ELSEVIER

Alzheimer's & Dementia 4 (2008) S91–S97

Alzheimer's & Dementia

Apolipoprotein E represents a potent gene-based therapeutic target for the treatment of sporadic Alzheimer's disease

Judes Poirier*

McGill Centre for Studies in Aging and Douglas Mental Health University Institute, Montreal, Quebec, Canada

1. Introduction

Alzheimer's disease (AD) is associated with neuronal loss, synaptic damage, deposition of β-amyloid, and loss of cholinergic activity in susceptible brain regions. These three neuropathologic markers of AD are markedly modulated by the presence of the *apolipoprotein* e4 (*APOE* e4) allele in sporadic AD subjects. The *APOE* e4 allele is also a well-known risk factor for sporadic late-onset AD. Patients born with two E4 alleles were shown to exhibit (1) an earlier age of onset, (2) higher amyloid plaque counts [1–3], (3) cerebrovascular amyloid deposition [2], and (4) marked reductions in choline acetyltransferase [4–7], nicotinic, and nerve growth factor receptor [5] density compared with non-e4 allele subjects.

Recent clinical evidence clearly indicates that the *APOE* polymorphism significantly affects the rate of conversion from mild cognitive impairment (MCI) to probable AD [8]. It concomitantly affects the decline in cognitive performance of MCI subjects in an *APOE* e4 allele dose-dependent manner on cognitive performance (according to the Alzheimer's Disease Assessment Scale, cognitive subscale [ADAS-cog]) in 2-to-4 year follow-up studies with donepezil, rivastigmine, and galantamine [8–10]. Moreover, it was shown that whereas reductions of hippocampal and entorhinal cortex volumes appear to act as predictors of conversion from MCI to AD, they do so only in *APOE* e4 carriers [10,11].

When one examines the effect of the *APOE* e4 allele on rate of conversion to AD, rate of decline, synaptic remodeling, pathologic accumulation of amyloid, and even on extent of cholinergic drug response in sporadic AD subjects, it is tempting to postulate that specific pharmacologic manipulations designed to counter the impact of *APOE* e4 on the physiology of the adult central nervous system (CNS) are bound to provide beneficial relief to both "genetically at risk" subjects and patients with a clinical diagnostic of possible or probable AD.

2. Proposed apoE functions in the mature brain

Several different hypotheses were suggested to explain how the e4 allele modulates the age of onset, clinical progression, and conversion from MCI to AD status. These include perturbations of (1) cholesterol/phospholipid homeostasis and synaptic integrity [12,13], (2) amyloid metabolism [14], (3) tau phosphorylation and tangle accumulation [15,16], and neuronal survival through the generation of proteolytic breakdown products [17–19].

All these working hypotheses propose interesting links between established pathologic landmarks of sporadic AD and postulated functions attributed to *APOE* e4 in the brain. However, none of these, except one, provides a testable biochemical explanation for the observed effect of the e4 allele on the onset and progression of AD, and the clinical response to memory-enhancing medication: the "*APOE* e4 lipid imbalance hypothesis" [13]. Furthermore, the proposed mechanism must take into consideration the fact that the clinical manifestations of *APOE* e4 are silent for more than six decades.

The lipid imbalance hypothesis was first presented by our group some 14 years ago [13]. It was based on the observation that one of the apoE core functions in the brain is to transport cholesterol and phospholipids from astrocytes to neurons. During development, and in response to brain damage or neurodegeneration in adults, apoE is actively involved in the recycling of cholesterol from dead or dying cells to neurons undergoing terminal remodeling and synaptic replacement [20]. In absence of apoE, such as in apoE knockout mice, the recycling/reinnervating system is inoperative. Similarly, in the absence of apoE's main receptor, i.e., the low-density lipoprotein receptor, synaptic remodeling and plasticity are gravely impaired [21]. Consequently, synapses progressively lose their integrity with aging in apoE-deficient mice [22], the reinnervation process becomes markedly impaired with age [23,24],

*Corresponding author. Tel.: 450-766-2010; Fax: 450-888-4094.
E-mail address: judes.poirier@mcgill.ca

1552-5260/08/$ – see front matter
doi:10.1016/j.jalz.2007.11.012

and cognitive impairment progresses to a point of no return by age 10 months (middle-aged mice) [25,26].

Introduction of human *APOE* e3 or *APOE* e4 genes into apoE knockout mice completely prevents the cognitive deficit that characterizes apoE-deficient mice [27,28]. More interestingly, crossbreeding of *APOE* e4 or *APOE* e3 mice with APP-717 amyloid overexpresser transgenic mice almost completely abolishes the characteristic accumulation of β-amyloid deposits reported in hippocampal and cortical areas [29]. This is completely consistent with the proposed notion that apoE in the brain acts as an local active scavenger of extracellular amyloid in the extracellular space [30,31].

