Apolipoprotein E in the Brain and Its Role in Alzheimer's Disease

Judes Poirier

Douglas Hospital Research Centre, Aging Research Program, Verdun, Quebec, Canada

Submitted: July 20, 1995
Accepted: December 6, 1995

Recent evidence indicates that apolipoprotein E (apoE) plays a central role in the brain response to injury. The coordinated expression of apoE and its main receptor, the apoE/apoB (LDL) receptor, appears to regulate the transport of cholesterol and phospholipids during the different phases of the reinnervation process. The recent discovery that a peculiar form of apoE, the apoE4, is strongly linked to both sporadic and familial late onset Alzheimer's disease (AD) raises the possibility that a dysfunction of the lipid transport system associated with compensatory sprouting and synaptic remodelling could be central to the AD process. The role of apoE in the central nervous system (CNS) is particularly important in relation to the function of the cholinergic system which relies to a certain extent on the integrity of phospholipid homeostasis in neurons. Recent evidence suggests that apoE4 allele has a direct impact on cholinergic function in AD.

Key Words: apolipoprotein E, Alzheimer's disease, synaptic plasticity, lipid, human, LDL receptors, cholesterol

INTRODUCTION

Apolipoprotein (apoE) has been extensively studied in nervous and nonnervous tissues as one of the key apolipoproteins that directs lipid metabolism. Because it facilitates cholesterol transport both into and out of cells, and among different tissues, apoE has been the focus of attention of many studies dealing with impaired lipid homeostasis. In general, apoE facilitates cholesterol removal from plasma and cerebrospinal fluid (CSF). ApoE is a constituent of several plasma lipoproteins such as chylomicron and very-low-density lipoprotein (VLDL) remnants, VLDL, and high-density lipoprotein (HDL). It mediates the cellular uptake of lipid complexes through interaction with the apoB/apoE low-density lipoprotein (LDL) receptor and distinct hepatic apoE receptors (Mahley and Rall 1989). The mature form of apoE present in human plasma and CSF is a single glycosylated 36 kDa to 37 kDa polypeptide containing 299 amino acids (Rall and others 1982). Human apoE is encoded by a 4-exon gene (3.6 Kb in length) on the long arm of chromosome 19 (Paik and others 1985; Olaisen and others 1982).

Three major isoforms of apoE (E4, E3 and E2), differing by a single unit of net charge, can be easily detected by isoelectrofocusing. These isoforms are expressed from multiple alleles at a single apoE genetic locus, giving rise to the 3 common homozygous phenotypes (E4/4, E3/3 and E2/2) and 3 common heterozygous phenotypes (E4/3, E4/2 and E3/2) (Poirier 1994). Functionally, apoE2 has a lower affinity for the LDL receptor than do E3 and E4. Lipoproteins associated with apoE4 are cleared more efficiently than are those

---

Based on the CCNP Young Investigator Award Lecture presented by Dr Poirer at the 17th Annual Meeting of the Canadian College of Neuropsychopharmacology, May 29-June 1, 1994, Quebec City, Quebec, Canada.

Address reprint requests to: Dr Judes Poirier, Director, Aging Research Program, Douglas Hospital Research Centre, 6875 Lasalle Boulevard, Verdun, Quebec, H4H 1R3 Canada.

containing apoE3 and apoE2. As a result, serum apoE levels are lower in apoE4 than in apoE3 homozygotes. It has been estimated that 60% of the variation in serum cholesterol is genetically determined, and that apoE polymorphisms account for 15% of this genetic variation (Davignon and others 1988).

The LDL (apoB/E) receptor, which recognizes apoE and apoB, has been extensively characterized in peripheral cell types. It is a glycoprotein of apparent molecular weight 160,000 kDa, which is encoded by a 45 Kb gene made up of 18 exons and 17 introns (Sudhof and others 1985). Several lines of evidence suggest that the positively charged domain of apoE between residues 140 to 150 interacts with negatively charged amino acids of the LDL receptor (Wilson and others 1991). The LDL receptor pathway consists of cell surface binding of apoE- or apoB-containing lipoprotein followed by internalization and lysosomal degradation of the LDL particle (Brown and Goldstein 1986). The exogenously derived cholesterol suppresses the expression of 3,3-hydroxymethyl-glutaryl CoA reductase (HMG-CoA reductase) (Brown and others 1973), the rate-controlling enzyme in cholesterol synthesis. Accumulation of intracellular cholesterol also reduces LDL receptor synthesis and favors esterification of the excess cholesterol.

