclerosis using quantitative coronary angiography or intravascular ultrasound showed that these drugs can reduce progression or even cause regression of atherosclerotic plaque. This improvement of vascular structure after statin treatment is actually correlated with reductions in LDL cholesterol levels (107). Regarding the association between statins and AD, retrospective studies revealed that AD risk was 70% reduced in patients with hypercholesterolemia treated with these drugs (12,13). However, more recent large-scale randomized clinical trials do not confirm that statins reduce the risk of dementia or decelerate cognitive decline (108,109). Still, because these trials were performed at old age, the possibility that the use of statins in middle age could be beneficial for cognitive function later in life cannot be ruled out.

7.2. Increasing HDL cholesterol levels

Levels of HDL cholesterol in blood show the opposite correlation with metabolic disorders and AD than those of LDL cholesterol. In fact, low and not high HDL levels are consistently present in the patients of these diseases and are a risk to suffer them. Evidences support that HDL decrease is as deleterious, or even more, for human health than LDL increase (110). Therefore, elevating HDL levels is envisioned as a potential therapy. Several strategies have been explored with this aim.

Decreasing cholesterol synthesis by statin treatment not only reduces serum total cholesterol and LDL levels but also increases those of HDL cholesterol as well as HDL/LDL and HDL/total cholesterol ratios (111,112,113). However, the incidence of major cardiovascular events remains considerable (25-45%) even in patients treated with most aggressive statin regimens. It is thought that the limited effect of statins in modulating HDL levels could explain this observation. Research to solve this problem led to the discovery of other compounds more efficient in raising HDL particles. The most effective agent currently available to increase HDL is nicotinic acid or niacin (114). Niacin blocks the breakdown of fats in adipose tissue, causing a decrease in the levels of triglycerides in the blood. Exchange with triglycerides promotes the transfer of cholesterol esters from HDL to VLDL or LDL particles that is mediated by the cholesterol ester transfer protein (CETP). Thus, trygliceride reduction attenuates such transfer increasing the levels of cholesterol HDL while decreasing those LDL associated (115,116). Consistently, a strong negative correlation exists between triglyceride levels and plasma HDL-cholesterol concentrations (117). Furthermore, inhibition of CETP results in similar effects on HDL cholesterol levels than niacin treatments (118) and mice transgenically expressing the human CETP have lower HDL levels, which are increased upon nicotinic acid treatment (117). Hence, inhibitors of this protein are also envisioned as a strategy to increase HDL levels. Several CETP chemical inhibitors have been identified (116). Phase I and phase II trials with some of them (i.e. anacetrapib) have revealed a good tolerance and efficacy as antiatherogenic agents (116,120). Suitability of these inhibitors to prevent AD needs

evaluation but studies reporting that CETP behaves as a modifier gene of the AD risk (121,122), supports the convenience of such evaluation. Yet another potential mechanism by which nicotinic acid increases HDL-cholesterol and decreases the progression of atherogenesis may involve macrophages that express the nicotinic receptor. Nicotinic acid enhances peroxisome proliferator-activated receptor (PPAR) gamma- and cAMP-dependent expression of receptors promoting reverse cholesterol transport, thus enhancing the removal of the lipid from peripheral macrophages and foam cells of atherosclerosis lesions (123,124,125). Recent trials showed that the combination of statin and niacin is an effective treatment not only for dyslipidaemia (high LDL cholesterol, high triglyceride and low HDL cholesterol), but also for carotid intima-media thickness, which is one of the important features of atherosclerosis (126). These effects are also beneficial in diabetic patients (127). That this could also be a suitable strategy to prevent AD comes from the results obtained in a prospective study, which concluded that dietary niacin protects against AD and age related cognitive decline (128).

Decreasing intestinal cholesterol absorption is another way to increase HDL cholesterol levels in the blood. It also leads to an upregulation of LDL-receptors on the cell surface and increased LDL-cholesterol uptake into cells, thus decreasing levels of serum LDL. Niemann Pick C1 like protein (NPC1L1) plays a key role in the absorption of intestinal cholesterol (129). In agreement, NPC1L1 null mice are completely resistant to diet-induced hypercholesterolemia (130). NPC1L1 was found to be the molecular target of Ezetimibe, a class 2-azetidinone that efficiently lowers plasma cholesterol (131,132). The combination of ezetimibe with statins, a therapeutic regimen that inhibits both the absorption and synthesis of cholesterol, offers a well-tolerated and efficacious treatment to lower LDL and increase HDL cholesterol and has been more effective than monotherapy alone in many randomized trials (133).

