Chapter 8

Cholesterol and Alzheimer's Disease

Iuliana Nicola-Antoniu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55502

1. Introduction

Cholesterol plays a central role in the brain's metabolism: the fact that the brain accounts for only 2% of the body mass and brain cholesterol represents 25% of the total body cholesterol speaks for itself. Overall, the brain is the organ with the highest content of cholesterol in the body.

Direct analysis of brain cholesterol metabolism is further complicated by the separation of brain cholesterol from plasma cholesterol owing to the blood-brain barrier.

It is commonly assumed that all brain cholesterol originates from in situ neo-synthesis. This conclusion is based mainly on studies tracking the incorporation of tritiated water into the pool of sterols contained in the brain.

Most brain cholesterol is unesterified (free) and is found within the specialized membranes of myelin. Since myelin has a very slow turnover rate, myelin-associated cholesterol is virtually immobilized.

The remaining brain cholesterol is found in neurons, glial cells and extracellular lipoproteins, and these pools of cholesterol participate in cholesterol homeostatis of the CNS. Considering that the large mass of cholesterol sequestered into myelin membranes, makes the analysis of cholesterol distribution in the brain (brain cholesterol) technically challenging.

Direct quantification of plasma cholesterol in the brain, which is very difficult, has thus far yielded negative results.

The membrane concentration of cholesterol is maintained within extremely fine variation limits owing to numerous homeostasis mechanisms. These mechanisms can be altered genetically, by environment factors, through aging or dietary induced.

The studies carried out throughout the years have shown cholesterol's vital importance for the brain:

Here are just a few examples:

- It is a limiting factor in the ability to form synapses. The "factor" searched for since 1997, that acts on the glial cells, stimulating them to increase synapse formation, was identified in 2001. It proved to be cholesterol.
- Synapses formed in the presence of cholesterol rich glial cells proved to be more effective and functional. When neurons deprived of this glial secretion were exposed to a solution of cholesterol, synapse formation increased by twelve times.
- THUS, cholesterol helps us think, learn and memorize by regulating the plasticity of synapses.
- Cholesterol has also been discovered to play an important role in forming what are called *lipid rafts*, areas in the plasma membrane of cells that anchor certain proteins important to cell signaling. Several of the proteins anchored in these *rafts* are responsible for stimulating and guiding the growth of nerve axons.
- It is the main regulator of the structure of lipids and neuronal membrane fluidity.

The interplay between Alzheimer's disease and cholesterol is very controversial, being supported by some authors and denied by others.

2. The involvement of cholesterol in the generation and deposit of amyloid beta

Although it is not completely elucidated, today it is generally acknowledged that the debut and evolution of AD's molecular mechanism consists in the overproduction and accumulation of toxic amyloid beta proteins.

Numerous studies show the direct relation between the cholesterol levels and the amyloid volume at brain level. High cholesterol level (more than 5.8 mmol/L) is significantly related to the brain plaques associated with Alzheimer's disease in autopsied people; there wasn't found any link between high cholesterol and the tangles that develop in the brain (plaques and tangles both known to be trademark signs of Alzheimer's disease)

Of the other part, a series of prospective studies did not support the hypothesis according to which high levels of cholesterol represent a risk factor for Alzheimer's disease.

- Cholesterol and the formation of the β-amyloid precursor protein

The amyloid processing of the amyloid precursor protein takes place only in certain areas of the cell membrane and is favored by its high cholesterol content.

http://dx.doi.org/10.5772/55502

Membrane rafts and isoprenylation play an important role in transforming the amyloid precursor protein at gamma-secretase level.

Lipid rafts are heterogenous, cholesterol and sphingolipid-rich membrane microdomains that mediate compartmentalized cellular processes by clustering receptors and signalling molecules. These dynamic lipid–protein assemblies are enriched in saturated glycerophospholipids and protein molecules with a high inherent affinity for ordered lipid domains.

Raft lipids are believed to be held together by relatively weak covalent bonds, establishing a dynamic equilibrium of raft and non-raft regions within the plasma membrane. The density, size, duration and exact composition of the rafts varies based on the cell type. In average they have a 50 nm diameter (between 10-100 nm), each comprising approximately 20 protein molecules. Theoretically, a cell may have approximately 1,000,00 membrane rafts, representing more than half of the total membrane surface.

