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Minireview

# Amyloid excess in Alzheimer's disease: What is cholesterol to be blamed for?

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**Abstract A link between alterations in cholesterol homeostasis and Alzheimer's disease (AD) is nowadays widely accepted. However, the molecular mechanism/s underlying such link remain unclear. Numerous experimental evidences support the view that changes in neuronal membrane cholesterol levels and/or subcellular distribution determine the aberrant accumulation of the amyloid peptide in the disease. Still, this view comes from rather contradictory data supporting the existence of either high or low brain cholesterol content. This is of particular concern considering that therapeutical strategies aimed to reduce cholesterol levels are already being tested in humans. Here, we review the molecular mechanisms proposed and discuss the perspectives they open.**



*Keywords:* Cholesterol; Alzheimer's disease; Membrane rafts; Amyloid peptide

## 1. Introduction

What causes Alzheimer's disease (AD), the most common form of dementia affecting up to 15 million individuals worldwide? Although there is not yet an answer to this question the search for it has provided a wealth of information that bring us closer to the understanding of this neurodegenerative disorder. Hence, its hystopathological hallmarks are well characterized: amyloid plaques and neurofibrillary tangles composed by the extracellular and intracellular accumulation in the brain of the amyloid peptide (Aβ) and the hyperphosphorylated protein Tau, respectively. Even though it is unclear whether these hallmarks are a consequence or a cause their analysis has been crucial towards the comprehension of the pathology. Thus, Aβ derives from the processing of the transmembrane amyloid precursor protein (APP) by the β- and γ-secretases [1]. Aβ production is a physiological event, and therefore it is necessary for relevant cellular functions including modulation of synaptic activity and facilitation of neuronal growth and survival [2]. On the other hand, abnormal increase in Aβ levels, even before its accumulation in plaques, appears to be toxic in vitro and in vivo [3]. Consistent with this peptide playing a key pathological role in AD, mutations in either APP or its secretases are a well established cause for the familial forms of the disease [4].

Being APP cleavage a membrane event the involvement of lipids in alterations of such cleavage is conceivable. The first link between a lipid defect and AD came with the observation that the inheritage of the e4 allele of the apolipoprotein E, the main cholesterol transport protein in the brain, constituted a risk factor for the disease [5]. Indeed, individuals who are homozygous for this allele and live longer than 80 years will almost invariably develop AD. Lately, genetic studies of the risk of AD have reported association with polymorphisms in three other cholesterol related genes: cholesterol 24-hydroxylase (CYP46A1), ATP-binding cassette transporter A1 (ABCA1) and lipoprotein receptor-related protein (LRP) [6]. In addition, other evidences support an involvement of cholesterol in the production and/or degradation of the amyloid peptide. However, no consensus arises on how defects in cholesterol homeostasis relate to AD. The purpose of this article is to review the data aimed at this understanding.

## 2. Why the brain regulates tightly the levels of cholesterol?

Cholesterol is an essential component of the cellular membranes determining the fluidity and biophysical properties by lowering the permeability and increasing the compacity. The distribution of this lipid in the membrane is not uniform but it is enriched in microdomains, the so-called rafts [7]. Numerous experimental evidences suggest that by means of raft formation cholesterol contributes to the dynamic compartmentalization of molecules allowing the fine-tuned modulation of events such as signaling and proteolysis [8]. In addition, cholesterol serves as a precursor or cofactor of several signaling molecules [9]. As the main component of rafts cholesterol also contributes to the sorting of certain membrane molecules to the right destination in polarized cells such as epithelia and neurons [7,10,11] and to raft molecule endocytosis [11,12]. More specifically, cholesterol is crucial for the most distinctive feature of neurons: their ability to communicate. First, it is required for the formation of synapses [13]. Second, it is a major component of the myelin sheath essential for an efficient electrical transmission [14]. Third, it serves as impermeant barrier against sodium leakage [15]. From the above it comes that the brain must posses a most robust mechanism to maintain the levels of cholesterol, in the neurons

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and their supporting cells, as independent as possible from the variations that occur in the circulation. In fact, to date there is no evidence that blood cholesterol crosses the brain–blood barrier [16].

