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Altered Cholesterol Intracellular Trafficking and the Development of Pathological Hallmarks of Sporadic AD

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Abstract

Compared to the rare familial early onset Alzheimer's disease (AD) that results from gene mutations in AβPP and presenilin-1, the pathogenesis of sporadic AD is much more complex and is believed to result from complex interactions between nutritional, environmental, epigenetic and genetic factors. Among those factors, the presence APOE4 is still the single strongest genetic risk factor for sporadic AD. However, the exact underlying mechanism whereby apoE4 contributes to the pathogenesis of sporadic AD remains unclear. Here, we discuss how altered cholesterol intracellular trafficking as a result of apoE4 might contribute to the development of pathological hallmarks of AD including brain deposition of amyloid beta (Aβ), neurofibrillary tangles, and synaptic 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, disturbed synaptic integrity, and the presence of amyloid plaques composed of amyloid beta (Aβ) protein and neurofibrillary tangles composed of hyperphosphorylated tau [1,2]. Although gene mutations in AβPP and presenilin-1 can lead to rare familial early onset AD [3], the pathogenic mechanisms responsible for sporadic AD, the major form of AD, have not yet been elucidated. It is believed that the pathogenesis of sporadic AD results from complex interactions between nutritional, environmental, epigenetic and genetic factors [4]. Central among the factors involved in AD pathogenesis might be the presence of the APOE4 allele, the single strongest genetic risk factor for sporadic AD [5-8]. Although several hypotheses (Aβ-dependent and Aβ-independent) have been proposed [9-12], the exact underlying mechanisms whereby apoE4 contributes to the pathogenesis of AD remain unclear. Here, we discuss how altered cholesterol intracellular trafficking as a result of apoE4 might contribute to the development of pathological hallmarks of AD including brain deposition of Aβ, neurofibrillary tangles, and synaptic dysfunction.

ApoE4 and altered cholesterol intracellular trafficking

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 [13,14]. In contrast to plasma cholesterol, essentially all cholesterol in the brain is unesterified cholesterol [13]. Such unesterified 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 [14,15]. As such, as an essential component of cellular membranes, cholesterol helps maintain such physiologically important neuronal functions as neurotransmitter release, neurite outgrowth, and synaptic plasticity [16-18].

Because the blood-brain barrier (BBB) restricts plasma lipoproteins from entering brain parenchyma, brain cholesterol is almost completely dependent on *in situ* synthesis of apoE-cholesterol by astrocytes [19]. 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 [20,21]. Such HDL-like apoE-cholesterol supplies the neuronal need of cholesterol via receptor-mediated endocytosis (Figure 1), a process where lipoproteins bound to their receptors are internalized, transported to endolysosomes, hydrolyzed to free cholesterol, and from where free cholesterol is transported to various intracellular compartments (ER, Golgi) or plasma membrane via a mechanism involving the Niemann-Pick type C (NPC) proteins type-1 (NPC1) and -2 (NPC2) proteins [22-24]. To accommodate the neuronal need for cholesterol, a large number of receptors for cholesterol uptake, including low-density lipoprotein receptor (LDLR), very low-density lipoprotein receptor (VLDLR), LDLR related protein-1 (LRP-1), apoE receptor, and sorting protein-related receptor containing LDLR class A repeats (sorLA-1), are highly expressed on neurons [9,25-27].

Similar to the role of plasma HDL [28,29], brain apoE-cholesterol may mediate cholesterol recycling and cholesterol efflux [20]; 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 [30,31], and apoE cholesterol, the natural source of neuronal cholesterol, is neuroprotective [32,33].