When activated, membrane rafts have been shown to function as a concentrating platform for a variety of signal transduction molecules. During activation, several rafts cluster forming large platforms in order to allow the functional proteins to concentrate and interact. An especially important aspect is that this concentration is cholesterol dependant. Thus, membrane rafts have a central role in regulating a few cellular processes, such as membrane sorting, trafficking and signal transduction.

Even clearer evidence shows that amyloid processing of APP takes place at raft level, especially due to the presence of the active functional pool of BACE 1 and gamma-secretase at the level of these micro-domains. An even more supported idea is that the decreased association of these proteins at raft level would be beneficial for AD. When supporting this theory, the possibility of interfering with bodily functions must be taken into account.

Although, APP, BACE1 and presenile domains are present both in raft areas, as well as in membrane areas without rafts, APP processing at raft level seems to be predominantly amyloidogenic, while outside the raft level, the APP processing is predominantly non amyloidogenic, on the alpha-secretase pathway.

Cholesterol decrease does not favour the association of BACE1 with the lipid rafts, which correlates with the decrease of amyloidogenesis. In contrast, the acute exposure of cells to cholesterol stimulates the co clustering of APP and BACE1 at raft level and their fast endocytosis.

Besides gamma-secretase, the beta-secretase component seems to be located at membrane raft level. Cholesterol depletion abrogates this localization.

Thus, we can draw the conclusion that the production of cholesterol-influenced amyloid is determined, at least partially, at BACE1 level present in lipid rafts. Moreover, APP's association with rafts stimulates the formation of amyloid.

Genetic, metabolic and biochemical studies have shown that intracellular cholesterol distribution, rather than total cholesterol levels, regulates APP processing and β-amyloid generation.

At cellular level, the highest concentration of cholesterol is at plasmatic membrane level, just like in the endocytic recycling compartment. Because the blood-brain barrier prevents any exchange of lipoproteins between the serum and the brain, most of the brain cholesterol is synthesized de novo de novo, at glial level.

The excess free cholesterol is transformed by acyl-conezyme A: cholesterol acyltransferase (ACAT) resulting with the intracellular accumulation of lipid droplets or trans-membrane efflux in the extra-cellular environment.

ACAT is essential for the regulation of intracellular cholesterol homeostasis and distribution of cholesterol throughout the body. In the small intestine and liver it also regulates the secretion of chylomicrons and very large-density lipoproteins (VLDL).

Mammals, including humans, express two different isoforms of ACAT, called ACAT-1 and ACAT-2. Whereas ACAT-1 is almost uniformly distributed among several tissues, including the brain, ACAT-2 is selectively expressed in the intestine and liver. Both forms of ACAT are ER resident enzymes, allosterically regulated by cholesterol available in the ER membrane.

Acyl-coenzyme A cholesterol acyltrasferase (ACAT) catalyzes the formation of cholesteryl-esters from cholesterol and long-chain fatty acids. ACAT controls the dynamic equilibrium between these two forms of cellular cholesterol, ultimately affecting cholesterol homeostasis. This dynamic equilibrium ultimately regulates the generation of β-amyloid (Aβ). A selective increase in cholesteryl-esters is sufficient to up-regulate the generation of Aβ and increase the steady-state levels of β-APP CTFs (C-terminal excerpt). It has been shown that at neuron level, the ACAT competitive inhibitors reduce both cholesteryl-ester and Aβ biosynthesis in a dose-dependant manner, while increasing free cholesterol. Similar results were obtained with agents that block delivery of free cholesterol to ACAT.

How free cholesterol and cholesteryl-ester distribution affects the Aβ synthesis is not yet clear. HOWEVER, the participation of free cholesterol in cellular membranes must be also taken into account because altered cholesteryl-ester levels modulate the free cholesterol pool. Even undetectable changes in free cholesterol levels may affect APP processing.

Second, studies have shown that ACAT regulates ALL three cleavages of APP. Thus, altered cholesterol distribution affects either the activity of all three secretases, APP itself, or an-yet-unidentified protetin that controls APP processing.

