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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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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

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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

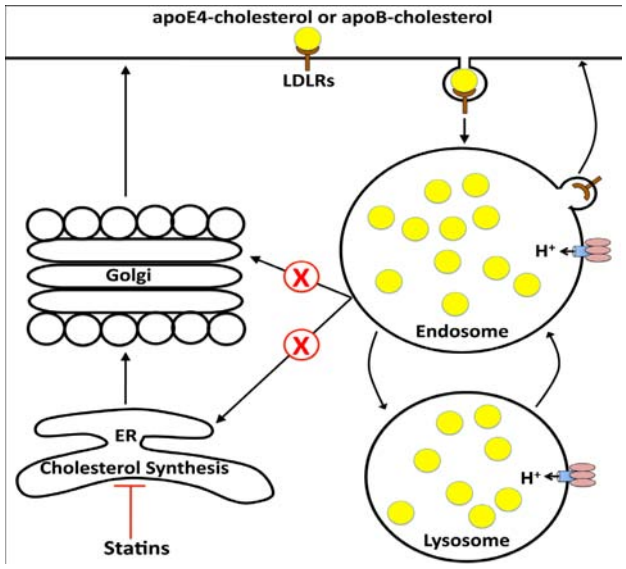

Figure 1: Statins worsen neuronal cholesterol dyshomeostasis as induced by apoE4 or increased levels of apoB.
Apo E-cholesterol or apoB-cholesterol (once it enters brain parenchyma) is up-taken by neurons via receptor-mediated endocytosis with the assistance of LDLRs. Different apolipoproteins have different 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.

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References

1. Goate A, Hardy J. Twenty years of Alzheimer's disease-causing mutations. J Neurochem. 2012; 120: 3-8.
2. Holtzman DM, Morris JC, Goate AM. Alzheimer's disease: the challenge of the second century. Sci Transl Med. 2011; 3: 77.
3. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol. 2011; 7: 137-152.
4. Linetti A, Fratangeli A, Taverna E, Valnegri P, Francolini M, Cappello V, et al. Cholesterol reduction impairs exocytosis of synaptic vesicles. J Cell Sci. 2010; 123: 595-605.
5. Koudinov AR, Koudinova NV. Essential role for cholesterol in synaptic plasticity and neuronal degeneration. FASEB J. 2001; 15: 1858-1860.
6. Fünfschilling U, Jockusch WJ, Sivakumar N, Möbius W, Corthals K, Li S, et al. Critical time window of neuronal cholesterol synthesis during neurite outgrowth. J Neurosci. 2012; 32: 7632-7645.
7. Reitz C, Rogaeva E, Foroud T, Farrer LA. Genetics and genomics of late-onset Alzheimer's disease and its endophenotypes. Int J Alzheimers Dis. 2011; 2011: 284728.
8. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997; 278: 1349-1356.
9. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet. 2009; 41: 1088-1093.
10. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009; 41: 1094-1099.
11. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261: 921-923.
12. Marzolo MP, Bu G. Lipoprotein receptors and cholesterol in APP trafficking and proteolytic processing, implications for Alzheimer's disease. Semin Cell Dev Biol. 2009; 20: 191-200.
13. Strand BH, Langballe EM, Hjellvik V, Handal M, Næss O, Knudsen GP, et al. Midlife vascular risk factors and their association with dementia deaths: results from a Norwegian prospective study followed up for 35 years. J Neurol Sci. 2013; 324: 124-130.
14. Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, et al. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology. 1998; 17: 14-20.
15. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen H, Alhainen K, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 2002; 137: 149-155.
16. Kuo YM, Emmerling MR, Bisgaier CL, Essenburg AD, Lampert HC, Drumm D, et al. Elevated low-density lipoprotein in Alzheimer's disease correlates with brain abeta 1-42 levels. Biochem Biophys Res Commun. 1998; 252: 711-715.
17. Matsuzaki T, Sasaki K, Hata J, Hirakawa Y, Fujimi K, Ninomiya T, et al. Association of Alzheimer disease pathology with abnormal lipid metabolism: the Hisayama Study. Neurology. 2011; 77: 1068-1075.
18. Reed B, Villeneuve S, Mack W, DeCarli C, Chui HC, Jagust W. Associations between serum cholesterol levels and cerebral amyloidosis. JAMA Neurol. 2014; 71: 195-200.
19. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord. 2009; 28: 75-80.
20. Barbero-Camps E, Fernandez A, Martinez L, Fernandez-Checa JC, Colell. APP/PS1 mice overexpressing SREBP-2 exhibit combined Abeta accumulation and tau pathology underlying Alzheimer's disease. Hum Mol Genet. 2013; 22: 3460-3476.
21. Thirumangalakudi L, Prakasam A, Zhang R, Bimonte-Nelson H, Sambamurti K, Kindy MS, et al. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice. J Neurochem. 2008; 106: 475-485.
22. Sharman MJ, Moussavi Nik SH, Chen MM, Ong D, Wijaya L, Laws SM, et al. The Guinea Pig as a Model for Sporadic Alzheimer's Disease (AD): The Impact of Cholesterol Intake on Expression of AD-Related Genes. PLoS One. 2013; 8: e66235.
23. Sparks DL, Scheff SW, Hunsaker JC, Liu H, Landers T, Gross DR. Induction