In addition, the LDL receptor-related protein/alpha$_2$-macroglobulin receptor (LRP) binds apoE-containing lipoproteins (Kowal and others 1989). Although the physiological function of this receptor and its function in the CNS remain to be clearly established, it was shown recently (Rebeck and others 1993) that the LRP expression is significantly increased in neurons surrounding amyloid plaque deposition in AD. It is postulated that the LRP has a role in scavenging amyloid plaques from the neuropil by mediating the internalization of apoE-bound amyloid fragments into lysosomes for degradation (Rebeck and others 1993).

ApoE expression in response to neuronal injury

Following neuronal cell loss and terminal deafferentation in the CNS, large amounts of lipids are released from degenerating axon membranes and myelin. In response to damage, astrocytes in the CNS (Poirier and others 1991) and macrophages in the peripheral nervous system (PNS) (Boyles and others 1989) synthesize and release apoE (see Figure 1) within the lesion, presumably to scavenge cholesterol and phospholipids from cellular and myelin debris. Much of the cholesterol generated during this phase is apparently stored in astrocytes (CNS) and macrophages (PNS) where it is reused during PNS regeneration (Boyles and others 1989) and CNS reinnervation (Poirier and others 1993). During this critical phase, the activity of HMG-CoA reductase is severely depressed in astrocytes and neurons in the CNS (Poirier and others 1993) and in macrophages (Goodrum 1990) in the PNS, suggesting receptor-mediated downregulation of cholesterol synthesis due to lipoprotein degradation (see Figure 1). ApoB and apoA1, both of which have predominant roles in cholesterol transport in blood and during PNS regeneration, are virtually absent from the CNS, which highlights the importance of apoE for lipid homeostasis in the CNS (Poirier 1994).

ApoE and the LDL receptor in CNS reinnervation

In the CNS, the ability of neurons to regenerate is very limited. However, specific brain areas have the ability to induce proliferation of presynaptic extensions from axons or terminals derived from undamaged neurons in order to compensate for the loss of specific input. A classical example of reactive synaptogenesis is illustrated by the compensatory response of the hippocampal formation to entorhinal cortex lesions (ECL). ECL has been shown to cause the loss of nearly 60% of the synaptic input to the granule cell layer of the hippocampus. The loss of synapses, however, is transient. Beginning a few days after denervation, new synapses are formed, virtually replacing the lost inputs within a few months (Matthews and others 1976).

Ultrastructural studies of the hippocampal molecular layer of the dentate gyrus following ECL showed that, throughout the 2 to 11 days postlesion, astrocytes progressively engulfed both presynaptic terminals and preterminal axons (Lee and others 1977). Once metabolized, these neuron-derived particles generated a large astroglial store of lipids, which provided a convenient and readily retrievable pool for membrane synthesis of precursors used in the formation of neuronal sprouts, and in the reorganization of the dendritic field of granule cell neurons (see Figure 1). Cholesterol, phospholipids and apoE were then combined to form a yet uncharacterized lipoprotein complex (presumably HDL-like) that was apparently secreted in the circulation and/or directed to specific target sites in the CNS (see Figure 1).

Analysis of the apoE (LDL) receptor binding sites distribution in the injured CNS revealed an increased expression of the LDL receptor in granule cell neurons (undergoing dendritic remodelling and synaptogenesis) during the acute phase of the reinnervation process (Poirier and others 1993). The increased expression of the receptor was preceded by a marked reduction of the hippocampal HMG-CoA reductase activity (Poirier and others 1993).

Following binding of the apoE complex with the LDL receptor, the apoE-cholesterol-LDL receptor complex is internalized and degraded, and the cholesterol is released into the neuronal cytoplasm (see Figure 1, #4 and #5). The cholesterol can then be transported to the dendritic field (granule cell neurons) or to the terminals (sprouting neurons in the molecular layer) for membrane and synapse formation.