The increase of cholesteryl-ester level in the cell cultures increases the release of Abeta, while the pharmacological inhibition of ACAT reduces the formation of cholesteryl-esters, as well as Aβ. The genetic ablation of ACAT1 in the mouse model with AD reduces the formation of AD as well as cognitive decline.

The ACAT1 ablation also increases the oxy-cholesterol levels and 24S-hydrocholesterol, thus suggesting a potential reduction role of amyloidogenesis for these cholesterol metabolites. THUS, a possible mechanism is that the excess brain cholesterol resulted from ACAT1 ablation can be transformed in 24S-hydroxycholesterol and in this form cross the blood-brain barrier to the periphery, reducing the brain cholesterol level. The corroborated data suggests that the

equilibrium (report) between free cholesterol and cholesteryl-esters is the key element for controlling amyloidogenesis.

3. Isoprenylation

Abeta in turn regulates cholesterol metabolism. Abeta 40 supresses the mevalonate pathway by inhibiting HMG CoA reductase, thus decreasing the cholesterol level.

The HMG-CoA reductase pathway, also called the mevalonate pathway, leads to cholesterol synthesis, as well as supplies indispensable lipids, such as isoprenoids, to eukaryotic cells.

(The statins that block the HMG-CoA reductase pathway can thus manifest their effects through a cholesterol independent mechanism).

Long-chain isoprenoids participate in membrane organization and proteic glycosylation, as well as in mitochondrial oxygen consumption.

The short-chain isoprenoids (farnesylpyrophosphate-FPP) and metabolite or geranylgeranyl-pyrophosphate (GGPP) are used for the isoprenylation of complex proteins, including nuclear lamins and GTPases.

Isoprenylation of proteins, respectively farnsylation and geranylgeranylation influence the signalling capacity of the respective proteins.

Recent studies indicate that AD has a metabolism interference at FPP and GGPP level, consequently affecting signalling through GTPases. This is relevant for AD because signalling through GTPases controls multiple aspects of amyloidogenesis, including trafficking of APP, BACE1 and the secretase complex.

- Cholesterol and intracellular accumulation of amyloid beta

Intracellular amyloid beta induces the increase of oxidative stress through mitochondrial perturbation.

Recent studies evince that the specific mitochondrial cholesterol pool sensitizes neurons to cell death (induced by oxidative stress) as well as at caspase-independent apoptosis. This is due to due to selective mitochondrial GSH (mGSH) depletion induced by cholesterol-mediated perturbation of mitochondrial membrane dynamics.

"MGSH replenishment by permeable precursors such as glutatione ethyl ester protected against Ab-mediated neurotoxicity and inflammation"

Thus, mitochondrial cholesterol determines amyloid beta neurotoxicity by regulating mitochondrial GSH.

In the relation between CHOLESTEROL-AMYLOID it is essential to analyze the hypercholesterolemia *subtypes.*

The increased levels of serum cholesterol are the result of different factors that should be taken into account. For instance, familial hypercholesterolemia involves a dysfunction of LDL

receptors. On the one hand, cholesterol levels in the blood increase because they cannot be received into cells, and on the other, the absence of properly functioning LDL receptors could be causing other intracellular problems. Thus this more likely results from a specific *defect of receptors*, rather than from high cholesterol, or even a *deficiency of intracellular cholesterol*.

The role of the LDL receptor-related protein is so much more important and disputed now that we know that its associated proteins are responsible in both increased free brain cholesterol and increased beta-amyloid in Alzheimer's disease. They are also responsible for bringing apolipoprotein-E-associated cholesterol into cells. Apparently, the deficiency or dysfunction of LRP could be a factor that results in both increased free brain cholesterol and increased beta-amyloid, which could be accidental.

4. Tau pathology and cholesterol

Together with amyloid deposits, the second defining element of AD from a histopathological point of view are the intraneuronal neurofibrillary tangles, formed from hyperphosphorylation of Tau protein.

In contrast with APP and secretases, which are membrane bound, tau is a protein that stabilizes microtubules, which are found in cytoplasm.

However there is an interaction between cholesterol and its pathology.