of Alzheimer-like beta-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. Exp Neurol. 1994; 126: 88-94.

24. Chen X, Wagener JF, Morgan DH, Hui L, Ghribi O, Geiger JD. Endolysosome mechanisms associated with Alzheimer's disease-like pathology in rabbits ingesting cholesterol-enriched diet. J Alzheimers Dis. 2010; 22: 1289-1303.

25. Ullrich C, Pirchl M, Humpel C. Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits. Mol Cell Neurosci. 2010; 45: 408-417.

26. Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. Arch Neurol. 2010; 67: 1491-1497.

27. Yasuno F, Asada T. Effect of plasma lipids and APOE genotype on cognitive decline. Dialogues Clin Neurosci. 2013; 15: 120-126.

28. Kandiah N, Feldman HH. Therapeutic potential of statins in Alzheimer's disease. J Neurol Sci. 2009; 283: 230-234.

29. Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry. 2009; 80: 13-17.

30. Hyttinen L, TuulioHenriksson A, Vuorio AF, Kuosmanen N, Harkanen T, Koskinen T, et al. Long-term statin therapy is associated with better episodic memory in aged familial hypercholesterolemia patients in comparison with population controls. J Alzheimers Dis. 2010; 21: 611-617.

31. McGuinness B, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. Cochrane Database Syst Rev. 2014; 7.

32. Silva T, Teixeira J, Remião F, Borges F. Alzheimer's disease, cholesterol, and statins: the junctions of important metabolic pathways. Angew Chem Int Ed Engl. 2013; 52: 1110-1121.

33. Shinohara M, Sato N, Shimamura M, Kurinami H, Hamasaki T, Chatterjee A, et al. Possible modification of Alzheimer's disease by statins in midlife: interactions with genetic and non-genetic risk factors. Front Aging Neurosci. 2014; 6: 71.

34. Wong WB, Lin VW, Boudreau D, Devine EB. Statins in the prevention of dementia and Alzheimer's disease: a meta-analysis of observational studies and an assessment of confounding. Pharmacoepidemiol Drug Saf. 2013; 22: 345-358.

35. Orsi A, Sherman O, Woldeselassie Z. Simvastatin-associated memory loss. Pharmacotherapy. 2001; 21: 767-769.

36. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy. 2009; 29: 800-811.

37. Harrison RW, Ashton CH. Do cholesterol-lowering agents affect brain activity? A comparison of simvastatin, pravastatin, and placebo in healthy volunteers. Br J Clin Pharmacol. 1994; 37: 231-236.

38. Goldstein MR, Mascitelli L, Pezzetta F, Haan MN, Cramer C, Kalbfleisch J, et al. Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology. 2009; 72: 1190-1191.

39. Kelley BJ, Glasser S. Cognitive effects of statin medications. CNS Drugs. 2014; 28: 411-419.

40. Appelqvist H, Wäster P, Kågedal K, Öllinger K. The lysosome: from waste bag to potential therapeutic target. J Mol Cell Biol. 2013; 5: 214-226.

