

## Peripheral cholesterol, metabolic disorders and Alzheimer's disease

Maria Dolores Ledesma<sup>1</sup>, Carlos Gerardo Dotti<sup>1,2,3</sup>

<sup>1</sup>Center for Molecular Biology Severo Ochoa CSIC-UAM, Madrid, Spain, <sup>2</sup>VIB Department of Molecular and Developmental Genetics, <sup>3</sup>Catholic University of Leuven, Department of Human Genetics, Leuven, Belgium

### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Peripheral cholesterol and AD
4. Cholesterol, diabetes and AD
5. Cholesterol, obesity and AD
6. Cholesterol, atherosclerosis and AD
7. Peripheral cholesterol as therapeutic target for metabolic disorders and AD
  - 7.1. Reducing LDL cholesterol levels
  - 7.2. Increasing HDL cholesterol levels
8. Perspective
9. Acknowledgements
10. References

## 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 posttranslational 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 inheritance 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  $\beta$ -cells are hallmarks of T2DM. The reasons for the  $\beta$ -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  $\beta$ -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  $\beta$ -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 an 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 A $\beta$  levels accompanied by decreased efflux of the peptide from the brain and decreased activity of A $\beta$  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 A $\beta$  (53). In agreement, it was reported that insulin increases A $\beta$  release by cultured neurons (54) and the infusion of insulin in human subjects led to a rapid increase in CSF A $\beta$  levels (55). Moreover, it has been proposed that high amounts of insulin will compete with A $\beta$  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/m<sup>2</sup>) 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 A $\beta$  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  $\beta$ -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 A $\beta$ , 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  $\beta$ -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 A $\beta$  fibrils, accelerated A $\beta$  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 therapeutic 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, triglyceride 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 A $\beta$  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, PPARGs 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 A $\beta$  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 A $\beta$ 42 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). Thiazolidinediones are another group of compounds with the ability to bind to PPARGamma. Among them, rosiglitazone, has been shown to upregulate ABCA1 in  $\beta$  cells improving insulin sensitivity and glucose tolerance. It is in fact used as an anti-diabetic drug. Moreover, it prevents binding of A $\beta$ oligomers 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

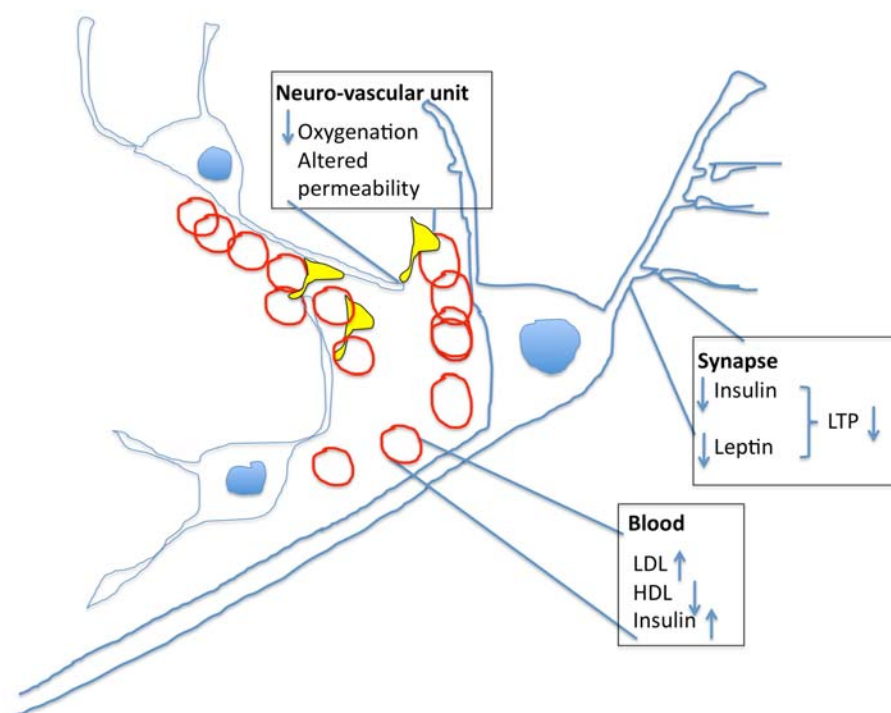
Hypercholesterolemia is a common pathological hallmark in a number of systemic diseases, such as T2DM, obesity or atherosclerosis, sometimes a cause sometimes a consequence. High LDL and low HDL cholesterol levels

## Hypercholesterolemia in Alzheimer's disease

**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.

### 9. ACKNOWLEDGEMENTS

This work was supported by an institutional grant of the Fundación Ramón Areces and by grants of the Ministerio de Ciencia e Innovación (SAF 2008-01473 to M.D.L.; SAF-2010-14906 to C.G.D and Consolider-Ingenio 2010 CSD2010-00045 to M.D.L and C.G.D) and of the Fund for Scientific Research Flanders (FWO), Federal Office for Scientific Affairs (IUAP P6/43), SAO-FRMA Grant and Flemish Government's Methusalem Grant to C.G.D.

