Molecular Neurobiology

ISSN0893-7648/05/31(1–3): 185–192/$30.00

Is Hypercholesterolemia a Risk Factor for Alzheimer's Disease?

W. Gibson Wood,*,[1] Urule Igbavboa,[1] Gunter P. Eckert,[2] Leslie N. Johnson-Anuna,[1] and Walter E. Müller[2]

[1]Department of Pharmacology, University of Minnesota School of Medicine and Geriatric Research, Education and Clinical Center, VA Medical Center, Minneapolis, MN; and [2]Department of Pharmacology, Biocenter Niederursel, Zafes, University of Frankfurt, Frankfurt, Germany

Abstract

There is considerable attention being given to the association of Alzheimer's disease and cholesterol homeostasis. To that end, some have suggested that elevated cholesterol levels are a risk factor for Alzheimer's disease. If elevated cholesterol is a risk factor for Alzheimer's disease, then it would be expected that patients with Alzheimer's disease would have elevated serum and brain cholesterol levels. Studies were reviewed that have examined cholesterol levels in Alzheimer's patients and control subjects, including prospective studies, and based on that review, the conclusion is reached that the majority of studies do not support elevated cholesterol levels in serum and brain as a risk factor for Alzheimer's disease. Alternative hypotheses are discussed, including cholesterol domains and subgroups of individuals with hypercholesteremia.

Index Entries: Amyloid β-protein; Alzheimer's disease; apolipoprotein E, cholesterol; lipoproteins; statins.

Introduction

Several different lines of evidence point to a potentially important but not well understood association between Alzheimer's disease (AD) and cholesterol (reviewed in refs. *1–3*). Experimental studies both in vitro and in vivo have reported that changes in cholesterol levels alter amyloid precursor protein abundance and amyloid-β protein (Aβ) levels and conversely that Aβ modifies cholesterol dynamics. ApoE4, a cholesterol carrier protein, is a major risk factor for AD *(4).* Epidemiological data have found that patients taking inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) lower the risk of developing AD *(5–8).* HMG-CoA reductase is

Received 6/21/04; Accepted 11/15/04.
* Author to whom correspondence and reprint requests should be addressed. E-mail: woodx002@umn. edu

the primary regulatory enzyme in cholesterol biosynthesis *(9).* Based on the above-mentioned findings, one might arrive at the uncomplicated conclusion that alterations in cholesterol homeostasis can cause and/or contribute to the progression of AD. To that end in a recent review, it was concluded that cholesterol was a "bona fide" risk factor in the pathogenesis of AD *(10).* If cholesterol is a risk factor for AD, then a reasonable hypothesis is that levels of serum and brain cholesterol should be elevated in AD patients when compared with controls. The purpose of this succinct review will be to examine data from human studies in support of and not supporting the aforementioned hypothesis. Experimental in vivo and in vitro studies related to cholesterol and AD have been recently reviewed elsewhere *(2,11,12)* and that body of work will not be reviewed in this article.

