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Role of LDL Cholesterol and Endolysosomes in Amyloidogenesis and Alzheimer's Disease

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Abstract

The pathogenesis of late-onset sporadic Alzheimer's disease (AD) is believed to result from complex interactions between nutritional, environmental, epigenetic and genetic factors. Among those factors, altered circulating cholesterol homeostasis, independent of the APOE genotype, continues to be implicated in brain deposition of amyloid beta protein (Aβ) and the pathogenesis of AD. It is believed that trafficking of amyloid beta precursor protein (AβPP) into endolysosomes appears to play a critical role in determining amyloidogenic processing of AβPP because this is precisely where two enzymes critically important in AβPP metabolism are located; beta amyloid converting enzyme (BACE-1) and gamma secretase enzyme. We have shown that elevated levels of LDL cholesterol promote AβPP internalization, disturb neuronal endolysosome structure and function, and increase Aβ accumulation in neuronal endolysosomes. Here, we will further discuss the linkage between elevated levels of LDL cholesterol and AD pathogenesis, and explore the underlying mechanisms whereby elevated levels of plasma LDL cholesterol promote amyloidogenesis.

Keywords: LDL cholesterol; Amyloid beta; Amyloid precursor protein; Sporadic Alzheimer's disease; Endosome; Lysosome

Introduction

Alzheimer's disease (AD), the most common neurodegenerative disorder of old age, is characterized clinically by a progressive decline in cognitive function, and pathologically by loss of synaptic integrity, loss of neurons and the presence of amyloid plaques composed of amyloid beta (Aβ) protein and neuronal tangles composed of hyperphosphorylated tau [1,2]. Brain deposition of amyloid beta protein (Aβ), a proteolytic cleavage product of amyloid beta precursor protein (AβPP) by the beta-site AβPP cleavage enzyme 1 (BACE1) and γ-secretase, continues to be considered an important pathogenic factor of AD [1, 2]. As such, gene mutations in AβPP and presenilin-1 can lead to relatively rare familial AD with early-onset [1]. However, the majority of AD cases is sporadic in nature and is late in onset. Currently, pathogenic mechanisms responsible for sporadic AD remain unclear, but are believed to result from complex interactions between nutritional, environmental, epigenetic and genetic factors [3]. Among these factors, elevated plasma LDL cholesterol represents a robust risk factor for AD pathogenesis. Here, we will discuss the amyloidogenic processing of AβPP, briefly describe cholesterol homeostasis in the periphery and in the brain, discuss the linkage between elevated levels of plasma LDL cholesterol and AD pathogenesis, and explore the underlying mechanisms with a focus on amyloidogenic processing of AβPP.

Amyloidogenic processing of AβPP

Full-length AβPP, a ubiquitously expressed type-I transmembrane protein with largely uncharacterized cellular functions is synthesized in the endoplasmic reticulum and is transported to the Golgi/trans-Golgi network apparatus, where it undergoes posttranslational modifications and maturation. Once inserted into plasma membranes via secretory vesicles, AβPP can traffic into endosomes via clathrin-dependent endocytosis whereupon it can either be recycled back to the cell surface or delivered to lysosomes for possible degradation [4,5].

Trafficking of AβPP into endolysosomes appears to play a critical role in determining the extent to which AβPP metabolism is non-amyloidogenic or is amyloidogenic [4,6,7]. For the non-amyloidogenic pathway, AβPP in plasma membranes is cleaved by α-secretase to produce sAPPα that is both neurotrophic and neuroprotective [8]. For the amyloidogenic pathway, once AβPP is internalized into the acidic environment of endolysosomes, amyloidogenic metabolism of AβPP is catalyzed by BACE-1 and γ-secretase [9-12]. Amyloidogenesis of endosome-derived Aβ is further influenced by the ability of Aβ degradation to be catalyzed by lysosome-resident cathepsins [13]. Remaining levels of Aβ can either accumulate in endolysosomes as intraneuronal Aβ or it can be undergo exocytotic release into extracellular spaces where diffuse Aβ plaque can form (Figure 1). Thus, amyloidogenesis can be enhanced by such factors as those that promote AβPP internalization [14], those that enhance protein levels and/or activities of BACE-1 and/or γ-secretase [15,16], those that prevent AβPP recycling back to the cell surface [17], and those that impair Aβ degradation in lysosomes [18].