### 10. REFERENCES

1. D.H. Small, S.S. Mok and J.C. Bornstein: Alzheimer's disease and Abeta toxicity: from top to bottom. *Nat. Rev. Neurosci.* 2, 595–598 (2001)
2. D.L. Price and S.S. Sisodia: Mutant genes in familial Alzheimer's disease and transgenic models. *Annu. Rev. Neurosci.* 21, 479–505 (1998)
3. K. Fassbender, M. Simons, C. Bergmann, M. Stroick, D. Lutjohann, P. Keller, H. Runz, S. Kuhl, T. Bertsch, K. von Bergmann, M. Hennerici, K. Beyreuther and T. Hartmann: Simvastatin strongly reduces levels of Alzheimer's disease beta-amyloid peptides Abeta 42 and Abeta 40 *in vitro* and *in vivo*. *Proc. Natl. Acad. Sci. U. S. A.* 98, 5856–5861 (2001)
4. J. Abad-Rodriguez, M.D. Ledesma, K. Craessaerts, S. Perga, M. Medina, A. Delacourte, C. Dingwall, B. De Strooper and C.G. Dotti: Neuronal membrane cholesterol loss enhances amyloid peptide generation. *J. Cell Biol.* 167, 953–960 (2004)
5. B. Hutter-Paier, H.J. Huttunen, L. Puglielli, C.B. Eckman, D.Y. Kim, A. Hofmeister, R.D. Moir, S.B. Domnitz, M.P. Frosch, M. Windisch and D.M. Kovacs: The ACAT inhibitor CP-113,818 markedly reduces amyloid pathology in a mouse model of Alzheimer's disease. *Neuron* 44, 227–238 (2004)
6. A. Crameri, E. Biondi, K. Kuehnle, D. Lutjohann, K.M. Thelen, S. Perga, C.G. Dotti, R.M. Nitsch, M.D. Ledesma and M.H. Mohajeri: The role of seladin-1/DHCR24 in cholesterol biosynthesis, APP processing and Abeta generation *in vivo*. *EMBO J.* 25, 432–443 (2006)
7. A.M. Nicholson and A. Ferreira: Increased membrane cholesterol might render mature hippocampal neurons more susceptible to beta-amyloid-induced calpain activation and tau toxicity. *J. Neurosci.* 29, 4640–4651 (2009)
8. M.D. Ledesma and C.G. Dotti CG: Amyloid excess in Alzheimer's disease: what is cholesterol to be blamed for? *FEBS Lett.* 580, 5525–5532 (2006)
9. L. Canevari and J.B. Clark: Alzheimer's disease and cholesterol: the fat connection. *Neurochem Res.* 32, 739–750 (2007)
10. R. Bhattacharyya and D.M. Kovacs: ACAT inhibition and amyloid beta reduction. *Biochim Biophys Acta.* 1801, 960–965 (2010)
11. J.M. Dietschy and S.D. Turley: Cholesterol metabolism in the brain, *Curr. Opin. Lipidol.* 12, 105–112 (2001)
12. H. Jick, G.L. Zornberg, S.S. Jick, S. Seshadri and D.A. Drachman: Statins and the risk of dementia, *Lancet* 356, 1627–1631 (2000)
13. B. Wolozin, W. Kellman, P. Ruosseau, G.G. Celesia and G. Siegel: Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, *Arch. Neurol.* 57, 1439–1443 (2000)
14. J.L. Goldstein and M.S. Brown: Regulation of the mevalonate pathway, *Nature* 343, 425–430 (1990)
15. K.J. Anstey, D.M. Lipnicki and L.F. Low: Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am J Geriatr Psychiatry.* 16, 343–354 (2008)
16. E.H. Corder, A.M. Saunders, W.J. Strittmatter, D.E. Schmechel, P.C. Gaskell, G.W. Small, A.D. Roses, J.L. Haines and M.A. Pericak-Vance: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261, 921–923 (1993)
17. A. Merched, Y. Xia, S. Visvikis, J.M. Serot and G. Siest: Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease. *Neurobiol Aging.* 21, 27–30 (2000)
18. J. Davignon, R.E. Gregg and S.F. Sing: Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis.* 8, 1–21 (1988)
19. L. Braeckman, D. De Bacquer, M. Rosseneu and G. De Backer: Apolipoprotein E polymorphism in middle-aged Belgian men: phenotype distribution and relation to serum lipids and lipoproteins. *Atherosclerosis.* 120, 67–73 (1996)
20. R. Frikke-Schmidt, B.G. Nordestgaard, B. Agerholm-Larsen, P. Schnohr and A. Tybjaerg-Hansen: Context-dependent and invariant associations between lipids, lipoproteins, and apolipoproteins and apolipoprotein E genotype. *J Lipid Res.* 41, 1812–1822 (2000)
21. T. Hoshino, K. Kamino and M. Matsumoto: Gene dose effect of the APOE-epsilon4 allele on plasma HDL cholesterol level in patients with Alzheimer's disease. *Neurobiol Aging.* 23, 41–45 (2002)