Serum and Plasma Cholesterol Levels and AD

Elevated serum cholesterol levels have been suggested to increase the risk of developing AD *(13).* However, data supporting elevated cholesterol as a risk factor in AD have not been consistently observed. A meta-analysis of 10 studies published between 1986 and 1999 found that cholesterol levels were actually significantly lower in AD patients than in control subjects *(14).* However, the average difference in cholesterol levels between AD and control subjects was 6.7 mg/dL, which is a relatively small difference. Additional studies on cholesterol levels in AD patients and control subjects are summarized in Table 1 and underscore the absence of consistent findings. Total serum cholesterol levels were not statistically significant between AD and control subjects, but it was observed that low-density lipoprotein cholesterol (LDL-C) was significantly higher and high-density lipoprotein cholesterol (HDL-C) was significantly lower in AD patients than control subjects *(15).* In contrast, LDL-C levels were reported to not be significantly different in AD patients compared with control subjects *(16),* but total cholesterol levels were significantly lower in AD patients than control subjects. Although the mean total cholesterol levels were significant, the physiological effects of such small changes are unclear. In a population-based study of elderly African-Americans compared to controls, serum cholesterol levels were significantly higher in AD patients without apoE4 alleles but were not significant in AD patients with one or two E4 alleles *(17).* In a longitudinal study at the first exam, cholesterol levels were significantly higher in AD patients compared with control subjects but were not significantly different at the second exam *(18).* In can be seen in Table 1 that the difference between the two means at the first exam was 19.33 mg/dL, which is certainly not a robust difference between the two groups. Another consideration is the disproportionate number of control subjects (n = 1352) vs AD patients (n = 48). A recent study that compared plasma cholesterol levels to brain amyloid deposition found that plasma cholesterol levels were similar and not significantly different among the groups studied, as shown in Table 1 *(13).* However data in Table 1 show that when groups were divided by age and presence or absence of amyloid, young amyloid-positive subjects had significantly higher levels of plasma cholesterol than did young amyloid-minus subjects *(13).* Further analysis involving logarithmic transformation of the data, nonparametric testing, and multiple regression modeling revealed that amyloid load was correlated with elevated plasma cholesterol in subjects 40–55 yr of age but not in subjects 55 yr and older. In contrast, an earlier study reported that neuritic plaque load in the neocortex and hippocampus was not associated with total plasma cholesterol *(19).* However, neuritic plaque load in the neocortex and hippocampus was associated with increasing late-life HDL-C levels but not midlife HDL-C levels *(19).* Even though the specific results of the two studies differ, it is interesting that both report that AD neuropathology is associated with elevated cholesterol levels. The majority of studies on cholesterol levels have been retrospective. In the well-recognized

Table 1
Serum and Plasma Cholesterol Levels in Control Subjects and AD Patients[a]

	Control subjects			AD patients			
Study	Mean	SD	*N*	Mean	SD	*N*	*p*
Kuo et al. *(15)*	152.8	7.1	36	176.0	8.2	64	NS
Romas et al. *(16)*	204.1	38.2	680	196.3	45	178	S
Evans et al. *(17)*	229[a]	50.1	17	224	45.7	24	NS
	202[b]	40.8	24	230	50.7	22	S
Kivipelto et al. *(18)*	259.06[c]	46.44	1352	278.39	38.7	48	S
	224.3[d]	38.7		232	38.7		NS
Pappolla et al. *(13)*	190[e]	58	41	209[f]	14	3	NS
				208[g]	53	17	NS
Pappolla et al. *(13)*	164[h]	8	23	219[i]	12	17	S
	190[j]	9	41	200[k]	6	59	NS

Cholesterol levels given as mg/dL.
[a] Subjects having one or more ε4 alleles.
[b] Subjects not having an ε4 allele.
[c] First exam.
[d] Re-examination after an average of 21 yr.
[e] Amyloid-negative subjects.
[f] AD diagnosis.
[g] All possible/probable/definite AD diagnostic categories.
[h,i] 40–55 yr of age amyloid minus and amyloid plus, respectively.
[j,k] >55 yr of age amyloid minus and amyloid plus, respectively.

Framingham study, total serum cholesterol levels were not associated with the risk for AD *(20).* Serum cholesterol levels were determined at baseline and across 15 biennial cycles as well as neurological and neuropsychological examinations for dementia.

Data supporting elevated serum cholesterol levels as being a risk factor for AD have yielded conflicting results. However, the majority of studies do not support the hypothesis that elevated cholesterol level is a risk factor for AD. Moreover, comparing the estimated number of American patients with AD (4.5 million) *(21)* and the estimated number of American adults with cholesterol values of 200 mg/dL and higher (105 million) *(22)* and of that number 37 million have cholesterol levels of 240 mg/dL higher, it would be expected that there should be more individuals with AD. It is certainly possible that a subset of individuals with elevated cholesterol levels are at risk for AD, but there have to be additional mechanisms that act in tandem with cholesterol. For example, the apoE ε4 allele is a risk factor for AD, and a recent review concluded that LDL and total cholesterol levels were in the order of apoE2 <apoE3<apoE4, whereas HDL cholesterol levels were apoE2>apoE3>apoE4 *(23).* However, in a study of over 9000 men and women examining total and HDL cholesterol levels and other lipid parameters as a function of apoE genotype, the association between apoE genotype and cholesterol levels does not support that conclusion *(24).* For example, differences in total cholesterol levels for male ε33 and ε44 genotypes were approx 0.4 mmol/L and HDL cholesterol levels differences were 0.05 mmol/L between ε33 and ε44 genotypes *(24).* Differences in the functional dynamics of the apoE isoforms might be more physiologically significant than apoE isoform-dependent cholesterol levels.

