Austin Journal of Pharmacology and Therapeutics

Austin Publishing Group

Open Access Full Text Article

Review Article

Role of Endolysosomes and Cholesterol in the Pathogenesis of Alzheimer's Disease: Insights into why Statins might not Provide Clinical Benefit

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Received: July 31, 2014; **Accepted**: August 22, 2014; **Published**: August 26, 2014

Abstract

Altered cholesterol homeostasis in general and increased levels of low-density lipoprotein (LDL) cholesterol specifically is a robust risk factor for the pathogenesis of sporadic Alzheimer's disease (AD). Because of this, the family of drugs known as statins has been tried extensively to lower cholesterol levels in attempting to prevent and/or lessen the neuro pathogenesis of AD. Unfortunately, evidence accumulated to date is insufficient to support the continued use of statins as a viable pharmacotherapeutic approach against AD. To understand these complex and inter-related issues it is important to review how altered cholesterol homeostasis contributes to AD pathogenesis and why statins have not provided clinical benefit against AD. Apolipoproteins with their different affinities for various lipids and the receptors that control cholesterol uptake can result in drastic differences in cholesterol trafficking into and its distribution within neurons. The presence of the apoE4 or elevated plasma levels of LDL cholesterol can lead to a set of conditions that resembles lysosomal lipid storage disorders observed in Niemen-Pick type C disease such as impaired recycling of cholesterol back to the endoplasmic reticulum (ER), Golgi and plasma membranes, cholesterol deficiencies in plasma membranes, and increased cholesterol accumulation in endolysosomes resulting in endolysosomes dysfunction. Consequently, the use of statins to block cholesterol synthesis in ER might not only decrease further plasma membrane cholesterol levels thus disturbing synaptic integrity, but also could also increase cholesterol burden in endolysosomes thus worsening endolysosomes dysfunction. Therefore, it is not surprising that the use of cholesterol-lowering strategies with statins has not resulted in clinical benefit for patients living with AD.

Keywords: ApoE4; LDL Cholesterol; Statins; Alzheimer's disease; Lysosomal lipid storage disorders; Endolysosome dysfunction

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 neurons, decreased neuronal synaptic integrity, and the presence of amyloid plaques composed of amyloid beta (Aβ) protein and neuro-fibrillary tangles composed of hyper-phosphorylated tau [1,2]. Intra-neuronal accumulation and extracellular deposition of 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]. Indeed it is well established that gene mutations in AβPP and presenilin-1 can lead to clinical and pathological features of AD in relatively young individuals albeit relatively rarely; so called familial early onset AD [1]. However, most AD cases are sporadic in nature and this neurodegenerative disorder occurs later in life. Although the pathogenic mechanisms responsible for sporadic AD have not yet been elucidated, complex interactions between nutritional, environmental, epigenetic and genetic factors have been proposed [3]. Central among the factors involved in AD pathogenesis might be altered cholesterol homeostasis.

Cholesterol, an essential component of plasma membranes, helps maintain such physiologically important neuronal functions as neurotransmitter release, neurite outgrowth, and synaptic plasticity [4-6]. Pathologically, altered cholesterol homeostasis has been linked to a number of devastating disease states including increased onset and severity of AD, and several lines of evidence support this link. First, the presence of the APOE4 allele is the single strongest genetic risk factor for sporadic AD [7-10] and apoE, the product of the APOE gene, is the carrier protein for cholesterol transport in brain. Second, ApoE4 is clearly associated with elevated levels of LDL cholesterol and decreased levels of HDL cholesterol [11,12]. Third, elevated levels of plasma LDL cholesterol, independent of APOE genotypes, are linked robustly to the pathogenesis of AD, as supported by epidemiological [13-19] and animal studies using AβPP transgenic mice [20,21], guinea pigs [22], rabbits [23,24], and rats [25]. Fourth, independent of the APOE genotype, low levels of HDL cholesterol are also associated with increased risk of developing AD [16,18,26,27].