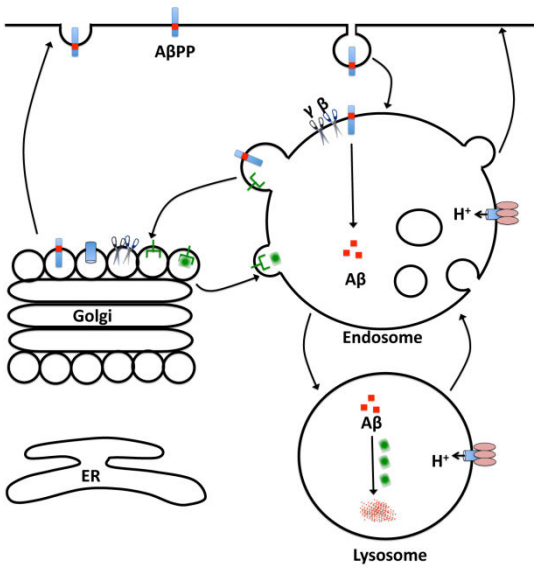

Figure 1: AβPP trafficking and amyloidogenic processing Full-length AβPP is synthesized in the endoplasmic reticulum (ER), transported to Golgi/trans-Golgi network (TGN), and inserted into the plasma membrane via secretory vesicles. Cell surface AβPP can be re-internalized to endosomes from which AβPP can either be recycled back to the cell surface or can be delivered to lysosomes for degradation. When AβPP is internalized into endosomes, the acidic environment if favorable for increased activities of BACE-1 and γ-secretase and stimulation of Aβ production. Endosome-derived Aβ can be degraded in lysosomes by cathepsins. Un-degraded Aβ can either be accumulated in endolysosomes or released to extracellular spaces via exocytosis.

Cholesterol homeostasis in the periphery and in the brain

Cholesterol, an essential component of cellular membranes, helps maintain such physiologically important neuronal functions as neurotransmitter release, neurite outgrowth, and synaptic plasticity [19-21]. Whether synthesized in brain or elsewhere throughout the body, cholesterol is the same chemically. However, there are differences in terms of its association with lipoprotein particles. Lipoproteins vary in size, lipid composition, and complex apolipoproteins that mediate their transport and uptake are different. In plasma, LDL is the main lipoprotein particle that mediates the transport of cholesterol and lipids into peripheral tissues, whereas HDL is the main lipoprotein particle that mediates the reverse cholesterol transport from peripheral tissues. LDL is a 20-25 nm sized particle that has the highest cholesterol content and apoB-100 is the exclusive apolipoprotein that mediates its transport and uptake. HDL, a protein-rich disc-shaped particles, is about 8-10 nm in size, has lower cholesterol content, and primary apolipoproteins that mediate its transport and uptake are apoA-I, apoC-I, apoC-II and apoE.

Brain is the most cholesterol rich organ in the body and contains about 20% of the body's total cholesterol. About 70% of brain cholesterol lies in the myelin sheaths of oligodendroglia and membranes of astrocytes; cholesterol in neurons make up the rest. In contrast to plasma cholesterol, essentially all cholesterol in the brain is unesterified free cholesterol [22]. Such unesterifed free cholesterol is of particular importance to neurons because neurons are extraordinarily polarized cells with extensive processes that require constant membrane trafficking and free cholesterol recycling to maintain physiologically important neuronal functions, including neurotransmitter release, neurite outgrowth, and synaptic plasticity [23,24].

Because the blood-brain barrier (BBB) restricts plasma lipoproteins, especially the larger LDL particles, from entering brain parenchyma, brain cholesterol is almost completely dependent on in situ synthesis of apoE-cholesterol by astrocytes [25]. As such, apoB, the major LDL cholesterol carrier protein in circulating blood, is not present in normal brain [26]. Although the structure and composition of apoE-cholesterol in brain parenchyma is not known, it is estimated that apoE-cholesterol synthesized in situ in brain is a discoidal shaped HDL-like particle composed of phospholipids and unesterified cholesterol, and such an estimation is based on the studies of astrocyte-derived lipoproteins and lipoproteins isolated from the CSF [27,28].