3. Is there a biological link between *APOE* polymorphisms and *APOE* concentrations in the brain?

The answer to this question actually came from the cardiovascular field more than 25 years ago. Utermann et al. [32], using young, healthy control subjects, reported that plasma concentrations of apoE were highly dependent on the isoform expressed by the subject. Humans with an *APOE* e2/e2 genotype express the highest levels of apoE of all humans, whereas those with an *APOE* e4/e4 genotype display the lowest concentrations of all humans. Interestingly, there is an inverse correlation between risk levels and *APOE* e2 < e3 < e4 [33], suggesting that those with low apoE levels (*APOE* e4/e4) seem to be at higher risk, whereas those with the highest levels (*APOE* e2/e2) display the lowest level of risk [34]. Subjects born carriers of the *APOE* e2 allele are also predisposed to become centenarians [35,36].

We carefully repeated these analyses in both plasma and brain tissues of large cohorts of autopsy-confirmed AD cases [37] and mild-to-moderate probable/possible AD patients [38], and found identical genotype-dependent apoE concentration gradients in sporadic AD subject (Fig. 1),

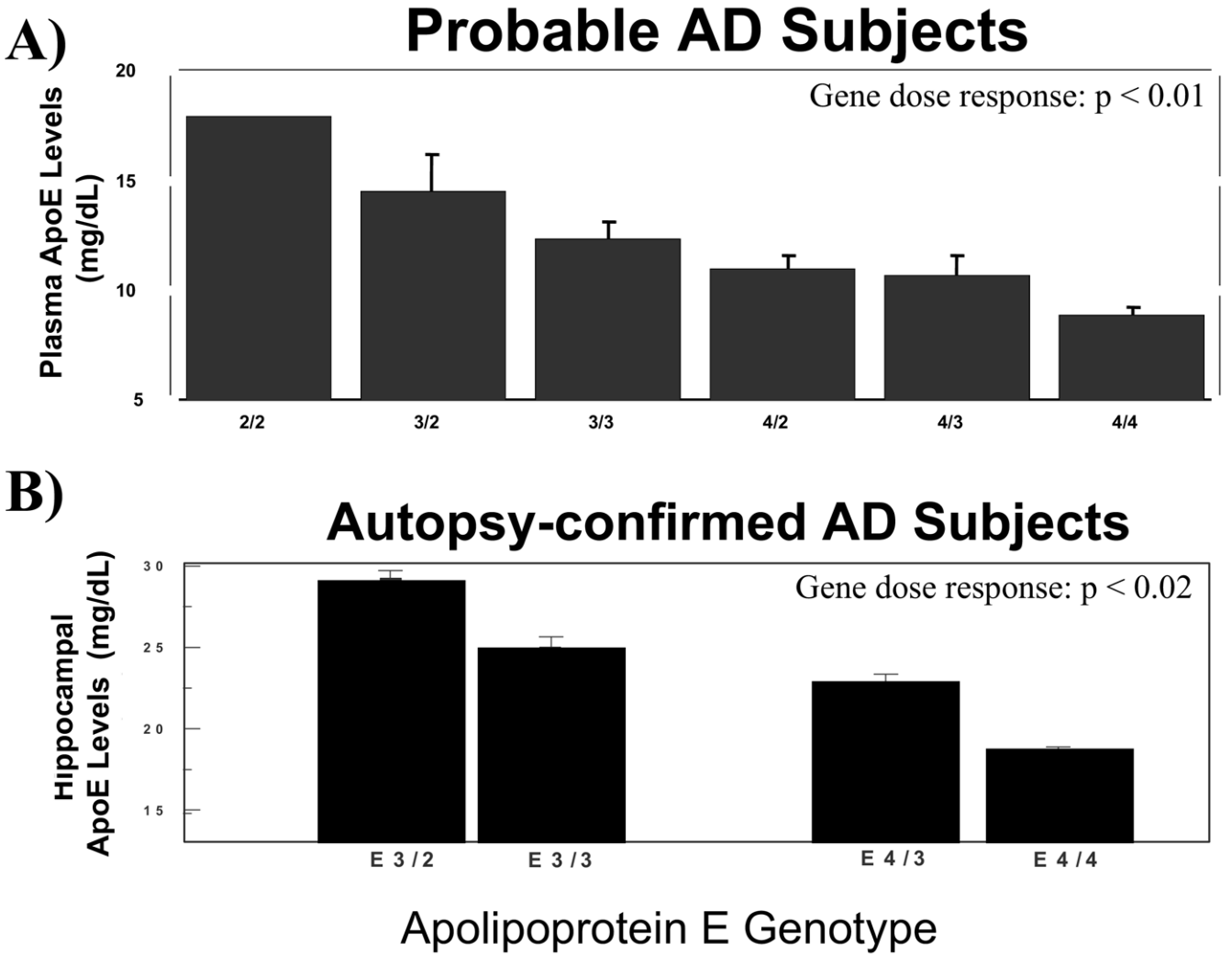

Fig 1. Apolipoprotein E concentrations in the plasma (**A**) and hippocampal brain tissues (**B**) in Alzheimer's disease as a function of *APOE* polymorphism. Concentrations were determined as described in Poirier [48].

where the highest CNS apoE levels were found in *APOE* e2 carriers (very rare in AD), and the lowest levels in *APOE* e4 cases (the majority of AD patients).