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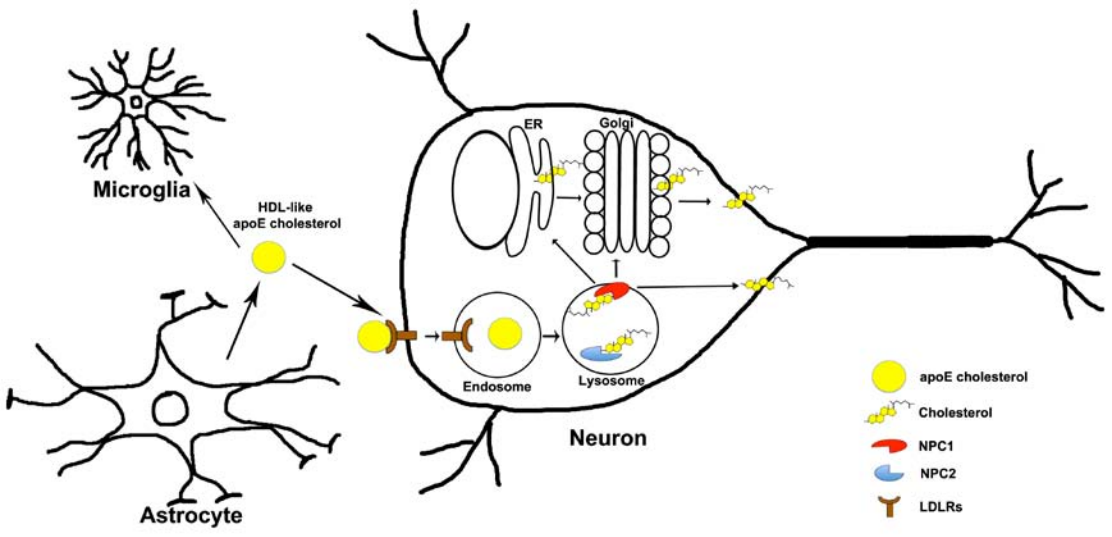

Figure 1: Cholesterol homeostasis in brain.

Brain cholesterol is almost completely dependent on *in situ* synthesis of HDL-like apoE-cholesterol by astrocytes. Such HDL-like apoE-cholesterol supplies the neuronal need of cholesterol via receptor-mediated endocytosis, a process where apoE-cholesterol bound to their receptors are internalized, transported to endolysosomes, hydrolyzed to free cholesterol, and from where free cholesterol is transported to various intracellular compartments (ER, Golgi) or plasma membrane via a mechanism involving the Niemann-Pick type C proteins type-1 and -2 proteins.

There are three 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 [11,34,35], with apoE4 having the highest binding affinity for LDLR and lipids, whereas apoE2 having the lowest binding affinity [36,37]. APOE4 is still the single strongest genetic risk factor for sporadic AD [5-8], whereas the APOE2 allele exerts protective effects against sporadic AD [38]. Associations between cholesterol and apoE isoforms can result in drastic differences in endocytic trafficking [39], with up to 87% of the intraneuronal apoE4 being co-localized with the lysosomal marker whereas only 9% of the apoE3 being co-localized. Indeed, apoE4 is associated with impaired cholesterol recycling, and such impaired recycling of cholesterol can lead to the accumulation of cholesterol in endolysosomes and reduced cholesterol recycling back to ER, Golgi and plasma membranes [37,40,41].

These apoE4-associated changes in cholesterol intracellular trafficking are similar, albeit less severe, to Niemann-Pick type C disease; a lysosomal lipid storage disorder caused by gene mutations in either the NPC1 or NPC2, both of which bind to cholesterol and act in tandem in late endosomes and/or lysosomes to mediate the egress of unesterified cholesterol derived from endocytosed lipoproteins [42]. 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 [30,31]. Moreover, endolysosome accumulation of cholesterol leads to endolysosome dysfunction, which contributes directly to the development of pathological hallmarks of AD including Aβ deposition [43], formation of neurofibrillary tangles [44], and synaptic and neuronal loss [45]. Thus, we hypothesize that apoE4 could contribute to the development of these pathological hallmarks of AD by disturbing cholesterol intracellular trafficking in a similar way as that of Niemann-Pick type C disease (Figure 2).

ApoE4 and increased Aβ generation

Brain deposition of Aβ is a pathological hallmark of AD. Intracellular accumulation and extracellular deposition of Aβ starts with specific proteolytic cleavage of AβPP, a ubiquitously expressed type-I transmembrane protein with largely uncharacterized physiological functions. AβPP 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 [46,47]. Endolysosomes appear to play a critical role in amyloidogenic processing of AβPP [46,48,49] 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 [50-53]. Amyloidogenesis of endosome-derived Aβ is further influenced by Aβ degradation catalyzed by lysosome-resident cathepsins [54]. Once formed, Aβ can accumulate in endolysosomes as intraneuronal Aβ or it can undergo exocytotic release into extracellular spaces where diffuse Aβ plaques can form. Thus, Aβ generation can be enhanced by such factors as those that promote AβPP internalization [55], those that enhance protein levels and/or activities of BACE-1 and/or γ-secretase, those that prevent AβPP recycling back to the cell surface [56], and those that impair Aβ degradation in lysosomes [57].