22. M. Michikawa, Q.W. Fan, I. Isobe, K. Yanagisawa: Apolipoprotein E exhibits isoform-specific promotion of lipid efflux from astrocytes and neurons in culture. *J Neurochem.* 74, 1008-1016 (2000)
23. J.S. Gong, M. Kobayashi, H. Hayashi, K. Zou, N. Sawamura, S.C. Fujita, K. Yanagisawa and M. Michikawa: Apolipoprotein E (ApoE) isoform-dependent lipid release from astrocytes prepared from human ApoE3 and ApoE4 knock-in mice. *J Biol Chem.* 277, 29919-29926 (2002)
24. A.M. Fagan, L.H. Younkin, J.C. Morris, J.D. Fryer, T.G. Cole, S.G. Younkin and D.M. Holtzman: Differences in the Abeta40/Abeta42 ratio associated with cerebrospinal fluid lipoproteins as a function of apolipoprotein E genotype. *Ann Neurol.* 48, 201-210 (2000)
25. K. Fassbender, M. Stroick, T. Bertsch, A. Ragoeschke, S. Kuehl, S. Walter, J. Walter, K. Brechtel, F. Muehlhauser, K. Von Bergmann and D. Lütjohann: Effects of statins on human cerebral cholesterol metabolism and secretion of Alzheimer amyloid peptide. *Neurology.* 59, 1257-1258 (2002)
26. R.P. Kloppenborg, E. van den Berg, L.J. Kappelle and G.J. Biessels: Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *Eur J Pharmacol.* 585, 97-108 (2008)
27. A. Jones, P. Kulozik, A. Ostertag and S. Herzig: Common pathological processes and transcriptional pathways in Alzheimer's disease and type 2 diabetes. *J Alzheimers Dis.* 16, 787-808 (2009)
28. J. Janson, T. Laedtke, J.E. Parisi, P. O'Brien, R.C. Petersen and P.C. Butler: Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes.* 53, 474-481 (2004)
29. J.K. Kruit, L.R. Brunham, C.B. Verchere and M.R. Hayden: HDL and LDL cholesterol significantly influence beta-cell function in type 2 diabetes mellitus. *Curr Opin Lipidol.* 21, 178-185 (2010)
30. A. von Eckardstein and G. Assmann: Prevention of coronary heart disease by raising high-density lipoprotein cholesterol? *Curr Opin Lipidol.* 11, 627-637 (2000)
31. L.R. Brunham, J.J. Kastelein and M.R. Hayden: ABCA1 gene mutations, HDL cholesterol levels, and risk of ischemic heart disease. *JAMA.* 300, 1997-1998 (2008)
32. M. Vergeer, L.R. Brunham, J. Koetsveld, J.K. Kruit, C.B. Verchere, J.J. Kastelein, M.R. Hayden and E.S. Stroes: Carriers of loss-of-function mutations in ABCA1 display pancreatic beta-cell dysfunction. *Diabetes Care.* 33, 869-74 (2010)
33. R.R. Singaraja, L.R. Brunham, H. Visscher, J.J. Kastelein and M.R. Hayden: Efflux and atherosclerosis: the clinical and biochemical impact of variations in the ABCA1 gene. *Arterioscler Thromb Vasc Biol.* 23, 1322-1332 (2003)
34. L.R. Brunham, J.K. Kruit, T.D. Pape, J.M. Timmins, A.Q. Reuwer, Z. Vasanji, B.J. Marsh, B. Rodrigues, J.D. Johnson, J.S. Parks, C.B. Verchere and M.R. Hayden: Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. *Nat Med.* 13, 340-347 (2007)
35. L.R. Brunham, J.K. Kruit, M.R. Hayden and C.B. Verchere: Cholesterol in beta-cell dysfunction: the emerging connection between HDL cholesterol and type 2 diabetes. *Curr Diab Rep.* 10, 55-60 (2010)
36. M.S. Brown and J.L. Goldstein: The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. *Cell.* 89, 331-340 (1997)
37. M. Ishikawa, Y. Iwasaki, S. Yatoh, T. Kato, S. Kumadaki, N. Inoue, T. Yamamoto, T. Matsuzaka, Y. Nakagawa, N. Yahagi, K. Kobayashi, A. Takahashi, N. Yamada and H. Shimano: Cholesterol accumulation and diabetes in pancreatic beta-cell-specific SREBP-2 transgenic mice: a new model for lipotoxicity. *J Lipid Res.* 49, 2524-2534 (2008)
38. E. Rodriguez-Rodriguez, I. Mateo, J. Llorca, C. Sánchez-Quintana, J. Infante, I. García-Gorostiaga, P. Sánchez-Juan, J. Berciano and O. Combarros: Association of genetic variants of ABCA1 with Alzheimer's disease risk. *Am J Med Genet B Neuropsychiatr Genet.* 144B, 964-968 (2007)
39. C.A. Reynolds, M.G. Hong, U.K. Eriksson, K. Blennow, A.M. Bennet, J.B. Johansson, B. Malmberg, S. Berg, F. Wiklund, M. Gatz, N.L. Pedersen and J.A. Prince: A survey of ABCA1 sequence variation confirms association with dementia. *Hum Mutat.* 1348-1354 (2009)
40. C.A. Reynolds, M.G. Hong, U.K. Eriksson, K. Blennow, F. Wiklund, B. Johansson, B. Malmberg, S. Berg, A. Alexeyenko, H. Grönberg, M. Gatz, N.L. Pedersen, J.A. Prince: Analysis of lipid pathway genes indicates association of sequence variation near SREBF1/TOM1L2/ATPAF2 with dementia risk. *Hum Mol Genet.* 19, 2068-2078 (2010)
41. S. Le Hellard, T.W. Mühleisen, S. Djurovic, J. Fernø, Z. Ouriaghi, M. Mattheisen, C. Vasilescu, M.B. Raeder, T. Hansen, J. Strohmaier, A. Georgi, F.F. Brockschmidt, I. Melle, I. Nenadic, H. Sauer, M. Rietschel, M.M. Nöthen, T. Werge, O.A. Andreassen, S. Cichon and V.M. Steen: Polymorphisms in SREBF1 and SREBF2, two antipsychotic-activated transcription factors controlling cellular lipogenesis, are associated with schizophrenia in German and Scandinavian samples. *Mol Psychiatry.* 15, 463-72 (2010)
42. G.J. Biessels, E.J. Stevens, S.J. Mahmood, W.H. Gispen, D.R. Tomlinson: Insulin partially reverses deficits in peripheral nerve blood flow and conduction in experimental diabetes. *J Neurol Sci.* 140, 12-20 (1996)
43. G.J. Biessels, A. Kamal, I.J. Urban, B.M. Spruijt, D.W. Erkelens and W.H. Gispen: Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic

rats: effects of insulin treatment. *Brain Res.* 800, 125-35 (1998)