4. *APOE*: A logical therapeutic target

At the moment, two opposite views prevail in the literature with regard to the possible mode of action of *APOE* e4 in the CNS. One view holds that *APOE* e4 is bad per se, and that it is toxic to neurons but not to other cells in the body, and that somehow this toxicity is latent for several decades in e4 carriers. The other point of view, which is less pessimistic, is articulated around the fact the *APOE* e4 allele is the ancestral form of the gene. Actually, it is the one found in all other mammals examined so far, including several primate species. Contrary to prevailing views, it is the *APOE* e3 and *APOE* e2 variants that humans have acquired in the past few hundred thousand years [39]. In this model, *APOE* e4 is not detrimental per se. Instead, it performs its duties in humans as well as in all other *APOE* e4 mammals. However, in humans, low levels of apoE characterize *APOE* e4 allele carriers and the poor ability of the e4 genetic variant to respond to physiologic inducers of expression, which is actually problematic in aging subjects. It is postulated that the presence of the e4 allele progressively compromises brain lipid homeostatic processes during normal aging, and more so in brains suffering from damage or degenerative conditions [13].

In this model, we postulate that the restoration of apoE concentrations in the brains of *APOE* e4 carriers to levels found normally in *APOE* e3 subjects (or *APOE* e2 subjects) would either delay disease onset or slow down the rate of progression. We previously demonstrated that the ability of *APOE* e4 to bind to its receptors, and to promote lipoprotein uptake in brain cells, is similar to that of *APOE* e3 in vitro. We believe that levels are at stake here, and because apoE concentrations are vital to the proper maintenance of synaptic integrity and remodeling, the first casualty of a lifelong deficit is the synaptic network of the aging brain, particularly in neurons with long, projecting axons that use massive amounts of lipids such as cholesterol and phospholipids to maintain their structural integrity during normal aging.

In an attempt to address this issue, we developed a low-throughput screening assay using primary type 1 astrocytes from rodent cortical areas, and tested a large numbers of drugs, proteins, and hormones capable of enhancing apoE synthesis or secretion in vitro. The most interesting candidates were then tested in vivo for efficacy and safety. Finally, one compound among many others that met our biochemical and physiological criteria was tested in a pilot study in mild-to-moderate AD subjects. Of several hundred compounds tested, we identified three significant up-regulators of apoE synthesis and secretion, and two repressor compounds. We also examined several members of the Statin family (cholesterol synthesis inhibitors), but

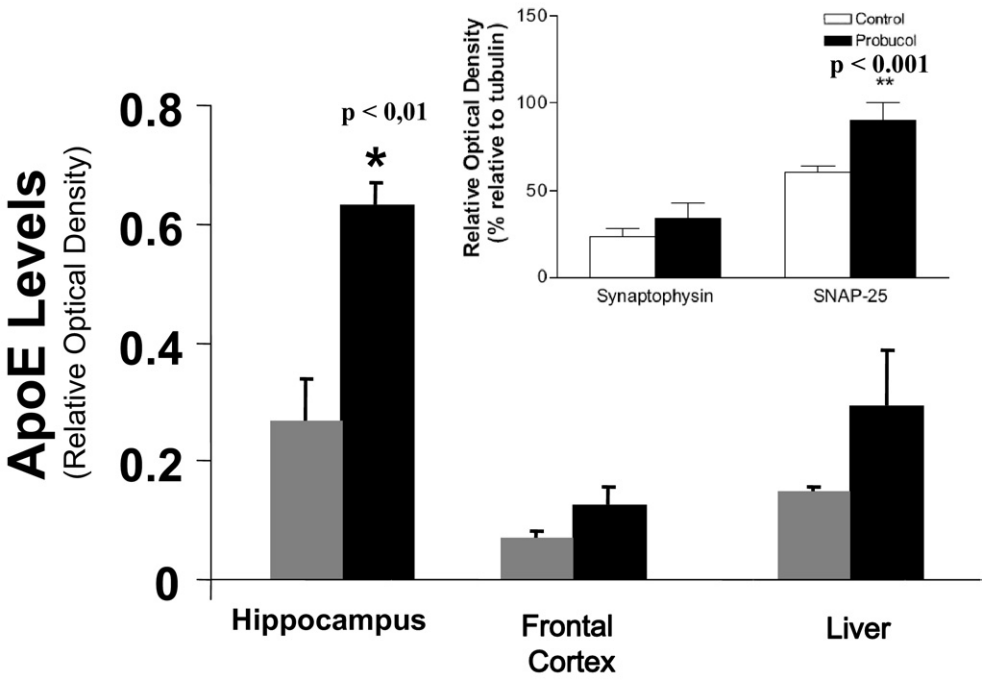

Fig 2. Effect of probucol administration on apolipoprotein E concentrations in the brain and in periphery in the adult rat. Insert illustrated the effect of probucol on synaptophysin and GAP-43 levels, two makers of synaptic density and integrity. Adapted from Champagne et al. [49].

none of these modified apoE synthesis and secretion at physiologically relevant concentrations.