- The Aβ signalling pathway perturbs pathways involving lipid metabolizing enzymes ultimately affecting tau phosphorylation
- The cholesterol levels are a key parameter controlling Aβ-induced tau proteolysis by calpain and proteolytic cleavage of tau by this protease, but also by caspases. These seem to be the early steps leading to tau pathology.
- A pool of hyperphosphorylated tau is present in lipid rafts, along with APP metabolites, BACE1, the γ-secretase complex and ApoE. Thus, evincing that significant crosstalk may exist between Aβ and tau at the raft interface.
- Kinases implicated in tau phosphorylation, such as Cdk5 and GSK-3β, are activated on cellular membranes and thus dysregulation of lipid metabolism may affect the activity of these kinases.
- The aggregate treatment pathway is also influenced by the lipidic metabolism. Cdk5 phosphorylates the lipid kinase Vps34, whose product PtdIns3P, may regulate the clearance of tau aggregates by stimulating the autophagy pathway
- More and more theories support that the propagation of the tau pathology is similar to prion-like infections, by crossing cell membranes, case in which the importance of the cell MEMBRANE's functionality comes forefront.

http://dx.doi.org/10.5772/55502

5. HDL colesterol and AD

HDL is one of the main protein carriers in the brain. It can cross the brain-blood barrier. It is difficult to estimate to what extent its serum value reflects its brain concentration. Studies carried out throughout the years regarding the correlation between cholesterol HDL – AD have not allowed to reach a decisive conclusion. Some authors say that the HDL association is more relevant with stroke, and stroke is associated with AD.

Other authors have found an interplay between the high levels of HDL cholesterol and the presence of plaques and intraneuronal neurofibrillary tangles (study carried out in 2001 by Launer on "Japanese-American men".)

Until now, the data offered by the studies do not allow to make a recommendation regarding the HDL cholesterol levels for preventing AD. We have no reasonable argument for boosting the HDL levels to try to prevent AD.

It should be considered to keep cholesterol under control (within the recommended values) in order to reduce the risk of heart diseases. This has sense because by reducing the risk of heart disease, you also reduce the risk of AD.

Guidelines recommend an optimal HDL level of 60 mg/dL or higher, under 40 mg/dL for men and under 50 mg/dL for women.

6. APOE- cholesterol and AD

ApoE is one of the major plasma apolipoproteins and the principal cholesterol carrier in the brain.

ApoE encodes a 34kDa protein that is an essential regulator of the brain cholesterol metabolism and triglycerides in the body. It mediates the capturing of lipoprotein particles from the brain via associated receptor for LDL (LRP) and VLDL.

In humans, there are three common alleles of the ApoE gene: ε2, ε3 and ε4. The protein isoforms produced by these alleles differ in the amino acids at positions 112 and/or 158: E2 (Cys112, Cys158), E3 (Cys112, Arg158), which is the most common, and E4 (Arg112,Arg158), which is present in at least one copy in less than 25% of the population.

Peripheral apolipoprotein E is synthesized in the liver, while apolipoprotein E from the brain is synthesized in situ, especially by astrocytes.

It has been confirmed that APOE ε4 allele is the most prevalent risk factor for the development of sporadic AD.

The risk for Alzheimer's disease conferred by APOE ε4 increases in a dose-dependant manner; individuals that are homozygous for APOE ε4 alleles are 8 times more likely to develop AD than are homozygotes for APOE ε3. Less than 2% of the population is homozygous for APOE ε4. This is neither necessary nor sufficient to cause AD; it only increases risk for the disease.

The mechanisms through which APOE leads to the development of the disease are partially unknown.

ApoE may alter brain cholesterol homeostasis by modifying lipoprotein-particle formation. In the plasma, ApoE4 is associated with VLDL particles, which contain more cholesterol, whereas ApoE3 is associated with HDL. Subjects homozygous for the ApoE ε4 allele have higher levels of cholesterol in the plasma and 25-hydroxycholesterol in the cerebrospinal fluid. 25-hydroxycholesterol is a catabolic derivative of cholesterol and represents the major metabolic route for cholesterol clearance from the brain. The lipoproteins produced in the brain are very different from the particles found in the plasma, in what concerns composition as well density or other properties.