41. Nixon RA, Cataldo AM. The endosomal-lysosomal system of neurons: new roles. Trends Neurosci. 1995; 18: 489-496.

42. Nixon RA, Cataldo AM. Lysosomal system pathways: genes to neurodegeneration in Alzheimer's disease. J Alzheimers Dis. 2006; 9: 277-289.

43. Tate BA, Mathews PM. Targeting the role of the endosome in the pathophysiology of Alzheimer's disease: a strategy for treatment. Sci Aging Knowledge Environ. 2006; 2006: re2.

44. Boland B, Kumar A, Lee S, Platt FM, Wegiel J, Yu WH, et al. Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer's disease. J Neurosci. 2008; 28: 6926-6937.

45. Cataldo AM, Petanceska S, Terio NB, Peterhoff CM, Durham R, Mercken M, et al. Abeta localization in abnormal endosomes: association with earliest Abeta elevations in AD and Down syndrome. Neurobiol Aging. 2004; 25: 1263-1272.

46. Arriagada C, Astorga C, Atwater I, Rojas E, Mears D, Caviedes R, et al. Endosomal abnormalities related to amyloid precursor protein in cholesterol treated cerebral cortex neuronal cells derived from trisomy 16 mice, an animal model of Down syndrome. Neurosci Lett. 2007; 423: 172-177.

47. Cataldo AM, Peterhoff CM, Troncoso JC, Gomez-Isla T, Hyman BT, Nixon RA. Endocytic pathway abnormalities precede amyloid beta deposition in sporadic Alzheimer's disease and Down syndrome: differential effects of APOE genotype and presenilin mutations. Am J Pathol. 2000; 157: 277-286.

48. Kenessey A, Nacharaju P, Ko LW, Yen SH. Degradation of tau by lysosomal enzyme cathepsin D: implication for Alzheimer neurofibrillary degeneration. J Neurochem. 1997; 69: 2026-2038.

49. Bendiske J, Bahr BA. Lysosomal activation is a compensatory response against protein accumulation and associated synaptopathogenesis--an approach for slowing Alzheimer disease? J Neuropathol Exp Neurol. 2003; 62: 451-463.

50. Jiang S, Li Y, Zhang X, Bu G, Xu H, Zhang YW. Trafficking regulation of proteins in Alzheimer's disease. Mol Neurodegener. 2014; 9: 6.

51. Haass C, Kaether C, Thinakaran G, Sisodia S. Trafficking and proteolytic processing of APP. Cold Spring Harb Perspect Med. 2012; 2: a006270.

52. Rajendran L, Annaert W. Membrane trafficking pathways in Alzheimer's disease. Traffic. 2012; 13: 759-770.

53. Morel E, Chamoun Z, Lasiecka ZM, Chan RB, Williamson RL, Vetanovetz C, et al. Phosphatidylinositol-3-phosphate regulates sorting and processing of amyloid precursor protein through the endosomal system. Nat Commun. 2013; 4: 2250.

54. Nixon RA. Endosome function and dysfunction in Alzheimer's disease and other neurodegenerative diseases. Neurobiol Aging. 2005; 26: 373-382.

55. Rajendran L, Schneider A, Schlechtingen G, Weidlich S, Ries J, Braxmeier T, et al. Efficient inhibition of the Alzheimer's disease beta-secretase by membrane targeting. Science. 2008; 320: 520-523.

56. Sannerud R, Declerck I, Peric A, Raemaekers T, Menendez G, Zhou L, et al. ADP ribosylation factor 6 (ARF6) controls amyloid precursor protein (APP) processing by mediating the endosomal sorting of BACE1. Proc Natl Acad Sci U S A. 2011; 108: E559-568.

57. Shimizu H, Tosaki A, Kaneko K, Hisano T, Sakurai T, Nukina N. Crystal structure of an active form of BACE, an enzyme responsible for amyloid beta protein production. Mol Cell Biol. 2008; 28: 3663-3671.