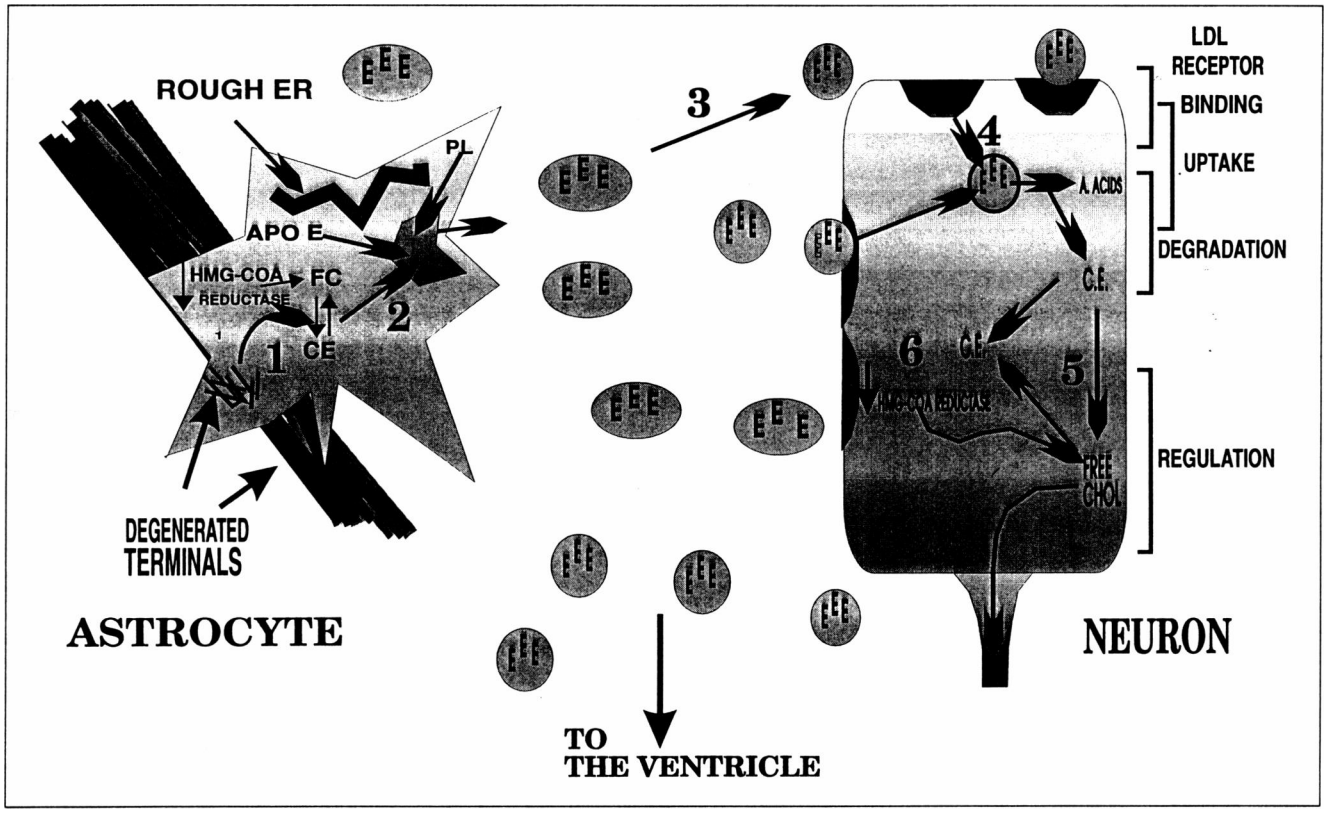

Figure 1. Schematic representation of hypothesized cholesterol/phospholipid recycling mechanisms in the injured central nervous system. Degenerating terminals are initially internalized and degraded. The nonesterified cholesterol (1) is used as free cholesterol (FC) for the assembly of an apoE/cholesterol/lipoprotein complex (2) or converted into cholesterol esters (CE) for storage purposes. The newly formed apoE/cholesterol/lipoprotein complexes (3) are then directed: 1. toward the circulation presumably through the ependymal cells surrounding the ventricles; and/or 2. to specific brain cells requiring lipids. ApoE complexes are apparently internalized by the neuronal LDL receptor pathway (4) and the cholesterol released for dendritic proliferation and/or synaptogenesis (5,7). As a consequence of the internalization process, cholesterol synthesis in neurons (via the HMG-CoA reductase pathway) becomes progressively repressed (6). E: apoE; PL: phospholipids; A.Acids: amino acids; CE: cholesterol ester; FC: free cholesterol.

Recently, we showed that apoE-lipoprotein complexes are selectively internalized by the LDL receptor in cultured primary hippocampal neuronal cells, and primary astrocytes are maintained in a serum-free condition (Guillaume and others 1995). Nearly 70% of the apoE-lipoprotein binding to neurons and astrocytes is displaced in the presence of an excess of LDL (apoB-enriched lipoproteins), indicating a high prevalence of LDL receptors in these cells.