HDL-like apoE-cholesterol synthesized in brain supplies the neuronal need of cholesterol via receptor-mediated endocytosis, via a mechanism involving the Niemann-Pick type C (NPC) proteins type-1 (NPC1) and -2 (NPC2) proteins Thus, similar to that of plasma HDL, brain in situ synthesized HDL-like apoE-cholesterol may mediate recycling and reverse cholesterol transport [27], and such a function is especially important for fundamental physiological functions of neurons. Indeed, apoE is important for the regulation of synapse formation, plasticity and repair [39, 40] and apoE cholesterol, the nature source of neuronal cholesterol, is neuroprotective [41,42]. Similarly, HDL is neuroprotective [43-45].

Altered cholesterol homeostasis and sporadic AD

Altered cholesterol homeostasis in general and elevation of plasma LDL cholesterol more specifically represents a robust risk factor for AD pathogenesis [46]. This increased risk for AD onset and severity comes from various studies including findings that the presence of the APOE4 allele is still the single strongest genetic risk factor for sporadic AD [47-50], and apoE, the product of the APOE4 gene, is a carrier protein for cholesterol and lipid transport. In plasma, apoE, which is mainly synthesized by the liver and by macrophages and is associated with VLDL, chylomicron remnants, and a subset of HDL particles, plays an important role in reverse cholesterol transport [51,52]. In brain, apoE is synthesized in astrocytes and functions as a cholesterol transport protein between astrocytes and neurons. Although several hypotheses (Aβ-dependent and Aβ-independent) have been proposed [34,53-55], the exact underlying mechanisms whereby apoE4 contributes to the pathogenesis of AD remains unclear.

ApoE4 is clearly associated with elevated levels of LDL cholesterol and decreased levels of HDL cholesterol [56,57]. In addition, elevated levels of plasma LDL cholesterol, independent of APOE genotypes, are also linked robustly to the pathogenesis of AD [58-63]. Epidemiologically, elevated levels of LDL cholesterol are associated with increased levels of Aβ deposition in brain [61] and an increased risk of developing AD [58,63]. Such findings in humans were supported by data from animal studies conducted with AβPP transgenic mice [64,65], guinea pigs [66], rabbits [59,67], and rats [68] - elevated levels of LDL cholesterol leads to memory deficits and

promotes the development of AD-like pathology including brain deposition of Aβ and/or tau pathology. Similarly, and again independent of the APOE genotype, low levels of HDL cholesterol are also associated with increased risk of developing AD. On the contrary, high levels of HDL cholesterol appear to protect against the occurrence of AD [61,63,69,70]. Thus, altered circulating cholesterol homeostasis, independent of APOE genotype status, is associated with the pathogenesis of sporadic AD. Next, we will explore the underlying mechanisms whereby altered cholesterol homeostasis in the periphery contribute to the pathogenesis of AD in brain with a focus on how elevated levels of plasma LDL cholesterol promote amyloidogenesis.

Plasma LDL cholesterol induces neuroinflammation

Mounting evidence supports the pathogenic role of an inflammatory cascade mediated by activated microglia and reactive astrocytes in the pathogenesis of AD [71-73]. In AD brain, neuroinflammation is deemed to be a secondary response and the likely sources of inflammation are brain deposition of Aβ, the formation of neurofibrillary tangles, or other neuronal insults and injury [73,74]. Elevated levels of LDL cholesterol have been shown to promote neuroinflammatory responses [65,75]. Although cholesterol-induced brain deposition of Aβ might be a possible source of neuroinflammation, it is also likely that cholesterol-induced neuroinflammation is a consequence of cholesterol-induced cerebral vascular damage [76]. Such a notion is supported by findings that elevated levels of plasma cholesterol disrupt the BBB [75], an early pathological feature of sporadic AD [77-83], thus allowing systemic macrophages to invade into the brain parenchyma thereby initiating a cascade of neuroinflammatory responses including microglia activation and the formation of reactive astrocytes [65,75]. Such cholesterol-induced neuroinflammation not only could lead to synaptic dysfunction [65] thus contributing to the development of mild cognitive impairment [84], but also could lead to enhanced amyloidogenesis by up-regulation of BACE-1 [65,85] thus contributing to the development of AD, especially when BACE-1 expression is subject to regulation by cytokines [15,16].