Improving reverse cholesterol transport is, besides decreasing synthesis or absorption of the lipid, yet a third strategy to elevate cholesterol associated HDL. ABCA1 is, as mentioned before, a key molecule in such process. ABCA1 exports cholesterol by a multistep pathway that involves its binding to apolipoproteins. ABCA1 mutations or deficiency reduce plasma HDL levels, accelerate atherogenesis (96) and increase the T2DM risk. Overexpression of ABCA1 reduces Aβ deposition in AD mouse models (134) and association of ABCA1 genetic variants have been made with risk for AD (135). The ABCA1 pathway has therefore become a promising new therapeutic pathway for all these conditions (136). The nuclear hormone receptors Liver X receptors (LXR) alpha and PPARgamma are direct or indirect regulators of ABCA1 expression. The synthesis of specific and potent ligands for these receptors has aided in ascertaining the potential therapeutic utility of modulators of these receptors in dyslipidemias and cardiovascular disease. Fibrates are among these ligands with ability to enhance the expression of LXRs, PPARs and ABCA1 mRNAs (137). They also lower levels of triglycerides thus reducing CETP activity (118). Fibrates reduce body weight gain and adiposity (136) and show beneficial effects in atherosclerosis and diabetes (116,139). It has been reported that their use also reduces plasma Aβ levels in humans (140) and the risk of dementia (141). However, other studies have shown the ability of a type of fibrate, fenofibrate, in increasing Aβ42 production in mice brains. This effect would not be directly related to the cholesterol lowering ability but to the targeting and activation of the amyloid producing gamma secretase (142). Thiazolisinediones are another group of compounds with the ability to bind to PPARgamma. Among them, rosiglitazone, has been shown to upregulate ABCA1 in β cells improving insulin sensitivity and glucose tolerance. It is in fact used as an anti-diabetic drug. Moreover, it prevents binding of Aβoligomers through its insulin signalling action (143), attenuates memory deficits in animal models for AD (144,145) and improves memory and cognition in clinical trials with AD patients (146,147).

The above reported evidences argue in favour of the use of common, cholesterol-related, strategies for the prevention and/or treatment of metabolic disorders like T2DM, obesity or atherosclerosis, and for AD (Table 1). Still, the timing of such strategies appears most critical (26). As a matter of fact, the effect of high serum cholesterol levels on dementia risk occurs in mid but not late-life (15). Likewise, the risk of dementia is generally larger when vascular factors appear in midlife (148). Because of the importance of early timing, diagnostic tools become essential to prevent and cure AD. CSF analysis, neuropsychological testing or neuroimaging techniques are currently used for AD diagnosis. Unfortunately, these are difficult and expensive protocols unable to detect disease in large-scale population samples at early stages when preventive intervention would be most useful. Simple-blood tests would be particularly useful for this purpose. In this regard, changes in the levels of a number of plasma signalling proteins have been identified as a signature predicting progression to AD. This, however, seems to be suitable only in preclinical patients already showing mild cognitive impairment (149). A recent analysis of lipid metabolism in plasma of AD patients and of their cognitively normal first-degree relatives, points to the use of peripheral cholesterol determinations as a tool for an even earlier diagnosis (150). In this regard, plasma HDL cholesterol levels identified a subset of midlife subjects with major risk to develop AD. Moreover, HDL cholesterol levels, but not those of triglycerides, had been shown to significantly predict vascular risk among T2DM patients (151). Therefore, results from peripheral cholesterol distribution could be the basis for initiation of cholesterol-related therapies to prevent not only AD but also, given the information here reviewed, metabolic disorders.

8. PERSPECTIVE

Hypercholesterolemia is a common pathological hallmark in a number of systemic diseases, such as T2DM, obesity or atherosclerosis, sometimes a cause sometimes a consequence. High LDL and low HDL cholesterol levels

Table 1. Strategies to modulate LDL and HDL serum cholesterol levels and their application in metabolic disorders and/or AD