Brain Cholesterol Levels and AD

Elevated serum cholesterol levels do not appear to be a risk factor for AD. The same conclusion applies to brain cholesterol levels. It can be seen in Table 2 that cholesterol levels have been determined in different brain regions and the cerebrospinal fluid (CSF) of AD patients compared with control subjects. If cholesterol contributes to AD pathogenesis, then it would be expected that AD patients would have higher brain cholesterol levels than normal individuals. There have been reports of reduced cholesterol levels, increased cholesterol levels, and no changes in cholesterol levels in AD patients vs control subjects. Cholesterol levels were lower in the temporal gyrus of autopsied brains of AD patients in contrast to control subjects *(25).* The cholesterol-to-phospholipid ratio of the temporal gyrus was reduced by 30% in the AD brains and no differences were observed in the cholesterol-to-phospholipid ratio in the cerebellum of the two groups. The reduction in the cholesterol-to-phospholipid ratio in the temporal gyrus was attributed to cholesterol because the phospholipid-to-protein ratio was similar in brains of both groups. There was a small but significant increase in frontal cortex gray matter cholesterol levels of AD patients (2.65 ± 0.14 mg/g wet tissue weight) with the apoE4 genotype compared with apoE4 control subjects (2.04 ± 0.18) *(26).* Cholesterol levels did not differ in hippocampal tissue of AD patients compared with control subjects *(27).* A recent study reported that cholesterol levels were similar in cerebral cortex of AD and control individuals with a small increase (approx 15 μg vs 12 μg) in cholesterol levels in the basal ganglia of AD patients compared with control subjects *(28).*

On the other hand, there also was a small but significant decrease in 24*S*-hydroxycholesterol levels in basal ganglia of AD patients in contrast to controls *(28).* This oxysterol is thought to be important in the regulation of brain cholesterol homeostasis *(29,30).* Changes in levels of 24*S*-hydroxycholesterol would imply changes in cholesterol turnover, but it is not clear how such changes relate to the amount of cholesterol in the brain. Levels of cholesterol in brain are in micromoles per milligram of protein, whereas 24*S*-hydroxycholesterol levels occur in nanomoles per milligram of protein. It is not clear how a relatively small change in 24*S*-hydroxycholesterol levels impacts on the much larger cholesterol pool. A recent study reported almost a 100% increase in cholesterol levels in the middle frontal gyrus of AD patients relative to controls *(31).* Such a finding is difficult to reconcile with the relatively small changes in those studies reporting differences, and the data showing that HMG-CoA reductase mRNA levels in brain were indistinguishable between AD samples and control samples *(32).*

Cholesterol and its metabolites have also been determined in the CSF. Levels of both free and esterified cholesterol were significantly lower in CSF of AD patients than levels in control subjects *(33).* Cholesterol levels were lower in the CSF of AD patients but were not significantly different when compared with control subjects *(34),* although another report did find significantly lower CSF cholesterol levels in AD patients *(35).* Total CSF cholesterol did not significantly differ between AD patients and control subjects, but 24*S*-hydroxycholesterol levels were significantly higher in CSF of AD patients compared with control subjects, and it was concluded that there was an increased turnover of cholesterol in AD patients *(36).* The data for CSF 24*S*-hydroxycholesterol levels were presented in a bar graph, but estimating from the bar graph the mean values for AD patients were 2.1 ng/mL and for control subjects 1.3 ng/mL. On the other hand, the data for CSF cholesterol shown in Table 2 from that study are expressed as milligrams per deciliter. There is an approx 166- to 207-fold difference in cholesterol abundance compared with 24*S*-hydroxycholesterol abundance. Even if there is increased turnover of cholesterol in AD patients, the linkage of 24*S*-hydroxycholesterol levels with cholesterol turnover is unclear.