Thus, the apparent contradiction of depressed cholesterol synthesis and increased apoE and LDL-receptor expression in the presence of active synaptogenesis in the lesioned rat brain can be reconciled by postulating a specific salvage and reutilization of cholesterol from degenerating terminals through the apoE transport/LDL receptor-uptake pathway. This finding is also consistent with a secondary inhibition of the HMG-CoA reductase activity by a high concentration of internalized cholesterol.

The importance of this pathway in the central nervous system has been highlighted recently by the work of Masliah and others (1995), who demonstrated that homozygous apoE-deficient (knockout) mice display significant loss of synapses and a marked disruption of the dendritic cytoskeleton in neurons with age. They also reported that knockout mice failed to induce compensatory synaptogenesis in response to ECL (Masliah and others 1995). Interestingly, the same strain of knockout mice were shown to exhibit near normal PNS (sciatic nerve) regeneration (Popko and others 1993). This finding is quite consistent with the fact that the CNS has to rely almost exclusively on apoE to transport lipids in response to injury whereas in the periphery, other apolipoproteins such as apoB, apoA1 and even apoD are available to

serve as a back-up to maintain lipid homeostasis and transport.

These recent results now firmly establish the fundamental role of apoE in the process of brain reinnervation following deafferentation and cell loss, due to either an experimental lesion or to normal aging.

Synaptic plasticity in Alzheimer's disease

Alzheimer's disease (AD) pathology is characterized by an early and extensive loss of entorhinal cortex neurons (Hyman and others 1984) and a marked loss of neurons in the CA_1 area of the hippocampus. Regenerative-like changes have been reported in the dentate granule area of a small group of subjects with AD (Geddes and others 1985; Hyman and others 1987). These changes are very similar to the hippocampal response of rats following entorhinal cortex lesions. However, the vast majority of subjects with AD fail to exhibit these regenerative challenges. For example, Ransmayr and others (1989) reported a marked reduction of hippocampal choline acetyltransferase (ChAT) immunoreactivity in almost every subject with AD they examined. Electron microscopy studies by Flood and Coleman (1986) also reported a loss of proliferating dendrites in the hippocampus in AD, while de Ruiter and Uyling (1987) showed a loss of dendritic spines and a decrease in spine length in the dentate of patients with AD.

These results clearly suggest that the usual compensatory growth of fibers associated with hippocampal deafferentation is compromised in most subjects with AD . Although the exact mechanism responsible for the lack of plasticity in AD is not known, it is intriguing that, despite marked loss of neurons and projections, apoE mRNA levels are reduced or unchanged in AD (Poirier and others 1990), and apoE protein levels are reduced in both brain tissues (Bertrand and others 1995) and CSF of subjects with AD (Blennow and others 1994).

Reduction of apoE expression could be explained by at least 2 different mechanisms: 1. misregulation of apoE gene expression; or 2. alteration of apoE structure (or integrity) in the patients.

Alzheimer's disease and apolipoprotein E isoforms

Numerous research teams have examined the frequency distribution of 3 principal apoE isoforms in living and autopsied patients with AD and control subjects in the US, Canada, France, Japan, and Germany. The frequency of the E4 allele was shown to be markedly increased in sporadic (Poirier and others 1993a; Saunders and others 1993; Rebeck and others 1993; Lucotte and others 1993), late-onset familial (Corder and others 1993; Payami and others 1993), and early-onset (Okuizumi and others 1994; VanDuijn and others 1994) AD. A gene dosage effect on risk and age of onset was observed