58. Miners JS, Barua N, Kehoe PG, Gill S, Love S. Aî²-degrading enzymes: potential for treatment of Alzheimer disease. J Neuropathol Exp Neurol. 2011; 70: 944-959.

59. Ma QL, Galasko DR, Ringman JM, Vinters HV, Edland SD, Pomakian J, et al. Reduction of SorLA/LR, a sorting protein limiting beta-amyloid production, in Alzheimer disease cerebrospinal fluid. Arch Neurol. 2009; 66: 448-457.

60. Torres M, Jimenez S, Sanchez-Varo R, Navarro V, Trujillo-Estrada L, Sanchez-Mejias E, et al. Defective lysosomal proteolysis and axonal transport are early pathogenic events that worsen with age leading to increased APP metabolism and synaptic Abeta in transgenic APP/PS1 hippocampus. Mol Neurodegener. 2012; 7: 59.

61. Oyama F, Murakami N, Ihara Y. Chloroquine myopathy suggests that tau is degraded in lysosomes: implication for the formation of paired helical filaments in Alzheimer's disease. Neurosci Res. 1998; 31: 1-8.

62. Wang Y, Martinez-Vicente M, Krüger U, Kaushik S, Wong E, Mandelkow EM, et al. Tau fragmentation, aggregation and clearance: the dual role of

lysosomal processing. Hum Mol Genet. 2009; 18: 4153-4170.

63. Hamano T, Gendron TF, Causevic E, Yen SH, Lin WL, Isidoro C, et al. Autophagic-lysosomal perturbation enhances tau aggregation in transfectants with induced wild-type tau expression. Eur J Neurosci. 2008; 27: 1119-1130.

64. Distl R, Treiber-Held S, Albert F, Meske V, Harzer K, Ohm TG. Cholesterol storage and tau pathology in Niemann-Pick type C disease in the brain. J Pathol. 2003; 200: 104-111.

65. Bi X, Liao G. Autophagic-lysosomal dysfunction and neurodegeneration in Niemann-Pick Type C mice: lipid starvation or indigestion? Autophagy. 2007; 3: 646-648.

66. Liao G, Yao Y, Liu J, Yu Z, Cheung S, Xie A, et al. Cholesterol accumulation is associated with lysosomal dysfunction and autophagic stress in Npc1 -/- mouse brain. Am J Pathol. 2007; 171: 962-975.

67. Vance JE. Lipid imbalance in the neurological disorder, Niemann-Pick C disease. FEBS Lett. 2006; 580: 5518-5524.

68. Bu B, Li J, Davies P, Vincent I. Deregulation of cdk5, hyperphosphorylation, and cytoskeletal pathology in the Niemann-Pick type C murine model. J Neurosci. 2002; 22: 6515-6525.

69. Sawamura N, Gong JS, Garver WS, Heidenreich RA, Ninomiya H, Ohno K, et al. Site-specific phosphorylation of tau accompanied by activation of mitogen-activated protein kinase (MAPK) in brains of Niemann-Pick type C mice. J Biol Chem. 2001; 276: 10314-10319.

70. Murthy VN, Stevens CF. Synaptic vesicles retain their identity through the endocytic cycle. Nature. 1998; 392: 497-501.

71. Kuromi H, Kidokoro Y. Two distinct pools of synaptic vesicles in single presynaptic boutons in a temperature-sensitive Drosophila mutant, shibire. Neuron. 1998; 20: 917-925.

72. Blumstein J, Faundez V, Nakatsu F, Saito T, Ohno H, Kelly RB. The neuronal form of adaptor protein-3 is required for synaptic vesicle formation from endosomes. J Neurosci. 2001; 21: 8034-8042.

73. Bezprozvanny I, Hiesinger PR. The synaptic maintenance problem: membrane recycling, Ca2+ homeostasis and late onset degeneration. Mol Neurodegener. 2013; 8: 23.

74. Callahan LM, Vaules WA, Coleman PD. Quantitative decrease in synaptophysin message expression and increase in cathepsin D message expression in Alzheimer disease neurons containing neurofibrillary tangles. J Neuropathol Exp Neurol. 1999; 58: 275-287.