Estrogen, indomethacin, and probucol were found to significantly enhance apoE synthesis and secretion in vitro and in vivo in the mature rodent CNS (mice and rats). Estrogen not only enhanced apoE synthesis and secretion in vivo, but also enhanced synaptogenesis and compensatory terminal remodeling in response to deafferentation in the mature rodent hippocampus [40]. Indomethacin, a cyclooxygenase inhibitor used a few years ago to slow down the progression of AD in a placebo-controlled, double-blind, clinical trial in mild-to-moderate AD [41], was found to act as a very potent apoE inducer in subnanomolar concentrations [42]. A subsequent systematic analysis of the structure-activity relationship of several indomethacin derivatives revealed that the portion of the molecule responsible for apoE induction activity is different from the cyclooxygenase inhibitory moiety, consistent with a non-immunosuppressing mode of action, and presumably involving the peroxisome proliferating activating receptor-γ (PPAR-γ) pathway [42].

This observation is consistent with a recent clinical study by Risner et al. at GlaxoSmithKline, who reported significant clinical improvement of cognitive deficit in a large, double-blind, placebo-controlled, 6-month clinical trial in mild-to-moderate AD using PPAR-γ agonist rosiglitazone [43]. Agonists belonging to the PPAR-γ family of drugs are well-known inducers of apoE synthesis and secretion in peripheral cells, and are potent anti-inflammatory agents [44].

The most interesting compound identified during our apoE induction screening assays was undoubtedly probucol, an old cholesterol-lowering drug used to treat familial hypercholesterolemia. It is still in use in Japan. The administration of probucol (1% w/w) in rat and mouse diets, at concentrations designed to mimic the dose used in humans, caused a significant induction of apoE synthesis and secretion after 30 days in cortical and hippocampal areas (Fig. 2). Synaptic density, as measured by hippocampal GAP-43 and synaptophysin immunohistochemistry, increased during treatment (Fig. 2) in 24-month-old rats. Similar results were found in the brains of C57/Bl mice exposed to probucol (intraperitoneal) for 2 weeks (not shown).

After authorization from the Health Protection Branch of Health Canada, we set up a small pilot clinical trial to test