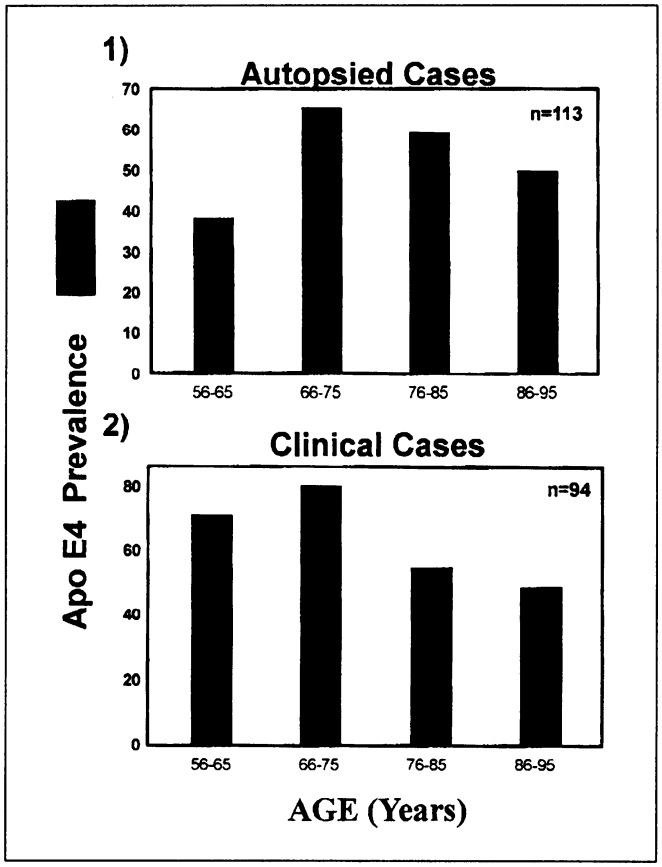

Figure 2. Apolipoprotein E4 allele prevalence in autopsy-confirmed (top) and clinical (bottom) cases of sporadic Alzheimer's disease from Eastern Canada. Note the reduction in prevalence of the apoE4 allele in both living and autopsied AD cases with age of onset greater than 85 years. (Adapted from Poirer and others [1993a]; Nalbantoglu and others [1994].)

in both familial (Corder and others 1993) and sporadic (Poirier and others 1993a) cases. A population-based study performed in eastern Finland confirmed the reported dose-response relationship between E4 allele copy number and the prevalence of sporadic AD (Kuusisto and others 1994).

Figure 2 depicts the 4 allele frequency and prevalence as a function of age distribution in: 1. autopsied-confirmed subjects with AD (Nalbantoglu and others 1994); and 2. living probable AD cases from Eastern Canada (Poirier and others 1993a). As many as 80% of our clinically identified AD subjects between 65 and 75 years of age carry at least one copy of the apoE4 allele. Interestingly, a lower prevalence of the E4 allele is observed in very old subjects (> 85 years), which suggests the presence of a very late-onset form of AD. A marked enrichment of the E4 allele prevalence was observed in women versus men (Poirier and others 1993a).

Analysis of apoE allele frequencies in 45 populations shows differences among Caucasian, Japanese, and Chinese population samples (Gerdes and others 1992). Differences in apoE allele frequencies among Caucasian populations were noted and discussed by Davignon and others (1988). Similar variation in prevalence and incidence of AD around the world has been reported (Breteler and others 1992). A careful examination of the published apoE genotypes and the age-adjusted prevalence of AD in 7 regions for which data are available reveals a highly significant correlation between E4 allele frequency and AD prevalence (Poirier 1994). In contrast, there is no correlation between the E3 and E2 allele frequencies and AD prevalence in the same regions. This observation further confirms the critical role of apoE4 in the etiopathology of Alzheimer's disease, and suggests that the well-established association between apoE4 and Alzheimer's disease is not population-specific.

Several years ago, Uterman and others (1985) showed that circulating concentrations of apoE are markedly reduced in apoE4 carriers when compared to non-E4 subjects. Recent analysis (Bertrand and others 1995) of apoE levels in the hippocampus and cortex of subjects with AD with different genotypes revealed an apoE4 allele dose-dependent reduction of apoE concentrations in both areas (in contrast to the predicted increase due to ongoing cell loss).

These results support the concept that apoE expression/synthesis is impaired in subjects with AD carrying the E4 allele and that lipid homeostasis is markedly compromised in these subjects. This is particularly important in the context of cholinergic function in AD where marked reductions in cholinergic activity have been reported. Furthermore, it is well known that the cholinergic system relies heavily on phospholipid, choline, and cholesterol to maintain proper cholinergic activity; 3 lipids directly or indirectly associated with apoE-containing lipoproteins.

Cholinergic dysfunction and apoE4 in AD

Brain membrane phospholipids, especially phosphatidylcholine (PC) and phosphatidylethanolamine (PE), have been shown to play important roles in the availability of choline, a rate-limiting precursor of acetylcholine (ACh) (Wurtman 1992). The release of the choline precursor for ACh synthesis from PC is accomplished in a one-step process through a phospholipase D-type enzyme in cholinergic neurons (Lee and others 1993). Brain levels of choline are decreased by up to 40% to 50% in frontal and panetal cortices of patients with AD (Nitsch and others 1992). Similarly, cholesterol that is decreased in the same brain areas in AD is apparently required for the proper functioning of certain cholinergic receptor subtypes (Jones and McNamee 1990). As losses of cholinergic neurons and/or ChAT activity are hallmarks of AD (Davies and Moloney 1976; Perry and others 1977), a possible relationship between the apoE4 genotype and cholinergic deficits was investigated. ChAT activity in the hippocampus and temporal cortex of AD cases was reported to be inversely proportional to the apoE4 allele copy number (Poirier and others 1994; Poirier 1994). These results clearly indicate the existence of distinct genetic entities in sporadic AD, which show differential degrees of alterations of cholinergic innervation, at least as revealed by residual postmortem ChAT activity. An isoform-dependent impaired regulation of the transport of phospholipids and/or fatty acid precursor molecules in the brain of apoE4 carriers, resulting in diminished synthesis of ACh, could explain the low levels of PC, PE, and especially choline reported in subjects with AD. This hypothesis is also consistent with membrane defects reported in subjects with AD such as changes in membrane fluidity in the hippocampus and platelets (Nitsch and others 1992).