44. W. Kern, A. Peters, B. Fruehwald-Schultes, E. Deininger, J. Born, H.L. Fehm: Improving influence of insulin on cognitive functions in humans. *Neuroendocrinology.* 74, 270-280 (2001)

45. M. Mulder, A. Blokland, D.J. van den Berg, H. Schulten, A.H. Bakker, D. Terwel, W. Honig, E.R. de Kloet, L.M. Havekes, H.W. Steinbusch and E.C. de Lange: Apolipoprotein E protects against neuropathology induced by a high-fat diet and maintains the integrity of the blood-brain barrier during aging. *Lab Invest.* 81, 953-960 (2001)

46. R. Kalayci, M. Kaya, H. Uzun, B. Bilgic, B. Ahishali, N. Arican, I. Elmas, M. Küçük: Influence of hypercholesterolemia and hypertension on the integrity of the blood-brain barrier in rats. *Int J Neurosci.* 119, 1881-904 (2009)

47. R. Deane and B.V. Zlokovic: Role of the blood-brain barrier in the pathogenesis of Alzheimer's disease. *Curr Alzheimer Res.* 4, 191-197 (2007)

48. K.F. Neumann, L. Rojo, L.P. Navarrete, G. Fariás, P. Reyes and R.B. Maccioni: Insulin resistance and Alzheimer's disease: molecular links & clinical implications. *Curr Alzheimer Res.* 5, 438-447 (2008)

49. S. Craft, E. Peskind, M.W. Schwartz, G.D. Schellenberg, M. Raskind and D. Jr. Porte: Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. *Neurology.* 50, 164-168 (1998)

50. E. Planel, Y. Tatebayashi, T. Miyasaka, L. Liu, L. Wang, M. Herman, W.H. Yu, J.A. Luchsinger, B. Wadzinski, K.E. Duff and A. Takashima: Insulin dysfunction induces *in vivo* tau hyperphosphorylation through distinct mechanisms. *J Neurosci.* 27, 13635-13648 (2007)

51. Y.D. Ke, F. Delerue, A. Gladbach, J. Götz and L.M. Ittner: Experimental diabetes mellitus exacerbates tau pathology in a transgenic mouse model of Alzheimer's disease. *PLoS One.* 4:e7917 (2009)

52. Y.W. Liu, L. Liu, S.S. Lu, D.L. Wang, X.D. Liu, L. Xie and G.J. Wang: Impaired amyloid beta-degrading enzymes in brain of streptozotocin-induced diabetic rats. *J Endocrinol Invest.* 2010 Apr 22. [Epub ahead of print]

53. E. Carro and I. Torres-Aleman: The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of Alzheimer's disease. *Eur J Pharmacol.* 490, 127-133 (2004)

54. L. Gasparini, G.K. Gouras, R. Wang, R.S. Gross, M.F. Beal, P. Greengard and H. Xu: Stimulation of beta-amyloid precursor protein trafficking by insulin reduces

intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. *J Neurosci.* 21, 2561-2570 (2001)

55. G.S. Watson, E.R. Peskind, S. Asthana, K. Purganan, C. Wait, D. Chapman, M.W. Schwartz, S. Plymate and S. Craft: Insulin increases CSF Abeta42 levels in normal older adults. *Neurology.* 60, 1899-1903 (2003)

56. M. Kivipelto, T. Ngandu, L. Fratiglioni, M. Viitanen, I. Kåreholt, B. Winblad, E.L. Helkala, J. Tuomilehto, H. Soininen and A. Nissinen: Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol.* 62, 1556-1560 (2005)

57. R.A. Whitmer: The epidemiology of adiposity and dementia. *Curr Alzheimer Res.* 4, 117-122 (2007)

58. J.A. Luchsinger and D.R. Gustafson: Adiposity and Alzheimer's disease. *Curr Opin Clin Nutr Metab Care.* 12, 15-21 (2009)

59. K. Balakrishnan, G. Verdile, P.D. Mehta, J. Beilby, D. Nolan, D.A. Galvão, R. Newton, S.E. Gandy and R.N. Martins: Plasma Abeta42 correlates positively with increased body fat in healthy individuals. *J Alzheimers Dis.* 8, 269-282 (2005)

60. E.A. Sims, E. Jr Danforth, E.S. Horton, G.A. Bray, J.A. Glennon and L.B. Salans: Endocrine and metabolic effects of experimental obesity in man. *Recent Prog Horm Res.* 29, 457-96 (1973)

61. F.X. Pi-Sunyer: Medical hazards of obesity. *Ann Intern Med.* 119, 655-60 (1993)

62. E. Ferrannini: Insulin resistance is central to the burden of diabetes. *Diabetes Metab Rev.* 13, 81-86 (1997)

63. J.A. Luchsinger: Adiposity, hyperinsulinemia, diabetes and Alzheimer's disease: an epidemiological perspective. *Eur J Pharmacol.* 585, 119-129 (2008)

64. T.B. Van Itallie: Health implications of overweight and obesity in the United States. *Ann Intern Med.* 103, 983-988 (1985)