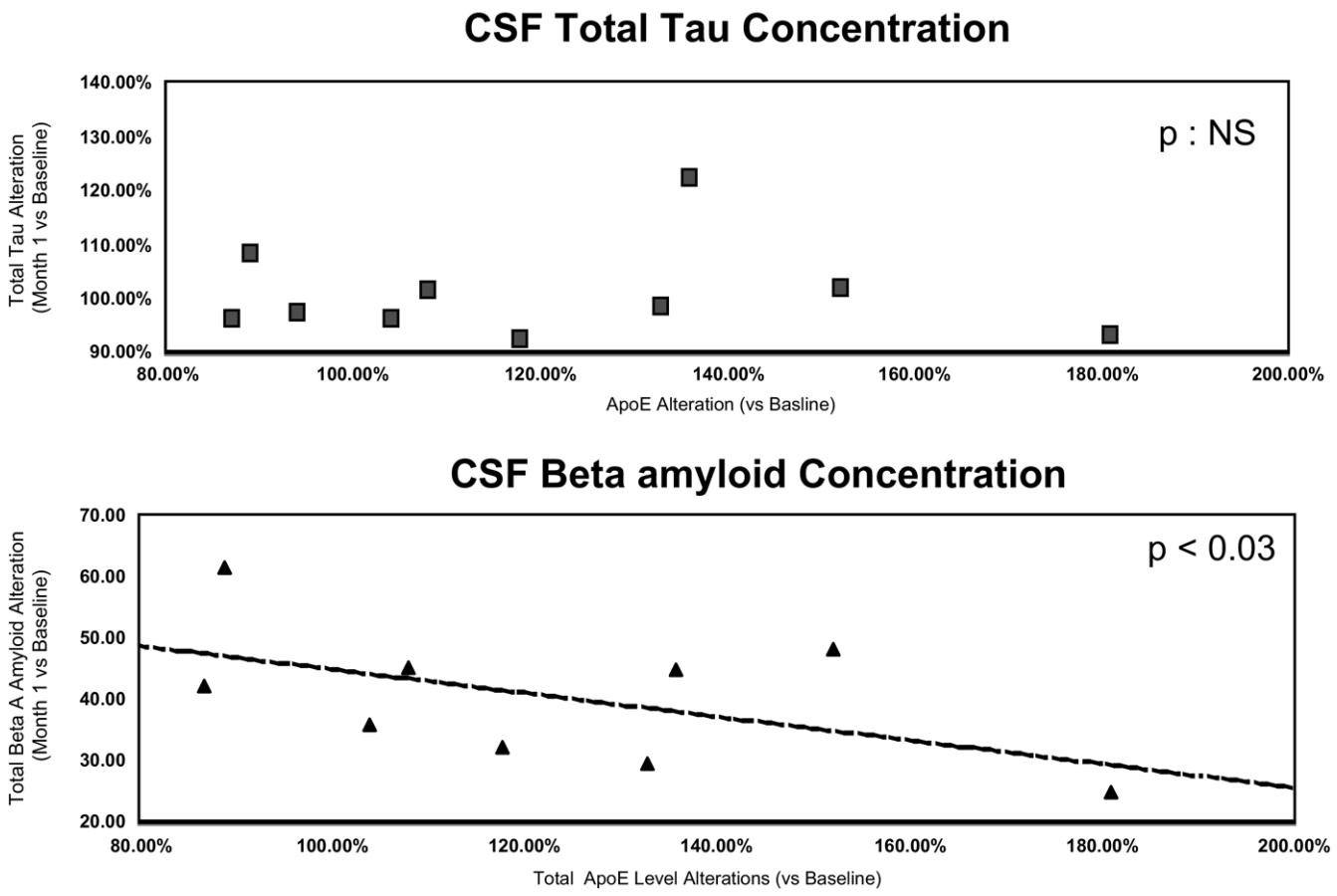

Fig 3. Effect of probucol administration on cerebrospinal fluid levels of total tau (top) and total β-amyloid (bottom) in probucol-treated Alzheimer's disease subjects. Graphs represent ratio values of 1 month of treatment over baseline concentrations for each subject enrolled in the clinical trial. Adapted from Poirier and Panisset [45] and Poirier [50].

probucol in a cohort of 12 mild-to-moderate AD subjects not using acetylcholinesterase inhibitors or Memantine. This proof-of-concept clinical study examined the effects of a standard dose of probucol (500 mg/bid) used to treat hypercholesterolemia before the introduction of statins almost a decade ago. Probucol was administered in mild-to-moderate AD subjects for period of 6 months. Clinical assessments revealed a concomitant stabilization of symptoms on the ADAS-cog and on the Disability Assessment of Dementia (DAD) scale over the course of the trial [45]. The clinical benefits according to the ADAS-cog correlate very well with the increase of apoE levels in the cerebrospinal fluid (CSF) of these patients ($P < 0.05$). More interestingly, there was a significant inverse relationship between the increase in apoE levels and the reduction of total β-amyloid levels in the CSF of probucol-treated AD subjects [46] (Fig. 3). Fig. 4A illustrates the cumulative effect of probucol administration on apoE level measured in the CSF at 1 month and at baseline. If one assumes that the overall probucol consumption was constant over the course of the trial, we can see that the impact of probucol on clinical parameters at 6 months (Fig. 4B) was more pronounced after 100 g (or 100 equivalent days of treatment), whereas the effect of probucol on apoE concentration in the CSF was