A working hypothesis

Although apoE4 is clearly associated with increased risk for developing AD and decreased age of onset, the mechanism underlying this association is still unknown. One popular hypothesis is that weaker interaction of apoE4 with microtubulin-associated protein tau may permit tau phosphorylation and promote formation of the helical bundles that compose neurofibrillay tangles in AD (Strittmatter and others 1994).

Alternatively, we proposed (Poirier and others 1990; Poirier 1994) that the well-established role of apoE in the transport of lipids could be compromised in the brain of subjects with AD, resulting in an inefficient cholesterol and phospholipid transport, loss of plasticity, and eventually, loss of synaptic integrity. The recent discoveries (Masliah and others 1995) that apoE4 AD carriers show reduced neuronal apoE immunoreactivity when compared to apoE3/3 control subjects and patients with AD, and that the apoE knockout mice show compromised synaptic integrity with age and impaired synaptic plasticity, support this hypothesis. Furthermore, the fact that compensatory synaptogenesis appears to be markedly compromised in the hippocampus of most subjects with AD suggests a possible link between apoE4, apoE levels, and impaired plasticity in AD.

Accordingly, we proposed that apoE4, but not apoE3, may interfere with the normal compensatory process occurring in vivo (Poirier 1994). Further evidence supporting this concept was provided by the observation (Nathan and others 1994) that apoE3-containing lipoproteins promote neurite outgrowth whereas apoE4-lipoproteins decrease normal outgrowth in cultured dorsal root ganglion neurons. Furthermore, the fact that cholinergic neurons rely heavily on an intact phospholipid metabolism (Wurtman 1992) puts these neurons at high risk in apoE4 carriers when compared to other cell types. The selective vulnerability of the brain to

injury could be explained, at least in part, by the fact that other potential phospholipid transporters such as apoB and apoA1 are absent from the mammalian brain.

Further studies are now required to clarify the role of apoE4 in acetylcholine metabolism and to determine whether or not genotype determination can be used to predict the occurrence of Alzheimer's disease in the general population, and if the association that links apoE4 to the cholinergic system could explain the therapeutic variability associated with the use of cholinomimetic treatments.

ACKNOWLEDGEMENTS

The author wishes to thank his close collaborators without whom this work would not have been possible: D Dea, A Baccichet, N Aumont, P Bertrand, D Guillaume, U Beffert, MC Delisle, M Hess, PC May, CE Finch, GM Pasinetti, R Quirion, I Aubert, S Gauthier, S Kogan, J Nalbantoglu, and BG Gilfix. This study was supported by the National Institute of Aging (USA), the Medical Research Council of Canada, le Fonds de la Recherche en Santé du Québec, and the FCAR.

REFERENCES

Bertrand P, Poirier J, Oda T, Finch CE, Pasinetti GM. 1995. Association between apolipoprotein E genotype with brain levels of apolipoprotein E and apolipoprotein J (clusterin) in Alzheimer's disease. Mol Brain Res. Forthcoming.

Blennow K, Hesse C, Fredman P. 1994. Cerebrospinal fluid apolipoprotein E is reduced in Alzheimer's disease. Neuroreport 5:2534-2536.

Boyles JK, Zoellner CD, Anderson LJ, Kosick LM, Pitas RE, Weisgraber KH, Hui DY, Malhey RW, Gebicke-Haeter PJ, Ignatius MJ, Shooter EM. 1989. A role for apolipoprotein E, apolipoprotein A_I, and low density lipoprotein receptors in cholesterol transport during regeneration and remyelination of rat sciatic nerve. J Clin Invest 83:1015-1031.

Breteler MMB, Claus JJ, Duijn CMV. 1992. Epidemiology of Alzheimer's disease. Epid Review 14:59-82.