65. P. Karhapää, M. Malkki and M. Laakso: Isolated low HDL cholesterol. An insulin-resistant state. *Diabetes.* 43, 411-417 (1994)

66. S.M. Grundy and G.L. Vega: Causes of high blood cholesterol. *Circulation.* 81, 412-427 (1990)

67. M.A. Austin and K.L. Edwards: Small, dense low density lipoproteins, the insulin resistance syndrome and noninsulin-dependent diabetes. *Curr Opin Lipidol.* 7, 167-171 (1996)

68. R.M. Krauss: Triglycerides and atherogenic lipoproteins: rationale for lipid management. *Am J Med.* 105, 58S-62S (1998)

69. K.J. Kaiyala, R.L. Prigeon, S.E. Kahn, S.C. Woods and M.W. Schwartz: Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. *Diabetes*. 49, 1525-1533 (2000)
70. M.W. Schwartz, S.C. Woods, D Jr. Porte, R.J. Seeley and D.G. Baskin: Central nervous system control of food intake. *Nature*. 404, 661-671 (2000)
71. S.P. Kalra: Central leptin gene therapy ameliorates diabetes type 1 and 2 through two independent hypothalamic relays; a benefit beyond weight and appetite regulation. *Peptides*. 30, 1957-1963 (2009)
72. E. Ur, D.A. Wilkinson, B.A. Morash and M. Wilkinson: Leptin immunoreactivity is localized to neurons in rat brain. *Neuroendocrinology*. 75, 264-272 (2002)
73. L.A. Campfield, F.J. Smith and P. Burn P: The OB protein (leptin) pathway--a link between adipose tissue mass and central neural networks. *Horm Metab Res*. 28, 619-632 (1996)
74. A.J. Kastin and V. Akerstrom: Glucose and insulin increase the transport of leptin through the blood-brain barrier in normal mice but not in streptozotocin-diabetic mice. *Neuroendocrinology*. 73, 237-242 (2001)
75. W.A. Banks: The source of cerebral insulin. *Eur J Pharmacol*. 49, 5-12 (2004)
76. W.A. Banks, C.R. DiPalma and C.L. Farrell: Impaired transport of leptin across the blood-brain barrier in obesity. *Peptides*. 20, 1341-1345 (1999)
77. L.J. Shanley, A.J. Irving and J. Harvey: Leptin enhances NMDA receptor function and modulates hippocampal synaptic plasticity. *J Neurosci*. 21, RC186 (2001)
78. P.R. Moulton, B. Milojkovic and J. Harvey: Leptin reverses long-term potentiation at hippocampal CA1 synapses. *J Neurochem*. 108, 685-696 (2009)
79. P.R. Moulton and J. Harvey: Regulation of glutamate receptor trafficking by leptin. *Biochem Soc Trans*. 37, 1364-1368 (2009)
80. N. Tezapsidis, J.M. Johnston, M.A. Smith, J.W. Ashford, G. Casadesus, N.K. Robakis, B. Wolozin, G. Perry, X. Zhu, S.J. Greco and S. Sarkar: Leptin: a novel therapeutic strategy for Alzheimer's disease. *J Alzheimers Dis*. 16, 731-740 (2009)
81. S.J. Greco, K.J. Bryan, S. Sarkar, X. Zhu, M.A. Smith, J.W. Ashford, J.M. Johnston, N. Tezapsidis and G. Casadesus: Leptin reduces pathology and improves memory in a transgenic mouse model of Alzheimer's disease. *J Alzheimers Dis*. 19, 1155-1167 (2010)
82. G. Marwarha, B. Dasari, J.R. Prasanthi, J. Schommer and O. Ghribi: Leptin reduces the accumulation of Abeta and phosphorylated tau induced by 27-hydroxycholesterol in rabbit organotypic slices. *J Alzheimers Dis*. 19, 1007-1019 (2010)
83. K.F. Holden, K. Lindquist, F.A. Tylavsky, C. Rosano, T.B. Harris and K. Yaffe: Serum leptin level and cognition in the elderly: Findings from the Health ABC Study. *Neurobiol Aging*. 30, 1483-1489 (2009)
84. W. Lieb, A.S. Beiser, R.S. Vasan, Z.S. Tan, R. Au, T.B. Harris, R. Roubenoff, S. Auerbach, C. DeCarli, P.A. Wolf and S. Seshadri: Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. *JAMA*. 302, 2565-2572 (2009)
85. A.B. Newman, A.L. Fitzpatrick, O. Lopez, S. Jackson, C. Lyketsos, W. Jagust, D. Ives, S.T. Dekosky, L.H. Kuller: Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc*. 53, 1101-1107 (2005)
86. L.S. Honig, W. Kukull and R. Mayeux: Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. *Neurology*. 64, 494-500 (2005)
87. C.M. Hulette and K. Welsh-Bohmer: Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers. *Neurology*. 68, 471 (2007)
88. L. Li, D. Cao, D.W. Garber, H. Kim and K. Fukuchi: Association of aortic atherosclerosis with cerebral beta-amyloidosis and learning deficits in a mouse model of Alzheimer's disease. *Am J Pathol*. 163, 2155-2164 (2003)
89. H. Imrie, A. Abbas and M. Kearney: Insulin resistance, lipotoxicity and endothelial dysfunction. *Biochim Biophys Acta*. 1801, 320-326 (2010)
90. G.H. Tomkin: Atherosclerosis, diabetes and lipoproteins. *Expert Rev Cardiovasc Ther*. 8, 1015-1029 (2010)
91. G. Poli, B. Sottero, S. Gargiulo and G. Leonarduzzi: Cholesterol oxidation products in the vascular remodeling due to atherosclerosis. *Mol Aspects Med*. 30, 180-189 (2009)
92. K. Alwaili, Z. Awan, A. Alshahrani and J. Genest: High-density lipoproteins and cardiovascular disease: 2010 update. *Expert Rev Cardiovasc Ther*. 8, 413-423 (2010)
93. X. Prieur, T. Roszer and M. Ricote: Lipotoxicity in macrophages: evidence from diseases associated with the metabolic syndrome. *Biochim Biophys Acta*. 1801, 327-337 (2010)
94. I. Tabas: Cholesterol in health and disease. *J Clin Invest*. 110, 583-590 (2002)