Among these mechanisms, apoE4 could alter endocytic trafficking of AβPP [58], such an effect might result from the fact that

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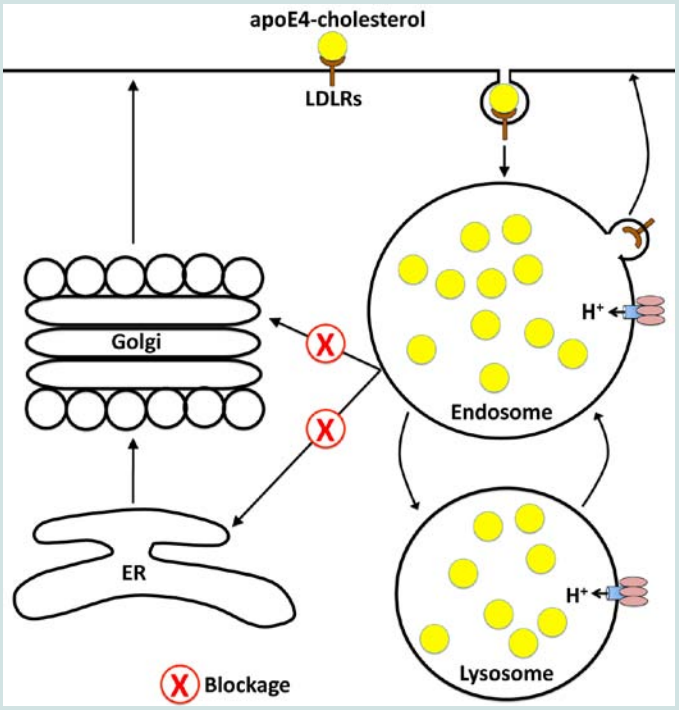

Figure 2: ApoE4-induced cholesterol dyshomeostasis.

ApoE-cholesterol is up-taken by neurons via receptor-mediated endocytosis with the assistance of LDLRs. Different apoE isoforms have different affinities for lipids and receptors for cholesterol uptake, and the associations between cholesterol and different apoE can result in drastic differences in endocytic trafficking and distribution of cholesterol in neurons. ApoE4 could lead to impaired recycling of cholesterol back to ER, Golgi and plasma membranes, where cholesterol is needed for membrane repair, neurite outgrowth, and synaptic plasticity. In addition, apoE4 could increase accumulation of cholesterol in endolysosomes thus disturbing endolysosome function.

apoE isoforms has different binding affinities to apoE receptors that mediates cholesterol uptake [59]. On one hand, apoE4 could promote AβPP internalization, because receptors for apoE uptake such as LRP1 and LRP10 have been shown to interact with AβPP and affect AβPP internalization [46,60,61]. On the other hand, apoE4 may have lower binding affinity to sorLA1, an apoE receptor that mediates the recycling of internalized AβPP from endosome back to Golgi and/or plasma membrane [62,63]. As a result, apoE4 may impair recycling of internalized AβPP, thus leading to accumulation of AβPP in endosome; the site where amyloidogenic processing of AβPP occurs [46,48,49]. Another mechanism whereby apoE4 promotes Aβ generation might result from endolysosome dysfunction, which has been elegantly brought out by studies from Nixon, Annaert, and others [64-68]. Indeed, it has been shown that apoE4 could lead to the accumulation of cholesterol in endolysosomes [37,40,41], an effect that could impair lysosomal degradation ability as occurs in Niemann-Pick type C disease [43]. Such apoE4-induced endolysosome cholesterol accumulation and endolysosome dysfunction could, on one hand, promote the interaction of APP with BACE-1 in endosome [69] thus enhancing Aβ generation in endosomes, and on the other hand impaire Aβ degradation in lysosomes thus leading to increased intraneuronal accumulation of Aβ [70]. In support, altered structure of endolysosome, an indication of endolysosome dysfunction, and intraneuronal accumulation of Aβ in endosomes correlate with apoE4 genotype [69-72]. Thus, by disturbing AβPP endocytic trafficking and/or impairing endolysosome function, apoE4 leads intraneuronal accumulation of Aβ (Figure 3).