Results of studies on brain and CSF cholesterol levels in AD patients compared with con-

Table 2
Cholesterol Values in Brain and CSF of Control Subjects and Patients

Study	Sample	Control				Ad Patients				S/NS[a]
		Mean	SD	SE	N	Mean	SD	SE	N	
Mason et al. *(25)*	Superior temporal gyrus	0.66	0.05		6	0.46	0.08		6	S
	Cerebellum (C/P ratio)	0.45	0.08		6	0.50	0.08		6	NS
Sparks *(26)*	Frontal cortex gray matter (cholesterol mg/g wet wt.)	2.04		0.18	6	2.65		0.14	5	S
Eckert et al. *(27)*	Hippocampus-free cholesterol (µg/100 µg protein)	29.5	10.6		12	26.0	6.1		12	NS
Heverin et al. *(28)*[b]	Frontal cortex				8				8	NS
	Occipital cortex									NS
	B. ganglia									S
	Pons (cholesterol µg/mg)									NS
Cutter et al. *(31)*[b]	Middle frontal gyrus				7				7	S
	Cerebellum (cholesterol % relative to control)									NS
Mulder et al. *(33)*	CSF-free cholesterol	0.25	0.19		31	0.13	0.09		27	S
	CSF-esterified cholesterol (mg/dL)	0.42	0.34		31	0.25	0.19		27	S
Demeester et al. *(34)*	CSF-free cholesterol (µg/mL)	4.4	1.31		8	3.5	1.12		8	NS
Wollmer et al. *(35)*	CSF-cholesterol (mg/dL)	0.58		0.05	22	0.44		0.03	24	S
Papassotiropoulos et al. *(36)*	CSF-total cholesterol (mg/dL)	0.27	0.08		7	0.35	0.12		32	NS

[a] S, statistically significant; NS, not statistically significant.
[b] data presented in bar graphs.

trol subjects are as highly variable as seen for studies on serum and plasma cholesterol. The "usual suspects," such as different brain regions, cholesterol assays, and patient variables, could certainly contribute to the lack of consistent findings. Alternatively, changes in bulk brain cholesterol might not contribute to AD pathogenesis. Perhaps changes in cholesterol levels of AD patients occur in cholesterol domains and not in bulk cholesterol levels. Cholesterol is not evenly distributed in cell organelles or even within organelles. We have recently shown in astrocytes that cholesterol levels are highest in the trans-Golgi region than in the cis-medial regions and that effects of Aβ were associated with cholesterol distribution in the Golgi complex regions *(37).* In cell membranes, cholesterol is asymmetrically distributed in the exofacial and cytofacial leaflets (i.e., the transbilayer cholesterol distribution) and this distribution was altered by apoE expression, isoform *(38,39),* increasing age *(40),* chronic alcohol treatment *(41),* and statins *(42).* Redistribution of cholesterol in the exofacial and cytofacial leaflets alters individual leaflet fluidity and function. Other brain cholesterol domains that could differ in AD patients are lipid rafts and caveolae that are enriched in cholesterol. There is some evidence that production of amyloid-β protein might be associated with lipid rafts *(43–46).* The point is that there might be substantial changes in cholesterol homeostasis in AD patients, but such proposed changes are occurring in cholesterol domains in contrast to changes in bulk cholesterol levels. Marked changes in cholesterol domains have been reported to occur in the absence of changes in bulk cholesterol levels *(38,39,41).*