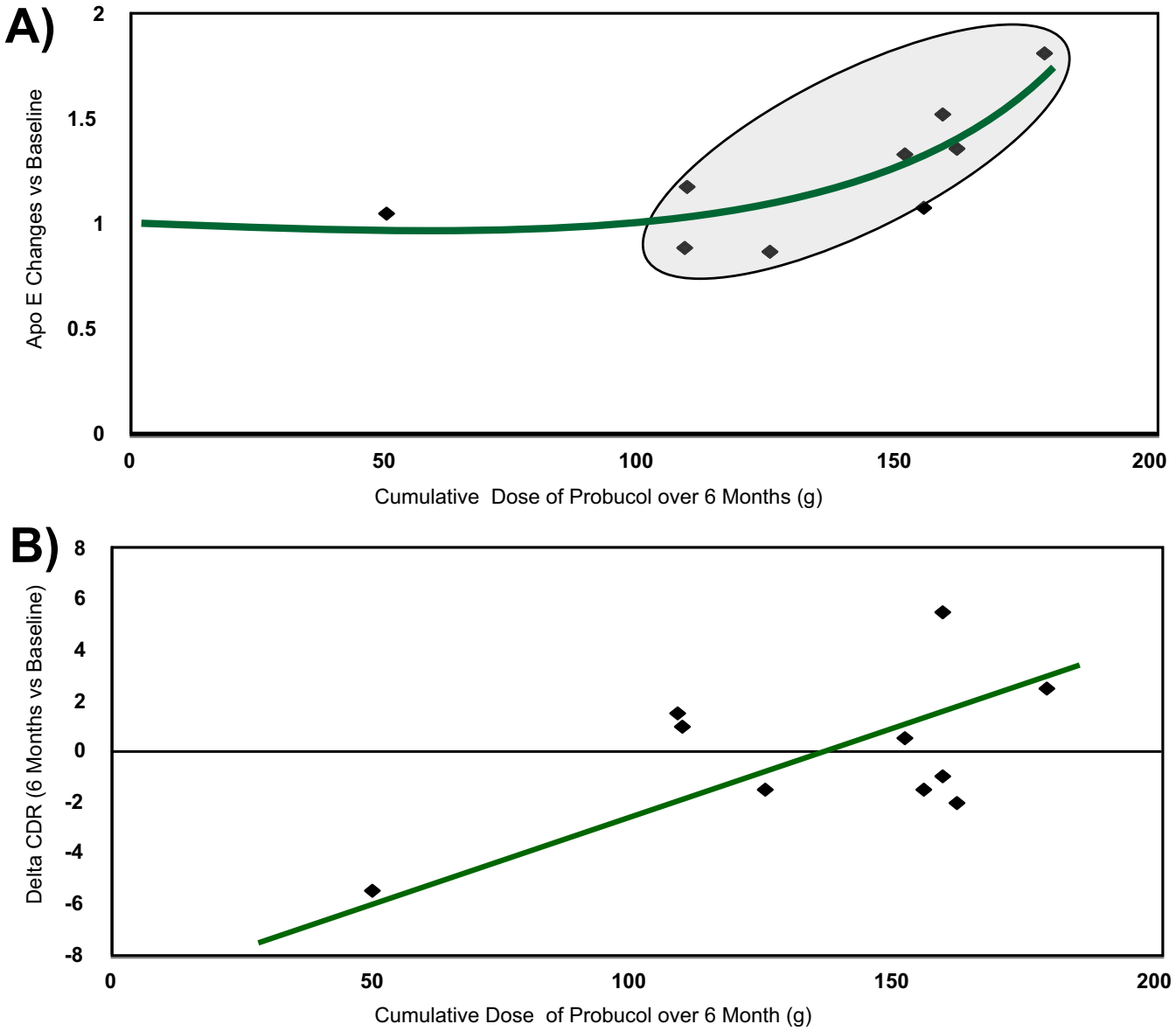

Fig 4. **A:** Alteration of apolipoprotein E concentration in the cerebrospinal fluid of Alzheimer's disease patients in response to probucol administration: compliance analysis of the effect of cumulative doses of probucol on brain *APOE* levels. **B:** Effect of cumulative dose of probucol on the Clinical Deterioration Scale (CDR) at month 6 vs. baseline in probucol-treated Alzheimer's disease patients not using esterase inhibitors or Memantine. Adapted from Poirier and Panisset [45].

more pronounced after 150 g (or 150 equivalent days of treatment; Fig. 4A).

These results are suggestive at best. Only a prospective, double-blind, placebo-controlled clinical trial of AD subjects with and without *APOE* e4 over a long period of time will allow us to confirm the beneficial effect of probucol in sporadic AD. It is interesting to note that the effect of probucol was significantly more pronounced in *APOE* e3 cases than in *APOE* e4 allele carriers [45], i.e., a pharmacogenomic response very similar to that described for rosiglitazone [43] and estrogen [47], two very potent *APOE*-inducer drugs, on cognitive performance in non-e4 subjects.

The recent discovery that nearly 80% of all *APOE* e4 MCI subjects convert into probable/possible AD cases within 3 years allows us to test the beneficial effects of apoE inducers such as probucol, estrogen, and rosiglitazone in a population heterozygous for the e4 allele, namely the *APOE* e4/e3 subgroup, which is characterized by (1) low circulating levels of apoE, (2) a high risk of conversion to AD, and (3) marked hippocampal and entorhinal cortical shrinkage in a relatively short-term perspective. Such a pharmacogenomic trial would not only allow us to test the effect of apoE-inducers such as probucol on the progression and conversion of the disease, but also to examine their potential use in the prevention of sporadic AD in *APOE* e4 carriers.

5. Conclusions

We have reviewed the apparent role of *APOE* e4 in the development of dementia and AD pathology. Although age remains a key determinant that modulates the onset and expression of AD pathology, genetic risk factors such as *APOE* appear to play a central role in the pathophysiology of this disease, for years, if not decades, before clinical diagnosis. The combined use of genetic profiling and gene-targeting will allow us to better identify the biochemical mechanisms regulating the loss of synaptic integrity and the accumulation of amyloid deposits in the aging brain. The recent discovery that estrogen and rosiglitazone, multifunctional agents with common apoE-inducing properties, perform best in *APOE* e3/e3 AD patients is consistent with early data from the probucol AD trial that also showed preferential benefits for *APOE* e3/e3 AD cases. The surprising convergence of these biochemical, pharmacogenomic, and clinical observations raises exciting new possibilities and certainly interesting new therapeutic avenues for the treatment and prevention of a genetically defined and sizeable subset of AD subjects.