Given the background summarized above it is not surprising that statins, a class of hydroxyl methylglutaryl-CoA (HMG-Co A) reductase inhibitors that block cholesterol biosynthesis thus lowering cholesterol levels, have been proposed as potential agents for the

Citation: Chen X, Hui L and Geiger JD. Role of Endolysosomes and Cholesterol in the Pathogenesis of Alzheimer's Disease: Insights into why Statins might not Provide Clinical Benefit. Austin J Pharmacol Ther. 2014; 2 (6).7

treatment and/or prevention of AD [28]. Although some beneficial effects have been reported in some case-controlled epidemiological studies [29,30], recent data and meta-analysis from randomized clinical trials indicates that statins have little or no beneficial effects against AD [31-34]. Furthermore, in some studies adverse effects of statins on memory and cognitions were reported [35-38]. Thus, currently statins have little support in terms of their use as a viable therapy for AD [39]. Here we focus our discussion on how altered cholesterol homeostasis contributes to the pathogenesis of AD and explore some reasons why the cholesterol-lowering strategy with statins does not appear to protect against AD.

Endolysosome Dysfunction and Pathogenesis of AD

Endolysosomes are acidic intracellular organelles consisting of emdosoms, lysosomes and autophagosomes. They play a key role in protein turnover and cellular homeostasis [40]. Substrates for degradation are delivered to lysosomes by two general routes, namely, endocytosis and autophagy. Endocytosis is responsible for up-taking extracellular nutrients as well as the maintenance of cellular integrity. Autophagy, on the other hand, is responsible for removing unwanted cytotoxic proteins and "worn out" organelles. Endolysosomes are especially important for regulating neuronal functions because neurons are mainly long-lived post-mitotic cells that require the endolysosomes/autophagy system in turning over cellular components and obsolete organelles, and because neurons are extraordinarily polarized cells with extensive processes that require endolysosomes for constant membrane trafficking to maintain such physiologically important neuronal functions as neurotransmitter release, neurite outgrowth, and synaptic plasticity [41,42].

Changes in the structure and function of neuronal endolysosomes have been reported to be one of the earliest pathological features of AD [43-46] and to be changes that precede extracellular deposition of Aβ [47]. The early onset of endo-lysosome dysfunction helps explain why investigators hypothesize that endo-lysosomes play an important role in the development of pathological hallmarks of AD including brain deposition of Aβ [45], tau-pathology [48], and synaptic disruption [49].

Intracellular accumulation and extracellular deposition of Aβ starts with specific proteolytic cleavage of AβPP. Full-length AβPP, a ubiquitously expressed type-I trans-membrane protein with largely uncharacterized physiological functions, is synthesized in the endoplasmic reticulum and it 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 it is delivered to lysosomes for possible degradation [50,51]. Endolysosomes appear to play a critical role in amyloidogenic processing of AβPP [50,52,53] in part because this is where the rate-limiting enzyme BACE-1 and γ-secretase are almost exclusively located. In addition, the acidic environment of endolysosomes is favorable for amyloidogenic metabolism of AβPP [54-57]. Amyloidogenesis of endosome-derived Aβ is further influenced by Aβ degradation catalyzed by lysosome-resident cathepsins [58]. Once formed, Aβ can accumulate in endolysosomes as intra-neuronal Aβ or it can undergo exocytotic release into extracellular spaces where diffuse Aβ plaques can form. Thus, by enhancing protein levels and/or activities of BACE-1 and/or γ-secretase, preventing AβPP recycling back to the cell surface [59], and/or impairing Aβ degradation in lysosomes [60], endo-lysosome dysfunction could lead to enhanced amyloidogenic processing of AβPP and Aβ accumulation has been observed in neuronal endolysosomes from AD brain [45].