## 3. How are cholesterol levels regulated in the brain?

The metabolism of cholesterol depends on three main aspects: synthesis, transport and catabolism. Cholesterol biosynthesis is a lengthy and energy consuming process that requires more than 20 reactions and intermediates. Production of mevalonate by the HMG-CoA reductase is the main regulatory step of the pathway. Developing neurons synthesize most of the cholesterol they need but the production is reduced once they reach maturation. At this point, neuronal cholesterol content becomes also dependent on the cholesterol synthesized and secreted by glial cells [16]. The transport of cholesterol among CNS cells appears to rely on the Apolipoprotein E that is synthesized by astrocytes [17]. ApoE-cholesterol complexes are then taken up by neurons via endocytosis through the LDL receptor related protein (LRP1) [18]. Assuming that the following step is conserved with that of other cells, endocytosed cholesterol-containing lipoproteins are hydrolyzed in the neuronal lysosomes allowing the intracellular release of free cholesterol. This can be utilized in two ways. On one hand, it is esterified in the endoplasmic reticulum by the acyl-coenzyme A cholesterol acyltransferase (ACAT), and stored in cytoplasmic droplets as a reserve pool [19]. On the other hand, free cholesterol provides feedback to the pathways regulating transcription factors that control the expression of cholesterol synthesizing enzymes and lipoprotein receptors. Examples of these are the sterol regulatory element-binding protein [20] or liver X receptors (LXRs). The later have been shown to enhance the release of cholesterol from cultured astrocytes and neurons by increasing the expression of the ATP-binding cassette transporter A1 (ABCA1) [21], a member of the family of ABC transporters, which mediates the transport of cholesterol from cells to Apolipoproteins, closing the cellular cycle of the lipid.

The fact that the neuronal membranes must be kept with a fairly constant amount of cholesterol, so to guarantee proper function, implies the existence of a mechanism for cholesterol removal. Because there is no degradation mechanism for this lipid any excess must exit the brain into the circulation. Hydroxylation of the side chain of cholesterol by the cholesterol 24-hydroxylase allows the sterol molecule to cross the blood–brain barrier freely [15]. This mechanism is responsible for the catabolism of most of the cholesterol that is turned over in the brain.

## 4. Is hypercholesterolemia a risk factor for AD because of higher cholesterol reaching the brain?

The striking reduction (almost 70%) in the prevalence of AD found in hypercholesterolemic patients treated with the cholesterol lowering drugs statins [22,23] led to establish the correlations ''high circulating cholesterol-predisposition to AD'' and its counterpart ''cholesterol lowering drugs-reduced AD risk''. This was further supported by studies in animals showing that high dietary cholesterol results in increased levels of Aβ and that treatment with cholesterol synthesis inhibitors leads to reduced amounts of Aβ40 and Aβ42 [24,25]. Mechanistically speaking the human and animal data can be explained in two different ways. The first is that high circulating cholesterol reaches the brain triggering neuronal dysfunction. The second is that neuronal dysfunction is the consequence of the numerous collateral defects that arise because of high blood cholesterol, most notably perturbed circulation and thus tissue oxygenation, without changes in the brain levels of this lipid. To distinguish between these possibilities it would be necessary to address certain issues. Most relevant is to know whether or not hypercholesterolemic individuals have more cholesterol in their brains than age-matched control individuals. Intuitively, this is not likely as brain cholesterol levels are controlled locally independently from the oscillations in peripheral cholesterol (see above). In agreement, high cholesterol diets or statin treatments in the experimental animals failed to change brain cholesterol levels significantly [26]. Although it could be argued that hypercholesterolemic individuals have, as consequence of this defect, a perturbation of the normal cholesterol-impermeant function of the blood–brain barrier, this possibility is also unlikely, as a permeability defect would lead to the leakage into the brain of blood components, not only cholesterol, producing rather acute syndromes but not AD.

From the above data and considerations one would have to conclude that there is no ground to think that hypercholesterolemia predisposes to AD because of the passage of circulating cholesterol to the brain making neurons ''fatter''. If this is accepted it then comes that hypercholesterolemia may lead to AD through a secondary event, most likely the poor-oxygenation of the brain due to cholesterol-clogged blood vessels. This would be consistent with the observation that people who had suffered brain trauma are also more prone to develop the disease [27]. Utilizing the same rationale, statins would not prevent or delay (if at all the case) the occurrence of the disease because of inhibiting cholesterol synthesis in brain cells or because of reducing the amount of peripheral cholesterol reaching the brain, but because of the overall improvement of circulation. Statins could also be beneficial because of their anti-inflammatory actions [28]. Considering all the above, and in following with the title of this review, high circulating cholesterol is not to be blamed for AD through a direct effect on the brain. Certainly, this does not rule out that changes in the content or distribution of cholesterol in neurons, by mechanism/s other than high circulating levels, occur in AD and are responsible for high amyloid production.

## 5. How does the e4 allele of the apolipoprotein E predispose to AD?

The only established molecular event directly linking cholesterol metabolism and AD comes from the discovery that the e4 allele of the ApoE predisposes to the disease [5]. The view that ApoE would contribute to AD by affecting Aβ levels came from the findings that mice lacking ApoE present reduced deposition of Aβ [29] whereas the expression of apoE3 and ApoE4 in a mouse model for AD resulted in higher accumulation of fibrilar Aβ substantially more abundant in the later [30]. While the early work did not make any assumption that