References

[1] Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. Neuron 1993;11:575–80.

[2] Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, et al. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proc Natl Acad Sci USA 1993;90:9649–53.

[3] Beffert U, Poirier J. Apolipoprotein E, plaques, tangles and cholinergic dysfunction in Alzheimer's disease. Neurobiol Alzheimers Dis 1996;777:166–74.

[4] Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci USA 1995;92:12260–4.

[5] Arendt T, Schindler C, Bruckner MK, Eschrich K, Bigl V, Zedlick D, et al. Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein epsilon 4 allele. J Neurosci 1997;17:516–29.

[6] Allen SJ, MacGowan SH, Tyler S, Wilcock GK, Robertson AG, Holden PH, et al. Reduced cholinergic function in normal and Alzheimer's disease brain is associated with apolipoprotein E4 genotype. Neurosci Lett 1997;239:33–6.

[7] Lai MK, Tsang SW, Garcia-Alloza M, Minger SL, Nicoll JA, Esiri MM, et al. Selective effects of the APOE epsilon4 allele on presynaptic cholinergic markers in the neocortex of Alzheimer's disease. Neurobiol Dis 2006;22:555–61.

[8] Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379–88.

[9] Gold M, Franke S, Nye JS, Goldstein HR, Fijal B, Cohen N. Impact of ApoE genotype on the efficacy of galantamine for the treatment of mild cognitive impairment. Neurobiol Aging 2004;24:521.

[10] Farlow MR, He Y, Tekin S, Xu J, Lane R, Charles HC. Impact of APOE in mild cognitive impairment. Neurology 2004;63:1898–901.

[11] de Leon MJ, Convit A, Wolf OT, Tarshish CY, DeSanti S, Rusinek H, et al. Prediction of cognitive decline in normal elderly subjects with 2-[F-18]fluoro-2-deoxy-D-glucose/positron-emission tomography (FDG/PET). Proc Natl Acad Sci USA 2001;98:10966–71.

[12] Poirier J. Apolipoprotein E and cholesterol metabolism in the pathogenesis and treatment of Alzheimer's disease. Trends Mol Med 2003;9:94–101.

[13] Poirier J. Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease. Trends Neurosci 1994;17:525–30.

[14] Strittmatter WJ, Weisgraber KH, Huang D, Dong LM, Salvesen GS, Pericak-Vance M, et al. Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. Proc Natl Acad Sci USA 1993;90:8098–102.

[15] Strittmatter WJ, Saunders AM, Goedert M, Weisgraber KH, Dong LM, Jakes R, et al. Isoform-specific interactions of apolipoprotein E with microtubule-associated protein tau: implications for Alzheimer disease. Proc Natl Acad Sci USA 1994;91:11183–6.

[16] Ohm TG, Kirca M, Bohl J, Scharnagl H, Gross W, Marz W. Apolipoprotein E polymorphism influences not only cerebral senile plaque load but also Alzheimer-type neurofibrillary tangle formation. Neuroscience 1995;66:583–7.

[17] Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas RE. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. Science 1994;264:850–2.

[18] Buttini M, Orth M, Bellosta S, Akeefe H, Pitas RE, Wyss-Coray T, et al. Expression of human apolipoprotein E3 or E4 in the brains of apoE −/− mice: isoform-specific effects on neurodegeneration. J Neurosci 1999;19:4867–80.

[19] Tolar M, Marques MA, Harmony JA, Crutcher KA. Neurotoxicity of the 22 kDa thrombin-cleavage fragment of apolipoprotein E and related synthetic peptides is receptor-mediated. J Neurosci 1997;17:5678–86.