ApoE4 and the formation of neurofibrillary tangle

Neurofibrillary tangle, composed of hyperphosphorylated tau, is another pathological hallmarks of AD. Besides the role of enhanced tau phosphorylation, as induced by apoE4 via apoE receptors and downstream signaling, in the development of neurofibrillary tangles [73-75], apoE4 could lead to the development of neurofibrillary tangle by altering intracellular cholesterol trafficking. As mentioned earlier, apoE4 could lead to the accumulation of cholesterol in endolysosomes [37,40,41], an effect that could impair lysosome degradation. In support, altered structure of endolysosome, which indicates endolysosome dysfunction, correlates with apoE4 genotype [71,72]. Because tau and hyperphosphorylated tau can be degraded by cathepsin D in autophagosomes-lysosomes [76-80], impaired lysosome degradation could lead to the development of neurofibrillary tangle. In support, increased accumulation of cholesterol in lysosomes and subsequent lysosome dysfunction has been linked to the development of neurofibrillary tangle in brains of patients with Niemann-Pick type C disease [81-86]. Thus, apoE4 could lead to the formation of neurofibrillary tangle by altering cholesterol intracellular trafficking and subsequent endolysosome dysfunction (Figure 3).

ApoE4 and synaptic dysfucntion

Synaptic dysfunction is the pathological hallmark of AD that correlates best with dementia [87,88]. Neurons are extraordinarily polarized cells with extensive processes that require constant

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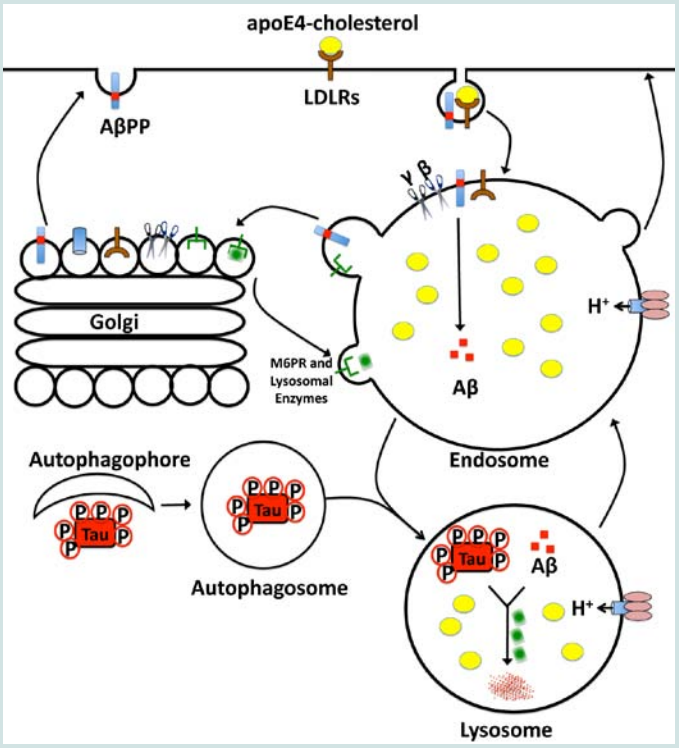

Figure 3: ApoE4-cholesterol contributes to the development of AD pathology.

ApoE4 could promote AβPP internalization or impair recycling of internalized AβPP, and thus to leads enhanced amyloidgenic processing of AβPP in endosome, the site where BACE-1 and γ-secretase are almost exclusively located and active in the acidic environment. Another mechanism whereby apoE4 promotes Aβ generation might result from apoE4-induced endolysosome cholesterol accumulation and endolysosome dysfunction, which could enhance Aβ generation in endosomes and inhibit Aβ degradation in lysosomes. Because hyperphosphorylated tau can be degraded in autophagosomes-lysosomes, apoE4-induced cholesterol accumulation in endolysosome and subsequent endolysosome dysfunction could impair tau degradation in autophagosome-lysosomes, thus leading to increased accumulation of hyperphosphorylated tau and the development of neurofibrillary tangle.