Endolysosomes have also been implicated in the development of other pathological hallmarks of AD including tau-pathology and synaptic disruption. Tau is degraded by cathepsin D in autophagosomes-lysosomes [48,61-63] and increased accumulation of cholesterol in lysosomes and lysosome dysfunction has been linked to the development of tau-pathology in brains of patients with Niemann-Pick type C disease [64-69]. Endolysosomes recycle synaptic proteins [70-72] thus playing an important role in maintaining synaptic integrity [73]. Endolysosome dysfunction has been linked to synaptic pathology in AD brain [74,75] and deacidification of endolysosomes with chloroquine results in synaptic dysfunction and synaptic loss [49,76,77]. Thus, endolysosomes are implicated strongly in the development of disrupted synaptic integrity, a pathological hallmark of AD that correlates best with dementia [78, 79].

Altered Cholesterol Homeostasis and Endolysosome Dysfunction

Under physiological conditions, the blood-brain barrier (BBB) restricts plasma lipoproteins, especially the larger LDL particles, from entering brain parenchyma. Accordingly, the brain has to rely almost completely on *in situ* synthesis of apoE cholesterol and it does so exclusively in astrocytes [80]. It makes sense then that under normal conditions apoB, the major LDL cholesterol carrier protein in circulating blood, is not present in brain [81]. In brain apoE cholesterol is up-taken by neurons via receptor-mediated endocytosis, a process where lipoproteins bound to their receptors are internalized, transported to endolysosomes, and hydrolyzed to free cholesterol. From the endolysosomes, free cholesterol can then be transported to various intracellular compartments (ER and Golgi) or plasma membranes via a mechanism involving the Niemann-Pick type C (NPC) proteins type-1 (NPC1) and -2 (NPC2) proteins [82-84].

Currently, the structure and composition of apoE-cholesterol in brain parenchyma is not known. However, brain apoE-cholesterol synthesized *in situ* is thought to be a discoidal shaped HDL-like particle composed of phospholipids and unesterified cholesterol based on studies of astrocytes-derived lipoproteins and lipoproteins isolated from the CSF [85,86]. Thus, similar to the role of plasma HDL [87,88], brain apoE-cholesterol may mediate recycling and reverse cholesterol transport [85]; two functions of great importance for fundamental physiological functions of neurons. In addition, neurons are extraordinarily polarized cells with extensive processes that require constant membrane trafficking to maintain a variety of physiologically important neuronal functions such as neurotransmitter release, neurite outgrowth, and synaptic plasticity. Indeed, apoE is important for the regulation of synapse formation, plasticity and repair [89,90], and apoE cholesterol, the natural source of neuronal cholesterol, is neuro protective [91,92]. Similarly, HDL is neuro protective [93-95].

In human, there are three separate apoE isoforms and their amino acid differences are restricted to residues 112 and 158; apoE2 (Cys112, Cys158), apoE3 (Cys112, Arg158), and apoE4 (Arg112, Arg158). Such sequence differences affect the structure of apoE isoforms and influence their ability to bind lipids and receptors [96,97]. APOE4 is still the single strongest genetic risk factor for sporadic AD [7-10], whereas the APOE2 allele exerts protective effects against sporadic AD [98]. Although several hypotheses (Aβ-dependent and Aβ-independent) have been proposed [99-102], the exact underlying mechanism whereby apoE4 contributes to the pathogenesis of AD remains unclear.

Associations between cholesterol and apoE isoforms can result in drastic differences in endocytic trafficking of cholesterol [103]. Impaired recycling of apoE4 in neurons can lead to the accumulation of cholesterol in endolysosomes [104,105], altered endocytic trafficking of AβPP, enhanced amyloidogenic processing of AβPP [106], and impairment of synaptic plasticity [107]. Thus, the presence of apoE4 can result in decreased cholesterol transport to the plasma membrane, cholesterol deficiency in plasma membranes, increased cholesterol accumulation in endolysosomes, and subsequent endo-lysosome dysfunction [47,108]. These changes (albeit less severely) are similarly observed in Niemann-Pick type C disease [109]; a lysosomal lipid storage disorder that leads to the development of pathological hallmarks of sporadic AD including intra-neuronal accumulation of Aβ [110], neuro-fibrillary tangles [111], and synaptic and neuronal loss [112].