[20] Poirier J, Minnich A, Davignon J. Apolipoprotein E, synaptic plasticity and Alzheimer's disease. Ann Med 1995;27:663–70.
[21] Mulder M, Jansen PJ, Janssen BJ, van de Berg WD, van der Boom H, Havekes LM, et al. Low-density lipoprotein receptor-knockout mice display impaired spatial memory associated with a decreased synaptic density in the hippocampus. Neurobiol Dis 2004;16:212–9.
[22] Masliah E, Mallory M, Ge N, Alford M, Veinbergs I, Roses AD. Neurodegeneration in the central nervous system of apoE-deficient mice. Exp Neurol 1995;136:107–22.
[23] Veinbergs I, Masliah E. Synaptic alterations in apolipoprotein E knockout mice. Neuroscience 1999;91:401–3.
[24] Champagne D, Rochford J, Poirier J. Effect of apolipoprotein E deficiency on reactive sprouting in the dentate gyrus of the hippocampus following entorhinal cortex lesion: role of the astroglial response. Exp Neurol 2005;194:31–42.
[25] Champagne D, Dupuy JB, Rochford J, Poirier J. Apolipoprotein E knockout mice display procedural deficits in the Morris water maze: analysis of learning strategies in three versions of the task. Neuroscience 2002;114:641–54.
[26] Veinbergs I, Mante M, Jung MW, Van Uden E, Masliah E. Synaptotagmin and synaptic transmission alterations in apolipoprotein E-deficient mice. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:519–31.
[27] Grootendorst J, Bour A, Vogel E, Kelche C, Sullivan PM, Dodart JC, et al. Human apoE targeted replacement mouse lines: h-apoE4 and h-apoE3 mice differ on spatial memory performance and avoidance behavior. Behav Brain Res 2005;159:1–14.
[28] Chapman S, Sabo T, Roses AD, Michaelson DM. Reversal of presynaptic deficits of apolipoprotein E-deficient mice in human apolipoprotein E transgenic mice. Neuroscience 2000;97:419–24.
[29] Holtzman DM, Bales KR, Wu S, Bhat P, Parsadanian M, Fagan AM, et al. Expression of human apolipoprotein E reduces amyloid-beta deposition in a mouse model of Alzheimer's disease. J Clin Invest 1999;103:R15–21.
[30] Wisniewski T, Golabek A, Matsubara E, Ghiso J, Frangione B. Apolipoprotein E: binding to soluble Alzheimer's beta-amyloid. Biochem Biophys Res Commun 1993;192:359–65.
[31] Beffert U, Aumont N, Dea D, Lussier-Cacan S, Davignon J, Poirier J. Apolipoprotein E isoform-specific reduction of extracellular amyloid in neuronal cultures. Brain Res Mol Brain Res 1999;68:181–5.
[32] Utermann G, Langenbeck U, Beisiegel U, Weber W. Genetics of the apolipoprotein E system in man. Am J Hum Genet 1980;32:339–47.
[33] Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC Jr, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994;7:180–4.
[34] Poirier J. Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease. Neurobiol Aging 2005;26:355–61.
[35] Blanche H, Cabanne L, Sahbatou M, Thomas G. A study of French centenarians: are ACE and APOE associated with longevity? C R Acad Sci III 2001;324:129–35.
[36] Frisoni GB, Louhija J, Geroldi C, Trabucchi M. Longevity and the epsilon2 allele of apolipoprotein E: the Finnish Centenarians Study. J Gerontol [A] Biol Sci Med Sci 2001;56:M75–8.
[37] Bertrand P, Poirier J, Oda T, Finch CE, Pasinetti GM. Association of apolipoprotein E genotype with brain levels of apolipoprotein E and apolipoprotein J (clusterin) in Alzheimer disease. Brain Res Mol Brain Res 1995;74:178–84.
[38] Poirier J. Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease. Neurobiol Aging 2005;26:355–61.
[39] Finch CE, Stanford CB. Meat-adaptive genes and the evolution of slower aging in humans. Q Rev Biol 2004;79:3–50.
[40] Stone DJ, Rozovsky I, Morgan TE, Anderson CP, Finch CE. Increased synaptic sprouting in response to estrogen via an apolipoprotein E-dependent mechanism: implications for Alzheimer's disease. J Neurosci 1998;18:3180–5.
[41] Rogers J, Kirby LC, Hempelman SR, Berry DL, McGeer PL, Kaszniak AW, et al. Clinical trial of indomethacin in Alzheimer's disease. Neurology 1993;43:1609–11.
[42] Aleong R, Aumont N, Dea D, Poirier J. Non-steroidal anti-inflammatory drugs mediate increased in vitro glial expression of apolipoprotein E protein. Eur J Neurosci 2003;18:1428–38.
[43] Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenom J 2006; 6:246–54.
[44] Yue L, Rasouli N, Ranganathan G, Kern PA, Mazzone T. Divergent effects of peroxisome proliferator-activated receptor gamma agonists and tumor necrosis factor alpha on adipocyte ApoE expression. J Biol Chem 2004;279:47626–32.
[45] Poirier J, Panisset M. Apolipoprotein E: a novel therapeutic target for the treatment of Alzheimer's disease. Adv Exp Med Biol 2002;51: 36–42.
[46] Poirier J. Apolipoprotein E and cholesterol metabolism in the pathogenesis and treatment of Alzheimer's disease. Trends Mol Med 2003; 9:94–101.
[47] Burkhardt MS, Foster JK, Laws S, Baker LD, Craft S, Gandy S, et al. Oestrogen replacement therapy may improve memory functioning in the absence of APOE epsilon4. J Alzheimers Dis 2004;6:221–8.
[48] Poirier J. Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease. Neurobiol Aging 2005;26:355–61.
[49] Champagne D, Pearson D, Dea D, Rochford J, Poirier J. The cholesterol-lowering drug probucol increases apolipoprotein E production in the hippocampus of aged rats: implications for Alzheimer's disease. Neuroscience 2003;121:99–110.
[50] Poirier J. Apolipoprotein E and cholesterol metabolism in the pathogenesis and treatment of Alzheimer's disease. Trends Mol Med 2003; 9:94–101.