95. F.R. Maxfield and I. Tabas: Role of cholesterol and lipid organization in disease. *Nature*. 438, 612-621 (2005)
96. R.R. Singaraja, L.R. Brunham, H. Visscher, J.J. Kastelein and M.R. Hayden: Efflux and atherosclerosis: the clinical and biochemical impact of variations in the ABCA1 gene. *Arterioscler Thromb Vasc Biol*. 23, 1322-1332 (2003)
97. L. Yvan-Charvet, M. Ranalletta, N. Wang, S. Han, N. Terasaka, R. Li, C. Welch, A.R. Tall: Combined deficiency of ABCA1 and ABCG1 promotes foam cell accumulation and accelerates atherosclerosis in mice. *J Clin Invest*. 117, 3900-3908 (2007)
98. I. Tabas: Cholesterol and phospholipid metabolism in macrophages. *Biochim Biophys Acta*. 1529, 164-174 (2000)
99. R.D. Bell and B.V. Zlokovic: Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol*. 118, 103-113 (2009)
100. C.G. Dotti and B. De Strooper: Alzheimer's dementia by circulation disorders: when trees hide the forest. *Nat Cell Biol*. 11, 114-116 (2009)
101. J.C. de la Torre: Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol*. 3, 184-190 (2004)
102. J.C. de la Torre: How do heart disease and stroke become risk factors for Alzheimer's disease? *Neurol Res*. 28, 637-644 (2006)
103. C. Zhiyou, Y. Yong, S. Shanquan, Z. Jun, H. Lianguo, Y. Ling and L. Jieying: Upregulation of BACE1 and beta-amyloid protein mediated by chronic cerebral hypoperfusion contributes to cognitive impairment and pathogenesis of Alzheimer's disease. *Neurochem Res*. 34, 1226-1235 (2009)
104. H. Kitaguchi, H. Tomimoto, M. Ihara, M. Shibata, K. Uemura, R.N. Kalaria, T. Kihara, M. Asada-Utsugi, A. Kinoshita and R. Takahashi: Chronic cerebral hypoperfusion accelerates amyloid beta deposition in APPSwInd transgenic mice. *Brain Res*. 1294, 202-210 (2009)
105. R.S. Rosenson: Statins in atherosclerosis: lipid-lowering agents with antioxidant capabilities. *Atherosclerosis*. 173, 1-12 (2004)
106. D.J. Betteridge: Lipid lowering in diabetes mellitus. *Curr Opin Lipidol*. 19, 579-584 (2008)
107. J. Ferrières: Effects on coronary atherosclerosis by targeting low-density lipoprotein cholesterol with statins. *Am J Cardiovasc Drugs*. 9, 109-115 (2009)
108. S. Trompet, P. van Vliet, A.J. de Craen, J. Jolles, B.M. Buckley, M.B. Murphy, I. Ford, P.W. Macfarlane, N. Sattar, C.J. Packard, D.J. Stott, J. Shepherd, E.L. Bollen, G.J. Blauw, J.W. Jukema, R.G. Westendorp: Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol*. 257, 85-90 (2010)
109. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360, 7-22 (2002)
110. G.A. Cardenas, C.J. Lavie, V. Cardenas, R.V. Milani and P.A. McCullough: The importance of recognizing and treating low levels of high-density lipoprotein cholesterol: a new era in atherosclerosis management. *Rev Cardiovasc Med*. 9, 239-258 (2008)
111. D.C. Hess, A.M. Demchuk, L.M. Brass and F.M. Yatsu: HMG-CoA reductase inhibitors (statins): a promising approach to stroke prevention. *Neurology*. 54, 790-796 (2000)
112. P.H. Chong, R. Kezele and C. Franklin: High-density lipoprotein cholesterol and the role of statins. *Circ J*. 66, 1037-1044 (2002)
113. C. Gagné, H.E. Bays, S.R. Weiss, P. Mata, K. Quinto, M. Melino, M. Cho, T.A. Musliner and B. Gumbiner: Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol*. 90, 1084-1091 (2002)
114. M.A. Al-Mohaissen, S.C. Pun and J.J. Frohlich: Niacin: from mechanisms of action to therapeutic uses. *Mini Rev Med Chem*. 10, 204-217 (2010)
115. P.J. Barter, H.B. Jr Brewer, M.J. Chapman, C.H. Hennekens, D.J. Rader and A.R. Tall: Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol*. 23, 160-167 (2003)
116. M.J. Chapman, W. Le Goff, M. Guerin and A. Kontush: Cholesteryl ester transfer protein: at the heart of the action of lipid-modulating therapy with statins, fibrates, niacin, and cholesteryl ester transfer protein inhibitors. *Eur Heart J*. 31, 149-164 (2010)
117. P.O. Szapary and D.J. Rader: Pharmacological management of high triglycerides and low high-density lipoprotein cholesterol. *Curr Opin Pharmacol*. 1, 113-20 (2001)
118. W. Le Goff, M. Guerin and M.J. Chapman: Pharmacological modulation of cholesteryl ester transfer protein, a new therapeutic target in atherogenic dyslipidemia. *Pharmacol Ther*. 101, 17-38 (2004)
119. M. Hernandez, S.D. Wright and T.Q. Cai: Critical role of cholesterol ester transfer protein in nicotinic acid-

mediated HDL elevation in mice. *Biochem Biophys Res Commun.* 355, 1075-1080 (2007)