Compound	Effect on HDL/LDL levels	Cellular process involved	Benefits in metabolic disorders	Benefits in AD
Statins	Decrease LDL Increase HDL	Reduce cholesterol synthesis by inhibiting HMG CoA reductase	Reduce atherosclerotic plaques	Reduce incidence
Niacin	Decrease LDL Increase HDL	Lowers cholesterol transfer from HDL to LDL by decreasing blood triglycerides	Reduces carotid thickness	Protects against AD/cognitive decline
CETP inhibitors	Decrease LDL Increase HDL	Lower cholesterol transfer from HDL to LDL by inhibiting CETP	Antiatherogenic agents	Not determined
Class 2-azetidinones	Decrease LDL Increase HDL	Decrease intestinal cholesterol absorption by inhibiting NPC1L1	Improve carotid atherosclerosis Reduce insulin resistance	Not determined
Fibrates	Decrease LDL Increase HDL	Upregulate ABCA1 by modulating nuclear hormone receptors	Reduce adiposity Antiatherogenic agents	Reduce dementia risk
Thiazolisinediones	Decrease LDL Increase HDL	Upregulate ABCA1 by modulating PPARgamma	Reduce insulin resistance Antiatherogenic potential	Improve memory and cognition

The table includes: i) compounds used in animal and/or human treatments; ii) effects on HDL and LDL levels; iii) cellular process involved and iv) benefits described for metabolic disorders and/or AD.

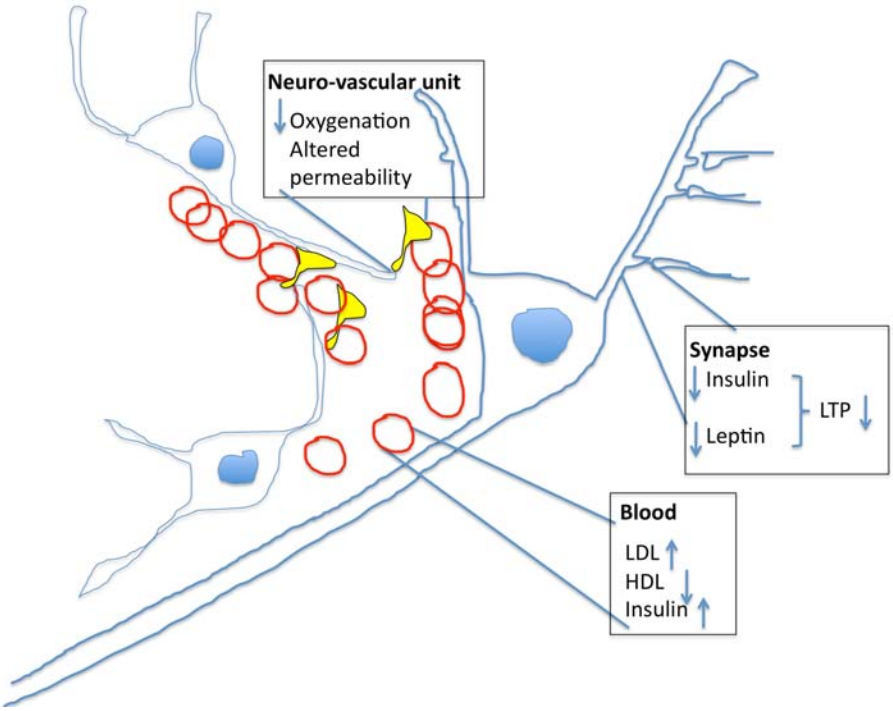

Figure 1. Direct and indirect effects of hypercholesterolemia-associated diseases. Schematized view of cholesterol-related features characterizing peripheral metabolic disorders (diabetes, obesity, atherosclerosis) and Alzheimer's disease, which support common disease mechanisms.

are shared features in these diseases and appear to play key pathological roles. In individuals who carry particular SNPs, mutations or were exposed to environmental insults in critical stages of development or in the adult life, these peripheral pathologies can lead to brain dysfunction of different degrees, including AD. Brain dysfunction can occur through direct impact in brain cell physiology (i.e. due to altered brain insulin levels) or indirectly, due to changes in brain oxygenation and permeability. Most likely, severe dysfunction is due to both (Figure 1). Irrespective of what makes certain individuals more prone to acquire cognitive problems than others or what mechanisms produce brain dysfunction, strategies that correct LDL and HDL alterations appear as a most promising approach to prevent that an individual affected by a peripheral disease in any given stage of life, becomes mentally ill later on.

All in all, the above correlations reinforce the view that, except for a few cases, peripheral conditions are crucially involved in AD. This opens the perspective to use more straightforward strategies for prevention and/or

treatment of the disease than those a priori envisioned for brain pathologies. In this context, a healthy lifestyle that prevents metabolic disorders like T2DM, obesity or atherosclerosis, and the immediate intervention when these pathologies arise, appear as good ways to enjoy a mentally healthy aging.

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