Conclusions

Data on both serum and brain cholesterol levels of AD patients compared with control subjects do not support the hypothesis that bulk cholesterol levels contribute to AD pathogenesis. Actually, this conclusion is not surprising when one considers that there are substantially more individuals with high cholesterol levels than there are AD patients. Ostensibly, however, what would appear to be paradoxical to that conclusion is that epidemiological data show that patients taking statins have a lower risk of developing AD compared with individuals not taking statins *(5–7)* and in vivo and in vitro studies of cholesterol and Aβ protein (reviewed in refs. *3* and *10*). The potential efficacy of statins in reducing the risk of AD could be unrelated to cholesterol biosynthesis. There is a growing recognition that statins have cholesterol-independent effects (reviewed in refs. *47* and *48*). Pleiotropic effects of statins have been described that include, for example, upregulation of eNOS expression, anti-inflammatory actions, glucose metabolism, and antioxidant activity *(47,48).* We have recently reported that in vivo chronic administration of statins had pleiotropic effects on mouse cerebral cortex gene expression and for the first time levels of lovastatin, pravastatin, and simvastatin were quantified in brain *(49).* What is more difficult to explain are the in vivo and in vitro studies showing that modification of cholesterol levels alters amyloid precursor protein and Aβ levels. Thus, the majority of human data on serum and brain cholesterol levels appear to be in conflict with results of studies using cell culture and animal models. Can the findings of the majority of human studies on serum and brain cholesterol levels be reconciled with the results of the experimental studies? We propose the following admittedly speculative suggestions in answer to the aforementioned question. Elevated cholesterol levels might not contribute to the development of AD in most individuals. There might be a subgroup of individuals in which elevated cholesterol levels and an unidentified cofactor(s) are involved in the development of AD. Studies using cell culture of neurons and animal studies where either cholesterol levels are reduced, or increased, might be models of this hypothesized subgroup.

Acknowledgments

This work was supported by NIH grants AG23524, AG-18357, NATO Collaborative Linkage grant 980136, and the Medical Research Program of the Department of Veterans Affairs.

References

1. Burns M. and Duff K. (2002) Cholesterol in Alzheimer's disease and tauopathy. *Ann. NY Acad. Sci.* **977,** 367–375.
2. Wood W.G., Eckert G.P., Igbavboa U., and Müller W.E. (2003) Amyloid beta-peptide interactions with membranes and cholesterol: causes or casualties of Alzheimer's disease. *Biochim. Biophys. Acta.* **1610,** 281–290.
3. Wolozin B. (2004) Cholesterol and the biology of Alzheimer's disease. *Neuron* **41,** 7–10.
4. Saunders A.M., Strittmatter W.J., Schmechel D., et al. (1993) Association of apolipoprotein E allele E4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43,** 1467–1472.
5. Wolozin B., Kellman W., Ruosseau P., Celesia G.G., and Siegel G. (2000) Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch. Neurol.* **57,** 1439–1443.