120. R. Gurfinkel and T.R. Joy: Anacetrapib: Hope for CETP Inhibitors? *Cardiovasc Ther.* 2010 Apr 9.

121. E. Rodríguez, I. Mateo, J. Infante, J. Llorca, J. Berciano and O. Combarros: Cholesteryl ester transfer protein (CETP) polymorphism modifies the Alzheimer's disease risk associated with APOE epsilon4 allele. *J Neurol.* 253, 181-185 (2006)

122. D.W. Chen, J.F. Yang, Z. Tang, X.M. Dong, X.L. Feng, S. Yu and P. Chan: Cholesteryl ester transfer protein polymorphism D442G associated with a potential decreased risk for Alzheimer's disease as a modifier for APOE epsilon4 in Chinese. *Brain Res.* 1187, 52-57 (2008)

123. H.J. Knowles, R.H. te Poele, P. Workman and A.L. Harris: Niacin induces PPARGgamma expression and transcriptional activation in macrophages via HM74 and HM74a-mediated induction of prostaglandin synthesis pathways. *Biochem Pharmacol.* 71, 646-656 (2006)

124. T. Rubic, M. Trottmann and R.L. Lorenz: Stimulation of CD36 and the key effector of reverse cholesterol transport ATP-binding cassette A1 in monocytoid cells by niacin. *Biochem Pharmacol.* 67, 411-419 (2004)

125. A. Gille, E.T. Bodor, K. Ahmed and S. Offermanns: Nicotinic acid: pharmacological effects and mechanisms of action. *Annu Rev Pharmacol Toxicol.* 48, 79-106 (2008)

126. R.S. Blumenthal and E.D. Michos: The HALTS trial--halting atherosclerosis or halted too early? *N Engl J Med.* 361, 2178-2180 (2009)

127. H. Neeli, R. Gadi and D.J. Rader: Managing diabetic dyslipidemia: beyond statin therapy. *Curr Diab Rep.* 9, 11-17 (2009)

128. M.C. Morris, D.A. Evans, J.L. Bienias, P.A. Scherr, C.C. Tangney, L.E. Hebert, D.A. Bennett, R.S. Wilson and N. Aggarwal: Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. *J Neurol Neurosurg Psychiatry.* 75, 1093-1099 (2004)

129. S.W. Altmann, H.R. Jr Davis, L.J. Zhu, X. Yao, L.M. Hoos, G. Tetzloff, S.P. Iyer, M. Maguire, A. Golovko, M. Zeng, L. Wang, N. Murgolo and M.P. Graziano: Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science.* 303, 1201-1204 (2004)

130. H.R. Jr Davis, L.J. Zhu, L.M. Hoos, G. Tetzloff, M. Maguire, J. Liu, X. Yao, S.P. Iyer, M.H. Lam, E.G. Lund, P.A. Detmers, M.P. Graziano and S.W. Altmann: Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. *J Biol Chem.* 279, 33586-33592 (2004)

131. M. Garcia-Calvo, J. Lisnock, H.G. Bull, B.E. Hawes, D.A. Burnett, M.P. Braun, J.H. Crona, H.R. Jr Davis, D.C.

Dean, P.A. Detmers, M.P. Graziano, M. Hughes, D.E. MacIntyre, A. Ogawa, K.A. O'Neill, S.P. Iyer, D.E. Shevell, M.M. Smith, Y.S. Tang, A.M. Makarewicz, F. Ujjainwalla, S.W. Altmann, K.T. Chapman and N.A. Thornberry: The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1) *Proc Natl Acad Sci U S A.* 102, 8132-8137 (2005)

132. R.E. Temel, W. Tang, Y. Ma, L.L. Rudel, M.C. Willingham, Y.A. Ioannou, J.P. Davies, L.M. Nilsson and L. Yu: Hepatic Niemann-Pick C1-like 1 regulates biliary cholesterol concentration and is a target of ezetimibe. *J Clin Invest.* 117, 1968-1978 (2007)

133. S. Katragadda, F. Rai and R. Arora: Dual inhibition, newer paradigms for cholesterol lowering. *Am J Ther.* 17, e88-99 (2010)

134. S.E. Wahrle, H. Jiang, M. Parsadanian, J. Kim, A. Li, A. Knoten, S. Jain, V. Hirsch-reinshagen, C.L. Wellington, K.R. Bales, S.M. Paul and D.M. Holtzman: Overexpression of ABCA1 reduces amyloid deposition in the PDAPP mouse model of Alzheimer disease. *J Clin Invest.* 118, 671-682 (2008)

135. E. Rodríguez-Rodríguez, I. Mateo, J. Llorca, C. Sánchez-Quintana, J. Infante, I. García-Gorostiaga, P. Sánchez-Juan, J. Berciano and O. Combarros: Association of genetic variants of ABCA1 with Alzheimer's disease risk. *Am J Med Genet B Neuropsychiatr Genet.* 144B, 964-968 (2007)