75. Bahr BA, Bendiske J. The neuropathogenic contributions of lysosomal dysfunction. J Neurochem. 2002; 83: 481-489.

76. Bendiske J, Caba E, Brown QB, Bahr BA. Intracellular deposition, microtubule destabilization, and transport failure: an "early" pathogenic cascade leading to synaptic decline. J Neuropathol Exp Neurol, 2002; 61: 640-650.

77. Kanju PM, Parameshwaran K, Vaithianathan T, Sims CM, Huggins K, Bendiske J, et al. Lysosomal dysfunction produces distinct alterations in synaptic alpha-amino-3-hydroxy-5-methylisoxazolepropionic acid and N-methyl-D-aspartate receptor currents in hippocampus. J Neuropathol Exp Neurol. 2007; 66: 779-788.

78. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002; 298: 789-791.

79. Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991; 30: 572-580.

80. Nieweg K, Schaller H, Pfrieger FW. Marked differences in cholesterol synthesis between neurons and glial cells from postnatal rats. J Neurochem. 2009; 109: 125-134.

81. Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH. Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B,E (LDL) receptors in the brain. J Biol Chem. 1987; 262: 14352-14360.

82. Maxfield FR, Tabas I. Role of cholesterol and lipid organization in disease. Nature. 2005; 438: 612-621.

83. Vance JE, Karten B, Hayashi H. Lipid dynamics in neurons. Biochem Soc Trans. 2006; 34: 399-403.

84. Sleat DE, Wiseman JA, El-Banna M, Price SM, Verot L, Shen MM, et al. Genetic evidence for nonredundant functional cooperativity between NPC1 and NPC2 in lipid transport. Proc Natl Acad Sci U S A. 2004; 101: 5886-5891.

85. de Chaves EP, Narayanaswami V. Apolipoprotein E and cholesterol in aging and disease in the brain. Future Lipidol. 2008; 3: 505-530.

86. Vance JE. Dysregulation of cholesterol balance in the brain: contribution to neurodegenerative diseases. Dis Model Mech. 2012; 5: 746-755.

87. Mahley RW, Huang Y, Weisgraber KH. Putting cholesterol in its place: apoE and reverse cholesterol transport. J Clin Invest. 2006; 116: 1226-1229.

88. Matsuura F, Wang N, Chen W, Jiang XC, Tall AR. HDL from CETP-deficient subjects shows enhanced ability to promote cholesterol efflux from macrophages in an apoE- and ABCG1-dependent pathway. J Clin Invest. 2006; 116: 1435-1442.

89. Rebeck GW, Kindy M, LaDu MJ. Apolipoprotein E and Alzheimer's disease: the protective effects of ApoE2 and E3. J Alzheimers Dis. 2002; 4: 145-154.

90. Poirier J. Apolipoprotein E represents a potent gene-based therapeutic target for the treatment of sporadic Alzheimer's disease. Alzheimers Dement. 2008; 4: S91-97.

91. Hayashi H, Eguchi Y, Fukuchi-Nakaishi Y, Takeya M, Nakagata N, Tanaka K, et al. A potential neuroprotective role of apolipoprotein E-containing lipoproteins through low density lipoprotein receptor-related protein 1 in normal tension glaucoma. J Biol Chem. 2012; 287: 25395-25406.

92. Hayashi H, Campenot RB, Vance DE, Vance JE. Apolipoprotein E-containing lipoproteins protect neurons from apoptosis via a signaling pathway involving low-density lipoprotein receptor-related protein-1. J Neurosci. 2007; 27: 1933-1941.

93. Kontush A, Chapman MJ. HDL: close to our memories? Arterioscler Thromb Vasc Biol. 2008; 28: 1418-1420.

94. Paternò R, Ruocco A, Postiglione A, Hubsch A, Andresen I, Lang MG. Reconstituted high-density lipoprotein exhibits neuroprotection in two rat models of stroke. Cerebrovasc Dis. 2004; 17: 204-211.

95. Lapergue B, Moreno JA, Dang BQ, Coutard M, Delbosc S, Raphaeli G, et al. Protective effect of high-density lipoprotein-based therapy in a model of embolic stroke. Stroke. 2010; 41: 1536-1542.