6. Jick H., Zornberg G.L., Jick S.S., Seshadri S., and Drachman D.A. (2000) Statins and the risk of dementia. *Lancet* **356,** 1627–1631.
7. Rockwood K., Kirkland S., Hogan D.B., et al. (2002) Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch. Neurol.* **59,** 223–227.
8. Zamrini E., McGwin G., and Roseman J.M. (2004) Association between statin use and Alzheimer's disease. *Neuroepidemiology* **23,** 94–98.
9. Hamelin B.A. and Turgeon J. (1998) Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol. Sci.* **19,** 26–37.
10. Puglielli L., Tanzi R.E., and Kovacs D.M. (2003) Alzheimer's disease: the cholesterol connection. *Nat. Neurosci.* **6,** 345–351.
11. Hartmann T. (2001) Cholesterol, A beta and Alzheimer's disease. *Trends Neurosci.* **24,** S45–S48.
12. Michikawa M. (2003) The role of cholesterol in pathogenesis of Alzheimer's disease: dual metabolic interaction between amyloid beta-protein and cholesterol. *Mol. Neurobiol.* **27,** 1–12.
13. Pappolla M.A., Bryant-Thomas T., Herbert D., et al. (2003) Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. *Neurology* **61,** 199–205.
14. Knittweis J.W. and McMullen W.A. (2000) The effect of apoE on dementia is not through atherosclerosis: The Rotterdam Study: to the Editor. *Neurology* **54,** 2356–2358.
15. Kuo Y.-M., Emmerling M.R., Bisgaier C.L., et al. (1998) Elevated low-density lipoprotein in Alzheimer's disease correlates with brain Aβ 1–42 levels. *Biochem. Biophys. Res. Commun.* **252,** 711–715.
16. Romas S.N., Tang M.X., Berglund L., and Mayeux R. (1999) ApoE genotype, plasma lipids, lipoproteins, and AD in community elderly. *Neurology* **53,** 517–521.
17. Evans R.M., Emsley C.L., Gao S., et al. (2000) Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. *Neurology* **54,** 240–242.
18. Kivipelto M., Helkala E.-L., Laakso M.P., et al. (2001) Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal population based study. *Br. Med. J.* **322,** 1447–1451.
19. Launer L.J., White L.R., Petrovitch H., Ross G.W., and Curb J.D. (2001) Cholesterol and neuropathologic markers of AD: a population-based autopsy study. *Neurology* **57,** 1447–1452.
20. Tan Z.S., Seshadri S., Beiser A., et al. (2003) Plasma total cholesterol level as a risk factor for Alzheimer disease. *Arch. Int. Med.* **163,** 1053–1057.
21. Hebert L.E., Scherr P.A., Bienias J.L., Bennett D.A., and Evans D.A. (2003) Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch. Neurol.* **60,** 1119–1122.
22. CDC/NCHS. (2003) *National Health and Nutrition Examination Survey.* CDC/NCHS, Atlanta, GA.
23. Anon. (2003) Cholesterol paradox: is high total or low HDL cholesterol level a risk for Alzheimer's disease? *J. Neurosci. Res.* **72,** 141–146.
24. Frikke-Schmidt R., Nordestgaard B.G., Agerholm-Larsen B., Schnohr P., and Tybjaerg-Hansen A. (2000) Context-dependent and invariant associations between lipids, lipoproteins, and apolipoproteins and apolipoprotein E genotype. *J. Lipid Res.* **41,** 1812–1822.
25. Mason R.P., Shoemaker W.J., Shajenko L., Chambers T.E., and Herbette L.G. (1992) Evidence for changes in the Alzheimer's disease brain cortical membrane structure mediated by cholesterol. *Neurobiol. Aging* **13,** 413–419.
26. Sparks D.L. (1997) Coronary artery disease, hypertension, apoE, and cholesterol: a link to