In addition, apoE4 is clearly associated with elevated levels of LDL cholesterol [11,12]; independent of APOE genotypes increased levels of LDL cholesterol are linked to AD pathogenesis [13-19]. Mechanistically, under conditions when and where the BBB is disrupted, as occurs early in sporadic AD [113-118], LDL cholesterol can enter brain parenchyma and contribute to AD pathogenesis. Indeed, apoB-100, the exclusive apolipoprotein that mediates LDL transport and uptake in peripheral tissues, is present in AD brain and co-localizes with Aβ [24,81, 119-121]. In addition, we have shown that elevated levels of LDL cholesterol induced by cholesterol-enriched diet disrupt the integrity of the BBB and increase brain levels of apoB-100 [24,122].

Similar to apoE-cholesterol, apoB-containing LDL cholesterol can enter neurons via receptor-mediated endocytosis with the assistance of a family of LDLRs that are highly expressed on neurons [99,123-125]. However, because apoB and apoE have different affinities for receptors for cholesterol uptake, neuronal uptake of apoB containing LDL cholesterol may result in drastic differences from apoE cholesterol with regards to intracellular cholesterol transport and distribution. Additionally, while apoB leads to cholesterol being targeted by the lysosome degradation pathway [126,127], apoE mediates cholesterol recycling [104,107,128]. Thus, increased brain levels of apoB containing LDL cholesterol may result in increased cholesterol accumulation in endolysosomes and thereby disturb the structure and function of endolysosomes in neurons, decreased cholesterol transport to plasma membranes, and subsequent cholesterol deficiency at plasma membranes. This concept is supported experimentally by findings of others and us that LDL cholesterol treatment increases cholesterol accumulation in neuronal endolysosomes [129] and leads to endo-lysosome enlargement, elevation of endo-lysosome pH, and reduced endo-lysosome enzyme activities [130]. Importantly, we have shown that such LDL cholesterol-induced endo-lysosome dysfunction is linked directly to the development of pathological hallmarks of AD including intra-neuronal accumulation of Aβ, synaptic disruption, and tau-pathology [24,130].

Taken together, either the presence of apoE4 or elevated levels of circulating apoB-containing LDL cholesterol could lead to disturbed intracellular trafficking and distribution of cholesterol that resembles lysosomal lipid storage disorders as seen in Niemann-Pick type C disease, thus contributing directly to the development of sporadic AD.

Cholesterol-Lowering Strategy with Statins Worsens the Existing Neuronal Cholesterol Dyshomeostasis

Given that apoE4 leads to impaired recycling of cholesterol back to ER, Golgi and plasma membranes [104,105, 107], and that apoB leads to cholesterol being targeted by the lysosome degradation pathway [126,127], the presence of either apoE4 or increased levels of apoB could lead to decreased cholesterol transport to the plasma membrane and increased cholesterol accumulation in endolysosomes (Figure 1). The consequences of this might be two-fold. First, reduced recycling of cholesterol back to ER, Golgi, and plasma membrane