Brown MS, Dana SE, Goldstein JL. 1973. Regulation of 3-hydroxy-3methylglutarylcoenzyme A reductase activity in human fibroblasts by lipoproteins. Proc Natl Acad Sci USA 70:2162-2166.

Brown MS, Goldstein JL. 1986. A receptor mediated pathway for cholesterol homeostasis. Science 232:34-47.

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Pericak-Vance MA. 1993. Gene dose of apolipoprotein E type 4 and risk of Alzheimer's disease in late onset families. Science 261:921-923.

Davies P, Maloney AJR. 1976. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 2:1403-1408.

Davignon J, Gregg RE, Sing CF. 1988. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 8:1-21.

de Ruiter JP, Uylings HB. 1987. Morphometric and dendritic analysis of fascia dentata granule cells in human aging and senile dementia. Brain Res 402:217-229.

Flood DG, Coleman PD. 1986. Failed compensatory dendritic growth as a physiological process in Alzheimer's disease. Can J Neurol Sci 13:475-479.

Geddes JW, Monaghan DT, Cotman CW, Lott IT, Kim RC, Chui HC. 1985. Plasticity of hippocampal circuitry in Alzheimer's disease. Science 230:1179-1181.

Gerdes LU, Klausen C, Sihm I, Faergeman O. 1992. Apolipoprotein E polymorphism in a Danish population compared to findings in 45 other study populations around the world. Gen Epidem 9:155-167.

Goodrum JF. 1990. Cholesterol synthesis is down-regulated during regeneration of peripheral nerve. J Neurochem 54:1709-1715.

Guillaume D, Dea D, Davignon J, Poirier J. 1995. Low density lipoprotein pathways in the central nervous system and apolipoprotein E isoform-specific differences. In: Iqbal K, Mortimer JA, Winblad B, Winiewski H, editors. Research advances in Alzheimer's disease and related disorders. London: John Wiley and Sons. p 4-395.

Hyman BT, Kromer LJ, Van Horsen GW. 1987. Reinnervation of the hippocampal perforant pathway zone in Alzheimer s disease. Ann Neurol 21:259-267.

Hyman BT, Van Horsen GW, Damasio AR, Barnes CL. 1984. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 225:1168-1170.

Jones OT, MacNamee MG. 1988. Annular and nonannular binding sites for cholesterol associated with the nicotinic acetycholine receptor. Biochemistry 27: 2364-2374.

Kowal RC, Herz J, Goldstein JL, Esser V, Brown MS. 1989. Low density lipoprotein receptor-related protein mediates uptake of cholesteryl esters from apolipoprotein E-enriched lipoproteins. Proc Natl Acad Sci USA 86:5810-5814.

Kuusisto J, Koivisto K, Kervinen K, Mykkanene L, Laakso M. 1994. Association of apolipoprotein E phenotypes with late onset Alzheimer's disease: population-based study. Br Med J 309:636-639.

Lee HE, Fellez-Maloney MP, Liscovitch M, Blustajn JK. 1993. Phospholipase D-catalized hydrolysis of phosphatidylcholine provides the choline precursor for acetylcholine synthesis in a human neuronal cell line. Proc Natl Acad Sci 90:10086-10090.

Lee KS, Stanford EJ, Cotman CW, Lynch GS. 1977. Ultrastructural evidence for bouton proliferation in the partially

deafferented dentate gyrus of the adult rat. Exp Brain Res 29:475-485.

Lucotte G, David F, Visvikis S, and others. 1993. Apolipoprotein E4 allele and Alzheimer's disease. Lancet 342:1309.

Mahley RW, Rall Jr SC, Scriver CR, Beaudet AL, Sly WS, Valle D, editors. 1989. The metabolic basis of inherited disease. New York: McGraw-Hill Book Co. p 1195-1213.

Masliah E, Mallory M, Alford M, Muckle L. 1995. Abnormal synaptic regeneration in hAPP695 transgenic and apoE knockout mice. In: Iqbal K, Mortimer JA, Windblad B, Wisnieweski H, editors. Research advances in Alzheimer's disease and related disorders. London: John Wiley and Sons. p 405-414.

Matthews DA, Cotman CW, Lynch G. 1976. An electron microscopic study of lesion-induced synaptogenesis in the dentate gyrus of the adult rat. Brain Res 115:1-41.

Nalbantoglu J, Gilfix BM, Bertrand P, Robitaille Y, Gauthier S, Rosenblatt DS, Poirier J. 1994. Predictive value of apolipoprotein E4 genotyping in Alzheimer's disease: results of an autopsy series and an analysis of several combined studies. Ann Neurol 36:889-895.

Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas R. 1994. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science 264:850-852.

Nitsch RM, Blustajn JK, Pitas AG, Slack BE, Wurtman RJ. 1992. Evidence for a membrane defect in Alzheimer's disease. Proc Natl Acad Sci 89:1671-1675.

Okuizumi K, Onodera O, Tanaka H. 1994. ApoE4 and early-onset Alzheimer's. Nature Genet 7:10-11.

Olaisen B, Teisberg P, Gedde-Dahl Jr. 1982. The locus for apolipoprotein E (apoE) is linked to the complement component C3 (C3) locus on chromosome 19 in man. Hum Genet 62:233-236.

Paik Y, Chang DJ, Reardon CA, Davies GE, Mahley RW, Taylor JM. 1985. Nucleotide sequence and structure of the human apolipoprotein E gene. Proc Natl Acad Sci USA 82:3445-3449.

Payami H, Kaye J, Heston LL, Schellenberg GD. 1993. Apolipoprotein E and Alzheimer's disease [letter]. Lancet 342:738.

Perry EK, Gibson PH, Blessed G. 1977. Neurotransmitter enzyme abnormalities in senile dementia. J Neurol Sci 34:247-265.

Poirier J. 1994. Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease. Trends Neurosci 17:525-530.

Poirier J, Aubert I, Bertrand P, Quirion R, Gauthier S, Nalbantoglu J. 1994. Apolipoprotein E4 and cholinergic dysfunction in AD: a role for the amyloid/apoE4 complex? In: Giacobini E, Becker RE, editors. Alzheimer's disease: therapeutic strategies. Boston: Birkhauser. p 72-76.

Poirier J, Baccichet A, Dea D, Gauthier S. 1993. Role of hippocampal cholesterol synthesis and uptake during reactive synaptogenesis in adult rats. Neuroscience 55:81-90.

Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. 1993a. Apolipoprotein E phenotype and Alzheimer's disease. Lancet 342:697-699.

Poirier J, Hess M, May PC, Finch CE. 1991. Apolipoprotein E- and GFAP-RNA in hippocampus during reactive synaptogenesis and terminal proliferation. Mol Brain Res 11:97-106.

Poirier J, Hess M, May PC, Pasinetti G, Finch CE. 1990. Astroglial gene expression during reactive synaptogenesis. In: Tanaka T, Fisher A, editors. Basic and therapeutic strategies in Alzheimer's and Parkinson's diseases. New York: Plenum Press. p 191-194.

Popko B, Goodrum JF, Bouldin TW, Zhang SH, Maeda N. 1993. Nerve regeneration occurs in the absence of apolipoprotein E in mice. J Neurochem 60:1155-1158.

Rall SC Jr, Weisgraber KH, Mahley RW. 1982. Human apolipoprotein E. The complete amino acid sequence. J Biol Chem 257:4171-4178.

Ransmayr G, Cervera P, Hirsch E, Ruberg M, Hershi LB, Agid Y. 1989. Choline acetyltransferase-like immunoreactivity in the hippocampal formation of control subjects and patients with Alzheimer's disease. Neuroscience 32:701-714.

Rebeck GW, Reiter JS, Strickland DK, Hyman BT. 1993. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. Neuron 11: 575-580.

Saunders A, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BA, Gusella JF, McClaclans DR, Alberts MJ, Roses AD. 1993. Association of apolipoprotein E allele E4 with late onset familial and sporadic Alzheimer's disease. Neurology 43:1467-1472.

Strittmatter WJ, Weisgraber KH, Goedert M, and others. 1994. Microtubule instability and paired helical filament formation in the Alzheimer disease brain are related to apolipoprotein E genotype. Exp Neurol 125:163-171.

Sudhof TC, Goldstein JL, Brown MS, Russell DW. 1985. The LDL receptor gene: a mosaic of exons shared with different proteins. Science 228:815-822.

Utermann G. 1987. Apolipoprotein E polymorphism in health and diseases. Am Heart J 113:443-440.

Van Duijn CM, de Knijff P, Cruts M. 1994. Apolipoprotein E4 allele in a population-based study of early-onset Alzheimer's disease. Nature Genet 7:74-78.

Wilson C, Wardell MR, Weisgraber KH, Mahley RW, Agard DA. 1991. 3-dimensional structure of the LDL receptor-binding domain of human apolipoprotein-E. Science 252:1817-1822.

Wurtman RJ. 1992. Choline metabolism as a basis for the selective vulnerability of cholinergic neurons. TINS 1:117-122.