As ApoE4 shows differential preference for VLDL in the plasma, it is possible that different ApoE isoforms modify brain cholesterol homeostasis by preferentially associating with specific lipoprotein particles. The predominant nature of Apoe in brain lipoproteins would accentuate small differences in lipoprotein affinity for ApoE isoforms. The role of apoE in maintaining cholesterol homeostasis in the brain may contribute to the increased risk for AD associated with APOE ε4.

ApoE may up-regulate the rate of Aβ generation by increasing cellular cholesterol. After receptor-mediated internalization and enzymatic digestion of the lipoproteins, cholesterol is released to cellular membranes. APOEA tend to contain more cholesterol. The increased cholesterol content of cellular membranes promotes the increased production of amyloid-beta from its precursor, APP.

Epidemiologic studies suggest that high levels of cholesterol may contribute to the pathogenesis of AD. Individuals with elevated levels of plasma cholesterol have an increased susceptibility to AD, apparently influenced by the APOE ε4 genotype. Moreover, AD patients have increased levels of total serum and low density lipoprotein (LDL) cholesterol along with reduced levels of apoA/high-density lipoprotein (HDL) in their plasma, as compared to age-matched controls. This is strengthened by the significantly decreased lecithin cholesterol acyltransferase activity (LCAT) in AD patients. LCAT is an enzyme found in plasma that catalyzes an acyltransferase reaction on lipoprotein-associated cholesterol and is a key step in reverse cholesterol transport in humans (the process that eliminates cholesterol from peripheral cells).

APOE may mediate the internalization of amyloid-beta by binding to the proteins associated to the LDL receptor.

LRP is a multi-ligand receptor, a member of the LDL receptor family, with many common structural motifs and functional particularities, such as the high-affinity binding activity for LDL particles. LRP's main protein ligand is APOE, but it also binds other molecules such as α2-macroglobulin and APP751/750 containing the KPI domain.

LRP may be linked to the degradation of secreted amyloid-beta by facilitating the internalization of Aβ bound to APOE. The internalization of Aβ mediated by LRP is more likely followed by its intracellular aggregation, rather than degradation, suggesting that LRP might be involved in the process of Aβ deposition.

Soluble Aβ interacts with APOE associated with lipoparticles and under-goes receptor-mediated endocytosis. The lipoproteins are enzymatically digested in the lysosomal compartment, releasing cholesterol to the cell. A fraction of APOE and Aβ undergoes degradation at lysosomal level. The rest of APOE remains associated with Aβ and promotes its aggregation into amyloid fibrils and is then secreted back in the extracellular milieu.

The internalization of Aβ is not necessarily followed by its degradation. Amyloid aggregates from the endocytic compartment may be secreted in a more toxic fibrillar form. Finally, APOE may contribute to the aggregation of amyloid-beta through its internalization.

Moreover, the non-lypidic form of APOE seems to have a high-affinity binding activity to Aβ and favour the formation of Aβ fibrils rather than APOE3 isoforms.

7. Cholesterol — Common risk factor for AD and atherosclerosis

Epidemiologic studies indicate that people with risk factors such as high blood pressure, diabetes, cerebrovascular disease and high cholesterol are two times more likely to develop Alzheimer disease than those without vascular risk factor.

The causal chain between the high plasma cholesterol level and atherosclerosis is well defined.

We can discuss a risk factor profile for sporadic cases of AD, with late-onset, which account for 90-95% of all cases. In elderly patients that suffer from AD there is an obvious link between this disease and vascular risk factors and atherosclerosis. However, the nature of this link remains partially speculative. Some authors have suggested that AD occurs as a secondary event related to atherosclerosis of extracranial or intracranial vessels with secondary cerebral hypoperfusion or small cerebral strokes. The toxic effects of vascular risk factors on susceptible areas of the brain, such as the temporal lobe, have also been discussed.

Another approach is that both AD and atherosclerosis are common among elderly persons. They are similar with regard to the long prodromal period when specific, clinically "silent" lesions accumulate that manifest according to the symptomatology plan when the disease is already after many years of evolution. However, this fact does not impede us from considering them as two independent diseases with convergent evolution. This idea is supported by epidemiological observations, pathological elements and the answer to common therapy for both diseases.