96. Garai K, Baban B, Frieden C. Self-association and stability of the ApoE isoforms at low pH: implications for ApoE-lipid interactions. Biochemistry. 2011; 50: 6356-6364.

97. Yamamoto T, Choi HW, Ryan RO. Apolipoprotein E isoform-specific binding to the low-density lipoprotein receptor. Anal Biochem. 2008; 372: 222-226.

98. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet. 1994; 7: 180-184.

99. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013; 9: 106-118.

100. Verghese PB, Castellano JM, Garai K, Wang Y, Jiang H, Shah A, et al. ApoE influences amyloid-Î² (AÎ²) clearance despite minimal apoE/AÎ² association in physiological conditions. Proc Natl Acad Sci U S A. 2013; 110: E1807-1816.

101. Kanekiyo T, Xu H, Bu G. ApoE and AÎ² in Alzheimer's disease: accidental encounters or partners? Neuron. 2014; 81: 740-754.

102. Tai LM, Mehra S, Shete V, Estus S, Rebeck GW, Bu G, et al. Soluble apoE/AÎ² complex: mechanism and therapeutic target for APOE4-induced AD risk. Mol Neurodegener. 2014; 9: 2.

103. DeKroon RM, Armati PJ. The endosomal trafficking of apolipoprotein E3 and E4 in cultured human brain neurons and astrocytes. Neurobiol Dis. 2001; 8: 78-89.

104. Heeren J, Grewal T, Laatsch A, Becker N, Rinninger F, Rye KA, et al. Impaired recycling of apolipoprotein E4 is associated with intracellular cholesterol accumulation. J Biol Chem. 2004; 279: 55483-55492.

105. Gong JS, Morita SY, Kobayashi M, Handa T, Fujita SC, Yanagisawa K, et al. Novel action of apolipoprotein E (ApoE): ApoE isoform specifically inhibits lipid-particle-mediated cholesterol release from neurons. Mol Neurodegener. 2007; 2: 9.

106. Ye S, Huang Y, Müllendorff K, Dong L, Giedt G, Meng EC, Cohen FE. Apolipoprotein (apo) E4 enhances amyloid beta peptide production in cultured neuronal cells: apoE structure as a potential therapeutic target. Proc Natl Acad Sci U S A. 2005; 102: 18700-18705.

107. Chen Y, Durakoglugil MS, Xian X, Herz J. ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling. Proc Natl Acad Sci U S A. 2010; 107: 12011-12016.

108. Nixon RA. Niemann-Pick Type C disease and Alzheimer's disease: the APP-endosome connection fattens up. Am J Pathol. 2004; 164: 757-761.

109. Pacheco CD, Lieberman AP. The pathogenesis of Niemann-Pick type C disease: a role for autophagy? Expert Rev Mol Med. 2008; 10: e26.

110. Jin LW, Shie FS, Maezawa I, Vincent I, Bird T. Intracellular accumulation of amyloidogenic fragments of amyloid-beta precursor protein in neurons with Niemann-Pick type C defects is associated with endosomal abnormalities. Am J Pathol. 2004; 164: 975-985.

111. Suzuki K, Parker CC, Pentchev PG, Katz D, Ghetti B, D'Agostino AN, et al. Neurofibrillary tangles in Niemann-Pick disease type C. Acta Neuropathol. 1995; 89: 227-238.

112. Pressey SN, Smith DA, Wong AM, Platt FM, Cooper JD. Early glial activation, synaptic changes and axonal pathology in the thalamocortical system of Niemann-Pick type C1 mice. Neurobiol Dis. 2012; 45: 1086-100.

113. Zipser BD, Johanson CE, Gonzalez L, Berzin TM, Tavares R, Hulette CM, et al. Microvascular injury and blood-brain barrier leakage in Alzheimer's disease. Neurobiol Aging. 2007; 28: 977-986.

114. Ujiie M, Dickstein DL, Carlow DA, Jefferies WA. Blood-brain barrier permeability precedes senile plaque formation in an Alzheimer disease model. Microcirculation. 2003; 10: 463-470.