Plasma LDL cholesterol induces neuronal endolysosome dysfunction

Under conditions when and where the BBB is disrupted, as occurs early in sporadic AD [77-83], LDL cholesterol can enter brain parenchyma and contribute directly to enhanced amyloidogenesis. Indeed, apoB-100, the exclusive apolipoprotein of LDL-cholesterol thus a marker of peripheral-derived cholesterol [59], is present in AD brain and co-localizes Aβ [26,59,86-88]. Indeed, we have shown that rabbits fed a diet enriched in cholesterol exhibit elevated levels of LDL cholesterol, disruptions in the integrity of the BBB, and increased brain levels of apoB-100 [59,75]. Once it enters brain, can be internalized by neurons via receptor-mediated endocytosis with the assistance of highly expressed receptorsBecause some of these receptors for cholesterol uptake, including LRP1 and LRP10, have been shown to interact with AβPP and affect AβPP trafficking [4,89,90], LDL cholesterol internalization could promote AβPP internalization into neuronal endolysosomes and enhance amyloidogenic processing of AβPP. In support, we have shown that LDL cholesterol treatment promotes AβPP internalization and increases Aβ accumulation in endolysosomes of primary cultured neurons [60].

Because apoB and apoE have different affinities for receptors for cholesterol uptake, neuronal uptake of apoB-containing LDL cholesterol may result in drastic difference in intracellular cholesterol transport and distribution than that of apoE cholesterol. Additionally, while apoB leads to cholesterol being targeted by the lysosome degradation pathway [91,92], apoE mediates cholesterol recycling [93-95]. Thus, neuronal uptake of apoB-containing LDL cholesterol may lead to cholesterol accumulation in endolysosomes thereby disturbing endolysosome structure and function, a very early pathological feature of AD [9 96-99]. This concept is supported experimentally by findings by others and us that LDL cholesterol treatment increases cholesterol accumulation in neuronal endolysosomes and leads to endolysosome enlargement, elevation of endolysosome pH, and reduced endolysosome enzyme activities [60].

Because endolysosomes are the sites at which internalized AβPP cleavage to Aβ is catalyzed by BACE-1 and γ-secretase [9-12], and because lysosomes are the sites Aβ can be degraded by cathepsins [13], disturbed endolysosome structure and function could lead to intraneuronal Aβ accumulation, another early pathological feature of AD [100-102]. Indeed, we found that LDL cholesterol treatment of neurons increased endolysosome accumulation of BACE-1, enhanced BACE-1 activity, decreased cathepsin activity, and increased endolysosome accumulation of Aβ [60].

Thus, elevated levels of circulating apoB-containing LDL cholesterol could lead to disturbed intracellular trafficking and distribution of cholesterol that resembles lysosomal lipid storage disorders such as Niemann-Pick type C disease [103-105]. In Niemann-Pick type C disease, the accumulation of cholesterol in lysosomes results in reduced recycling of cholesterol back to ER, Golgi, and plasma membranes thus leading to cholesterol deficiency at sites where it is needed for membrane repair, neurite outgrowth, and synaptic plasticity [39,40]. Moreover, endolysosome accumulation of cholesterol leads to endolysosome dysfunction, which contributes directly to the development of pathological hallmarks of AD including Aβ deposition, formation of neurofibrillary tangles, and synaptic and neuronal loss [104,106]. It is interesting to note that the association of cholesterol with different apoE isoforms can also result in drastic differences in endocytic trafficking of cholesterol, where apoE4 results in impaired cholesterol recycling [94,107,108]. Such impaired recycling of apoE4-cholesterol in neurons can lead to the accumulation of cholesterol in endolysosomes [94,108], alter endocytic trafficking of AβPP, enhance amyloidogenic processing of AβPP [109], and impair synaptic plasticity [95]. Thus, similar to the effects of apoB-containing LDL cholesterol, the presence of apoE4 can result in decreased cholesterol transport to the plasma membrane and cholesterol deficiency in plasma membranes as well as increased cholesterol accumulation in endolysosomes and subsequent endolysosome dysfunction [97,110], a set of conditions similar to those in Niemann-Pick type C disease albeit less severely.