The APOE risk factor is also associated with atherosclerosis. In cell cultures, APOE is linked with the decreased cholesterol efflux from macrophages, as well as from neurons and astrocytes. At macrophage level, APOE promotes foam cell formation, at neuronal level it promotes the increased APP processing for forming Aβ.

Is has also been evinced that APOE 4 has a more reduced antioxidant capacity than its isoform APOE3. The pathogenic strain of both atherosclerosis and AD is the increase of the oxidative stress associated with the production of reactive oxygen and nitrogen species that oxidize

• ApoEe 4 polmorphism
• Hypercholesterolemia
• High blood pressure
• Hyperhomocysteinemia
• Diabetes mellitus
• Metabolic syndrome
• Smoking
• Systemic inflammatory response
• High level of fats and obesity

Table 1. Common risk factors for AD and atherosclerosis

amino acids and lipids. The loss of the antioxidant protection conferred by APOE may lead to increased alterations produced by oxidative stress.

Epidemiologic studies suggest that AD patients have increased levels of total serum and low density lipoprotein (LDL) cholesterol along with reduced levels of apoA/high-density lipoprotein (HDL) in their plasma, as compared to age-matched controls. LCAT is an enzyme found in plasma that catalyzes an acyltransferase reaction on lipoprotein-associated cholesterol and is a key step in reverse cholesterol transport in humans (the process that eliminates cholesterol from peripheral cells).

The same metabolic profile with high plasma cholesterol level, high LDL cholesterol and low HDL cholesterol is found with atherosclerosis patients.

8. Predictive value of cholesterol based on AGE

The study carried out in 2010 on Swedish women has not evinced any increase in AD risk associated with high plasma cholesterol values between the ages of 40 and 60. This finding contradicts several previous studies which did suggest a role for elevated plasma cholesterol at middle age in the later development of AD.

However, this study has evinced another association of cholesterol level to DA based on age. Namely, women whose cholesterol decreased the most from middle age to old age were more than twice (x2!) as likely to develop AD as women whose cholesterol levels increased or stayed the same between the same age intervals.

Rapidly declining cholesterol late in life (over 60) appears to be associated with increased frailty and may be an early sign of dementia.

It seems that this is due to the fact that 10 years earlier people develop symptoms of dementia, they tend to become more frail. They forget to eat and start to lose weight, which can impact cholesterol levels.

http://dx.doi.org/10.5772/55502

People with high cholesterol in their early 40s are more likely to develop Alzheimer's disease than those with low cholesterol. High levels of high-density lipoprotein-"good cholesterol" appear to be associated with a reduced risk for Alzheimer disease in older adults.

9. Statins and the evolution of AD

Is statin treatment protective?

Statins have a pleiotropic effect – they act on cholesterol, as well as on isoprenylation. They block the HGM-Co A reductase pathway and thus manifest their effects through a cholesterol independent mechanism.

10. Diet and the evolution of Alzheimer's disease

The usefulness of hyper or hypo-cholesterolemic diets in preventing AD is also another controversial issue. Most of the studies are carried out on rodents: 1998 studies found that the hypercholesterolemic diet lowers beta-amyloid at cerebral level, while 2000 studies found the opposite.

11. Conclusions

Although the link between cholesterol and AD remains an open issue, that still has many unresolved aspects, the studies have found strong evidence that cholesterol is a factor in the pathogenesis of AD.

Cholesterol is involved in the development of AD owing to its intervention, at different levels, on the formation and deposit of amyloid-beta and the genesis of intraneuronal neurofibrillary tangles, also favoring the atherogenesis process.

Based on these data and knowing cholesterol's essential role both at cerebral and body level, as well as the relative difficulty to estimate the exact link between the plasma cholesterol and the brain cholesterol level, it is important to maintain throughout your entire life, in correlation with age and sex, the cholesterol concentration (and its fractions) within the recommended limits in order to prevent cardio-vascular diseases.

It is also important to avoid the drastic "correction" of cholesterol, sometimes even under normal levels, especially in the case of elderly persons, in order to prevent Alzheimer's disease, considering that cholesterol is an essential substance for the entire body.

Author details

Iuliana Nicola-Antoniu

Departement of Neurology,"Colentina" Clinical Hospital, Bucharest, Romania

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