115. Kalaria RN. The blood-brain barrier and cerebrovascular pathology in Alzheimer's disease. Ann N Y Acad Sci. 1999; 893: 113-125.

116. Kalaria RN. The blood-brain barrier and cerebral microcirculation in Alzheimer disease. Cerebrovasc Brain Metab Rev. 1992; 4: 226-260.

117. Munoz DG, Erkinjuntti T, Gaytan-Garcia S, Hachinski V. Serum protein leakage in Alzheimer's disease revisited. Ann N Y Acad Sci. 1997; 826: 173-189.

118. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature. 2012; 485: 512-516.

119. Namba Y, Tsuchiya H, Ikeda K. Apolipoprotein B immunoreactivity in senile plaque and vascular amyloids and neurofibrillary tangles in the brains of patients with Alzheimer's disease. Neurosci Lett. 1992; 134: 264-266.

120. Takechi R, Galloway S, Pallebage-Gamarallage M, Wellington C, Johnsen R, Mamo JC. Three-dimensional colocalization analysis of plasma-derived apolipoprotein B with amyloid plaques in APP/PS1 transgenic mice. Histochem Cell Biol. 2009; 131: 661-666.

121. Bereczki E, Bernát G, Csont T, Ferdinandy P, Scheich H, Sántha M. Overexpression of human apolipoprotein B-100 induces severe neurodegeneration in transgenic mice. J Proteome Res. 2008; 7: 2246-2252.

122. Chen X, Gawryluk JW, Wagener JF, Ghribi O, Geiger JD. Caffeine blocks disruption of blood brain barrier in a rabbit model of Alzheimer's disease. J Neuroinflammation. 2008; 5: 12.

123. Beffert U, Danik M, Krzywkowski P, Ramassamy C, Berrada F, Poirier J. The neurobiology of apolipoproteins and their receptors in the CNS and Alzheimer's disease. Brain Res Brain Res Rev. 1998; 27: 119-142.

124. Dietschy JM. Central nervous system: cholesterol turnover, brain development and neurodegeneration. Biol Chem. 2009; 390: 287-293.

125. Holtzman DM, Herz J, Bu G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. Cold Spring Harb Perspect Med. 2012; 2: a006312.

126. Laatsch A, Panteli M, Sornsakrin M, Hoffzimmer B, Grewal T, Heeren J. Low density lipoprotein receptor-related protein 1 dependent endosomal trapping and recycling of apolipoprotein E. PLoS One. 2012; 7: e29385.

127. Rensen PC, Jong MC, van Vark LC, van der Boom H, Hendriks WL, van Berkel TJ, et al. Apolipoprotein E is resistant to intracellular degradation in vitro and in vivo. Evidence for retroendocytosis. J Biol Chem. 2000; 275: 8564-8571.

128. Heeren J, Grewal T, Laatsch A, Rottke D, Rinninger F, Enrich C, et al. Recycling of apoprotein E is associated with cholesterol efflux and high density lipoprotein internalization. J Biol Chem. 2003; 278: 14370-14378.

129. Cossec JC, Marquer C, Panchal M, Lazar AN, Duyckaerts C, Potier MC. Cholesterol changes in Alzheimer's disease: methods of analysis and impact on the formation of enlarged endosomes. Biochim Biophys Acta. 2010; 1801: 839-845.

130. Hui L, Chen X, Geiger JD. Endolysosome involvement in LDL cholesterol-induced Alzheimer's disease-like pathology in primary cultured neurons. Life Sci. 2012; 91: 1159-1168.

131. Mailman T, Hariharan M, Karten B. Inhibition of neuronal cholesterol biosynthesis with lovastatin leads to impaired synaptic vesicle release even in the presence of lipoproteins or geranylgeraniol. J Neurochem, 2011; 119: 1002-1015.

132. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009; 29: 431-438.

133. Michikawa M, Yanagisawa K. Apolipoprotein E4 induces neuronal cell death under conditions of suppressed de novo cholesterol synthesis. J Neurosci Res. 1998; 54: 58-67.

134. Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. Circulating cholesterol levels, apolipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: results of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. Acta Neurol Scand Suppl. 2006; 185: 3-7.

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