membrane trafficking and cholesterol recycling 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 [30,31]. Accordingly, impaired cholesterol recycling associated with apoE4 could lead to increased accumulation of cholesterol in endolysosome and reduced cholesterol recycling back and plasma membranes [37,40,41], where it is needed for membrane repair, neurite outgrowth, and synaptic plasticity. As such, impaired apoE4 recycling could lead to synaptic dysfunction [40,89]. Another mechanism whereby apoE4 could lead to synaptic dysfunction might result from the fact that apoE4 could lead to increased accumulation of cholesterol in endolysosome [37,40,41] and subsequent endolysosome dysfunction as occurs in Niemann-Pick type C disease [43]. In support, endolysosome dysfunction has been linked to synaptic pathology in AD brain [90,91] and deacidification of endolysosomes with chloroquine results in synaptic dysfunction and synaptic loss [92-94]. Thus, by impairing cholesterol recycling and disturbing endolysosome function, apoE4 could contribute to the development of synaptic dysfunction. Alternatively, apoE4 could contribute to synaptic dysfunction in AD via its effects on Aβ and tau pathologies [95-97].

Potential therapeutic strategies

Given the importance of altered cholesterol homeostasis in the pathogenesis of AD, cholesterol lowering drugs have been proposed as potential strategy for the treatment and/or prevention of AD [98]. However, the use of statins, a class of hydroxylmethylglutaryl-CoA (HMG-CoA) reductase inhibitors that block cholesterol biosynthesis thus lowering cholesterol levels, may not provide beneficial effects for AD. Because chronic use of statins results in over-expression of LDLRs and enhanced cholesterol uptake [99], and such an effect could increase the cholesterol burden in endolysosomes and worsen endolysosome dysfunction. Thus, it is not surprising that statins have no beneficial effects on Niemann-Pick type C disease [100,101], and that recent data from randomized clinical trials indicates that statins have little or no beneficial effects against AD [102-106] and in some cases statins result in adverse effects on memory and cognitions [107-110].

Thus, a more appropriate way in dealing with apoE4-associated disturbance in cholesterol homeostasis might be reducing cholesterol burden in endolysosomes. One such way is to promote cholesterol recycling, and the target protein might be SorLA, (also known as SORL1 or LR11), a mosaic member of LDL receptor family that could mediate protein retrograde transport from endosome to Golgi [27]. Besides its role in binding apoE cholesterol, SorLA, a Vps10p domain-containing receptor, is known to interact with APP and mediate its retrograde transport from endosome to Golgi [62,63,111]. Thus, over-expressing SorLA prevents amyloidogenic processing of

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APP in endolysosomes [63]. The other way in reducing cholesterol burden in endolysosome might be extracting endolysosome cholesterol into cytosol with cyclodextrin for further clearance [112]. Another way in reducing cholesterol burden in endolysosome might be suppressing cholesterol endocytosis and promoting cholesterol efflux, for instance, by using histone deacetylase inhibitors [113,114] or promoting lysosome exocytosis [115,116].

Besides direct targeting at cholesterol homeostasis, enhancing lysosome function represents another important strategy, which is recently reviewed by Nixon [117]. This strategy includes autophagy induction by inhibiting mTORC1 with rapamycin [118] or by activating AMPK with resveratrol [119], enhancing lysosome biogenesis by activating transcription factor EB [120,121], a master regulator of endolysosome biogenesis and function [122], and improving lysosome function by restoring lysosomal acidification [123].

Conclusion

ApoE4-associated alteration in cholesterol intracellular trafficking could lead to increased cholesterol accumulation in endolysosome and decreased recycling of cholesterol back to plasma membrane, a set of conditions share striking similarity (albeit less severely) to lysosomal lipid storage disorders as seen in Niemann-Pick type C disease. We propose that such an effect plays a key role in the apoE4-induced pathological hallmarks of sporadic AD including brain deposition of Aβ, neurofibrillary tangles, and disturbed synaptic integrity, a hypothesis that requires further evaluation. It should be noted that having one or two copies of the APOE4 gene does not mean a person will necessarily develop AD. Thus, other factors such as nutritional, environmental, epigenetic and genetic factors and their complex interactions are involved in the pathogenesis of sporadic AD [4].

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