Alzheimer's disease? *Ann. NY Acad. Sci.* **826,** 128–146.
27. Eckert G.P., Cairns N.J., Maras A., Gattaz W.F., and Müller W.E. (2000) Cholesterol modulates the membrane disordering effects of β-amyloid peptides in the hippocampus: specific changes in Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* **11,** 181–186.
28. Heverin M., Bogdanovic N., Lutjohann D., et al. (2004) Changes in the levels of cerebral and extracerebral sterols in the brain of patients with Alzheimer's disease. *J. Lipid Res.* **45,** 186–193.
29. Lutjohann D., Breuer O., Ahlborg G., et al. (1996) Cholesterol homeostasis in human brain: evidence for an age-dependent flux of 24*S*-hydroxycholesterol from the brain into the circulation. *Proc. Natl. Acad. Sci. USA* **93,** 9799–9804.
30. Lund E.G., Xie C., Kotti T., Turley S.D., Dietschy J.M., and Russell D.W. (2003) Knockout of the cholesterol 24-hydroxylase gene in mice reveals a brain-specific mechanism of cholesterol turnover. *J. Biol. Chem.* **278,** 22,980–22,988.
31. Cutler R.G., Kelly J., Storie K., et al. (2004) Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proc. Natl. Acad. Sci. USA* **101,** 2070–2075.
32. Yasojima K., McGeer E.G., and McGeer P.L. (2001) 3-Hydroxy-3-methylglutaryl–coenzyme A reductase mRNA in Alzheimer and control brain. *Neuroreport* **12,** 2935–2938.
33. Mulder M., Ravid R., Swaab D.F., et al. (1998) Reduced levels of cholesterol, phospholipids, and fatty acids in cerebrospinal fluid of Alzheimer disease patients are not related to apolipoprotein E4. *Alzheimer Dis. Assoc. Disord.* **12,** 198–203.
34. Demeester N., Castro G., Desrumaux C., et al. (2000) Characterization and functional studies of lipoproteins, lipid transfer proteins, and lecithin:cholesterol acyltransferase in CSF of normal individuals and patients with Alzheimer's disease. *J. Lipid Res.* **41,** 963–974.
35. Wollmer M.A., Streffer J.R., Lütjohann D., et al. (2003) ABCA1 modulates CSF cholesterol levels and influences the age at onset of Alzheimer's disease. *Neurobiol. Aging.* **24,** 421–426.
36. Papassotiropoulos A., Lutjohann D., Bagli M., et al. (2002) 24*S*-hydroxycholesterol in cerebrospinal fluid is elevated in early stages of dementia. *J. Psychiatr. Res.* **36,** 27–32.
37. Igbavboa U., Pidcock J.M., Johnson L.N.A., et al. (2003) Cholesterol distribution in the Golgi complex of DITNC1 astrocytes is differentially altered by fresh and aged amyloid beta-peptide$_{1–42}$. *J. Biol. Chem.* **278,** 17,150–17,157.
38. Igbavboa U., Avdulov N.A., Chochina S.V., and Wood W.G. (1997) Transbilayer distribution of cholesterol is modified in brain synaptic plasma membranes of knockout mice deficient in the low density lipoprotein receptor, apolipoprotein E, or both proteins. *J. Neurochem.* **69,** 1661–1667.
39. Hayashi H., Igbavboa U., Hamanaka H., et al. (2002) Cholesterol is increased in the exofacial leaflet of synaptic plasma membranes of human apolipoprotein E4 knock-in mice. *Neuroreport* **13,** 383–386.
40. Igbavboa U., Avdulov N.A., Schroeder F., and Wood W.G. (1996) Increasing age alters transbilayer fluidity and cholesterol asymmetry in synaptic plasma membranes of mice. *J. Neurochem.* **66,** 1717–1725.
41. Wood W.G., Schroeder F., Hogy L., Rao A.M., and Nemecz G. (1990) Asymmetric distribution of a fluorescent sterol in synaptic plasma membranes: effects of chronic ethanol consumption. *Biochim. Biophys. Acta* **1025,** 243–246.
42. Kirsch C., Eckert G.P., and Müller W.E. (2003) Statin effects on cholesterol micro-domains in brain plasma membranes. *Biochem. Pharmacol.* **65,** 843–856.
43. Lee S.-J., Liyanage U., Bickel P.E., Xia W., Lansbury P.T., and Kosik K.S. (1998) A detergent-insoluble membrane compartment contains amyloid-beta *in vivo*. *Nat. Med.* **4,** 730–734.
44. Fagan A.M., Watson M., Parsadanian M., Bales K.R., Paul S.M., and Holtzman D.M. (2002) Human and murine apoE markedly alters Aβ metabolism before and after plaque formation in a mouse model of Alzheimer's disease. *Neurobiol. Dis.* **9,** 305–318.
45. Morishima-Kawashima M. and Ihara Y. (1998) The presence of amyloid β-protein in the detergent-insoluble membrane compartment of human neuroblastoma cells. *Biochemistry* **37,** 15,247–15,253.
46. Yamamoto N., Igbavboa U., Shimada Y., et al. (2004) Accelerated Aβ aggregation in the presence of GM1-ganglioside-accumulated synaptosomes of aged apoE4-knock-in mouse brain. *FEBS Lett.* **569,** 135–139.
47. Werner N., Nickenig G., and Laufs U. (2002) Pleiotropic effects of HMG-CoA reductase inhibitors. *Basic Res. Cardiol.* **97,** 105–116.
48. Mcfarlane S.I., Muniyappa R., Francisco R., and Sowers J.R. (2002) Pleiotropic effects of statins: lipid reduction and beyond. *J. Clin. Endocrinol. Metab.* **87,** 1451–1458.
49. Johnson-Anuna N.L., Eckert G.P., Keller J.H., et al. (2005) Chronic adminstration of statins alters multiple gene expression patterns in mouse cerebral cortex. *J. Pharmacol. Exp. Ther.* **312,** 786–793.