Under such conditions, the use of statins, a class of hydroxylmethylglutaryl-CoA (HMG-CoA) reductase inhibitors that block cholesterol biosynthesis in the ER, would decrease cholesterol transport to plasma membranes thus worsening cholesterol deficits at the plasma membrane, synaptic disruption, and the ability to repair membranes once injured [19,21,111]. In addition, chronic use of statins results in over-expression of LDLRs and enhanced cholesterol uptake [112], and such an effect could increase the cholesterol burden in endolysosomes and worsen endolysosome dysfunction. As such, lipophilic statins, especially those that can cross the BBB and

effectively penetrate cell membranes, can reduce cholesterol synthesis below a critical level that induces neuronal death [113], whereas treatment with hydrophilic statins that do not cross the BBB easily may be appropriate for AD to reduce plasma LDL cholesterol levels without further disturbing neuronal cholesterol homeostasis [114]. Such a notion is supported by findings that statins have no beneficial effects on Niemann-Pick type C disease [103,115]. Such a notion is also supported by recent data and meta-analysis from randomized clinical trials showing that statins have little or no beneficial effects against AD [116-120] and in some cases statins result in adverse effects on memory and cognitions [121-124].

Conclusions

Elevated levels of circulating cholesterol, independent of APOE genotype, appear to contribute to the development of AD. On one hand, elevated levels of plasma LDL cholesterol could promote cerebral vascular damage thus initiating neuroinflammatory responses that contribute to the pathogenesis of AD. On the other hand, LDL cholesterol could disturb neuronal endolysosome function and contribute directly to the pathogenesis AD. Here, we propose a hypothesis that elevated levels of LDL cholesterol lead to lysosome cholesterol storage similar to Niemann-Pick type C disease thus contributing the pathogenesis of AD. Specifically, we propose that plasma LDL cholesterol once it enters brain parenchyma can be internalized by neurons via receptor-mediated endocytosis and can promotes AβPP internalization because LDLRs and AβPP physically associate with each other. Unlike apoE-cholesterol, increased apoB-containing LDL-cholesterol could lead to cholesterol accumulation in endolysosomes thus elevating endolysosome pH and impairing endolysosome function. Elevation of endolysosome pH on one hand could lead to increased BACE-1 protein levels and enhanced BACE-1 activity that leads to amyloidogenic processing of AβPP, and on the other hand could reduce cathepsin activity thus impairing Aβ degradation in lysosomes, thus leading to intraneuronal Aβ accumulation (Figure 2). Although findings from our animal studies support such a hypothesis, further studies conducted in humans are warranted. It also should be noted that cholesterol is not the only component of LDL particles and associated apolipoproteins, sphingolipids and phospholipids could also affect amyloidogenic processing of AβPP and contribute to the development of sporadic AD [125-128].

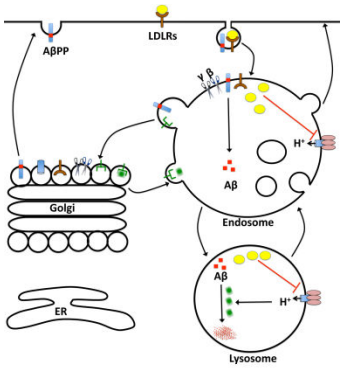

Figure 2: Propose model of LDL cholesterol-induced amyloidogenic processing of AβPP Elevated plasma LDL cholesterol, once it enters brain, can be internalized by neurons via receptor-mediated endocytosis. The LDL cholesterol internalization process promotes AβPP internalization. Increased apoB-containing LDL-cholesterol can lead to cholesterol accumulation in endolysosomes thus elevating endolysosome pH and impairing endolysosome function. Elevation of endolysosome pH can lead to increased BACE-1 protein levels and enhanced BACE-1 activity that leads to amyloidogenic processing of APP, and can reduce cathepsin activity thus impairing Aβ degradation in lysosomes.

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