136. C. Tang and J.F. Oram: The cell cholesterol exporter ABCA1 as a protector from cardiovascular disease and diabetes. *Biochim Biophys Acta.* 1791, 563-572 (2009)

137. M. Ogata, M. Tsujita, M.A. Hossain, N. Akita, F.J. Gonzalez, B. Staels, S. Suzuki, T. Fukutomi, G. Kimura and S. Yokoyama: On the mechanism for PPAR agonists to enhance ABCA1 gene expression. *Atherosclerosis.* 205, 413-419 (2009)

138. S. Jeong, M. Han, H. Lee, M. Kim, J. Kim, C.J. Nicol, B.H. Kim, J.H. Choi, K.H. Nam, G.T. Oh and M. Yoon: Effects of fenofibrate on high-fat diet-induced body weight gain and adiposity in female C57BL/6J mice. *Metabolism.* 53, 1284-1289 (2004)

139. G. Steiner: The use of fibrates and of statins in preventing atherosclerosis in diabetes. *Curr Opin Lipidol.* 12, 611-617 (2001)

140. I. Blasko, S. Jungwirth, K. Jellinger, G. Kemmler, W. Krampla, S. Weissgram, I. Wichart, K.H. Tragl, H. Hinterhuber and P. Fischer: Effects of medications on plasma amyloid beta (Aβeta) 42: longitudinal data from the VITA cohort. *J Psychiatr Res.* 42, 946-955 (2008)

141. C. Dufouil, F. Richard, N. Fiévet, J.F. Dartigues, K. Ritchie, C. Tzourio, P. Amouyel and A. Alperovitch: APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. *Neurology.* 64, 1531-1538 (2005)

142. T. Kukar, M.P. Murphy, J.L. Eriksen, S.A. Sagi, S. Weggen, T.E. Smith, T. Ladd, M.A. Khan, R. Kache, J. Beard, M. Dodson, S. Merit, V.V. Ozols, P.Z. Anastasiadis, P. Das, A. Fauq, E.H. Koo and T.E. Golde: Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Abeta42 production. *Nat Med.* 11, 545-550 (2005)

143. F.G. De Felice, M.N. Vieira, T.R. Bomfim, H. Decker, P.T. Velasco, M.P. Lampert, K.L. Viola, W.Q. Zhao, S.T. Ferreira and W.L. Klein: Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. *Proc Natl Acad Sci U S A.* 106, 1971-1976 (2009)

144. W.A. Pedersen, P.J. McMillan, J.J. Kulstad, J.B. Leverenz, S. Craft and G.R. Haynatzki: Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. *Exp Neurol.* 199, 265-273 (2006)

145. L. Escribano, A.M. Simón, A. Pérez-Mediavilla, P. Salazar-Colocho, J. Del Río and D. Frechilla: Rosiglitazone reverses memory decline and hippocampal glucocorticoid receptor down-regulation in an Alzheimer's disease mouse model. *Biochem Biophys Res Commun.* 379, 406-410 (2009)

146. G.S. Watson, B.A. Cholerton, M.A. Reger, L.D. Baker, S.R. Plymate, S. Asthana, M.A. Fishel, J.J. Kulstad, P.S. Green, D.G. Cook, Kahn S.E. M.L. Keeling and S. Craft: Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry.* 13, 950-958 (2005)

147. G. Landreth, Q. Jiang, S. Mandrekar and M. Heneka: PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease. *Neurotherapeutics.* 5, 481-489 (2008)

148. C. Qiu, W. Xu and L. Fratiglioni: Vascular and psychosocial factors in Alzheimer's disease: epidemiological evidence toward intervention. *J Alzheimers Dis.* 20, 689-697 (2010)

149. S. Ray, M. Britschgi, C. Herbert, Y. Takeda-Uchimura, A. Boxer, K. Blennow, L.F. Friedman, D.R. Galasko, M. Jutel, A. Karydas, J.A. Kaye, J. Leszek, B.L. Miller, L. Minthon, J.F. Quinn, G.D. Rabinovici, W.H. Robinson, M.N. Sabbagh, Y.T. So, D.L. Sparks, M. Tabaton, J. Tinklenberg, J.A. Yesavage, R. Tibshirani and T. Wyss-Coray: Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat Med.* 13, 1359-1362 (2007)

150. A. Pani, S. Dessì, G. Diaz, P. La Colla, C. Abete, C. Mulas, F. Angius, M.D. Cannas, C.D. Orru, P.L. Cocco, A. Mandas, P. Putzu, A. Laurenzana, C. Cellai, A.M. Costanza, A. Bavazzano, A. Mocali and F. Paoletti: Altered cholesterol ester cycle in skin fibroblasts from patients with Alzheimer's disease. *J Alzheimers Dis.* 18, 829-841 (2009)

151. C.H. Saelly, P. Rein and H. Drexel: Combination lipid therapy in type 2 diabetes. *N Engl J Med.* 363, 692 (2010)

**Key Words:** Hypercholesterolemia, Diabetes, Obesity, Atherosclerosis, Alzheimer's Disease, Insulin, Leptin, Brain Blood Barrier, Review

**Send correspondence to:** Maria Dolores Ledesma, Centro de Biología Molecular Severo Ochoa, Nicolas Cabrera 1, 28049 Madrid, Spain. Tel: 34911964535, Fax: 34911964420, E-mail: dledesma@cbm.uam.es

<http://www.bioscience.org/current/vol4E.htm>