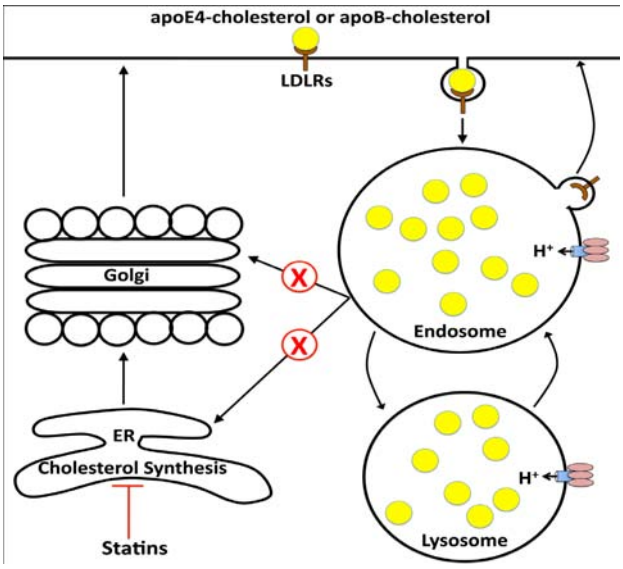

Figure 1: Statins worsen neuronal cholesterol dyshomeostasis as induced by apoE4 or increased levels of apoB.
Apo E-cholesterol or apoB-cholesterol (once it enters brain parenchyma) is up-taken by neurons via receptor-mediated endocytosis with the assistance of LDLRs. Different apolipoproteins have different affinities for lipids and receptors for cholesterol uptake, and the associations between cholesterol and different apolipoproteins can result in drastic differences in endocytic trafficking and distribution of cholesterol in neurons. ApoE4 or apoB can both lead to impaired recycling of cholesterol back to ER, Golgi and plasma membranes, as well as cholesterol deficits at plasma membranes and cholesterol accumulation in endolysosomes. Under such conditions, the use of statins that block the cholesterol biosynthesis in the ER could worsen cholesterol deficits at plasma membranes, increase expression levels of LDLRs, and enhance cholesterol uptake thus increasing the cholesterol burden in endolysosomes and worsening endolysosomes dysfunction.

could lead to cholesterol deficiency at sites where it is needed for membrane repair, neurite outgrowth, and synaptic plasticity [89,90]. Second, endo-lysosome accumulation of cholesterol could lead to endo-lysosome dysfunction, which could contribute directly to the development of pathological hallmarks of AD. 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, synaptic disruption, and the ability to repair membranes once injured [4,6,131]. In addition, statins-induced reduction of ER cholesterol synthesis can be sensed by sterol regulatory element-binding proteins with a subsequent increase in the expression of LDLRs and enhanced cholesterol uptake [132]. Such effects could increase the cholesterol burden in endolysosomes and worsen endo-lysosome dysfunction (Figure 1). 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 [133], 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 [134].

Conclusion

Altered cholesterol homeostasis continues to represent a robust risk factor for AD pathogenesis. Mechanistically, either the presence of apoE4 or elevated plasma levels of apoB-containing LDL cholesterol could lead to impaired recycling of cholesterol back to ER, Golgi and plasma membranes as well as increased endo-lysosome accumulation of cholesterol. The consequences of this might include cholesterol deficiency at plasma membranes and endo-lysosome dysfunction, a set of conditions that resemble lysosomal lipid storage disorders as occurs in Niemann-Pick type C disease. Together, those effects can lead to the development of pathological hallmarks of sporadic AD including intra-neuronal accumulation of Aβ, neuro fibrillary tangles, and synaptic and neuronal loss. Under such conditions, blocking cholesterol synthesis in ER with statins could worsen cholesterol deficiency at plasma membranes leading to disturbed synaptic integrity and impaired memory and cognition. Statins could also increase the expression of LDLRs and enhance cholesterol uptake; such effects could increase the cholesterol burden in endolysosomes and worsen endo-lysosome dysfunction. Thus, it is not surprising that evidence accumulated to date does not support the use of statins against AD.

Acknowledgement

The authors acknowledge grant support from P30GM103329, R01MH100972 and R21AG103329.

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Austin J Pharmacol Ther - Volume 2 Issue 6 - 2014
ISSN: 2373-6208 | www.austinpublishinggroup.com

Citation: Chen X, Hui L and Geiger JD. Role of Endolysosomes and Cholesterol in the Pathogenesis of Alzheimer's Disease: Insights into why Statins might not Provide Clinical Benefit. Austin J Pharmacol Ther. 2014; 2 (6).7