APOLIPOPROTEIN E4 AND CHOLINERGIC ACTIVITY IN ALZHEIMER’S DISEASE

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INTRODUCTION

Apolipoprotein E (apoE) is a well characterized lipophilic protein associated with plasma and CSF lipoproteins. ApoE is synthesized primarily by the liver, but also at other sites including brain, macrophages and adrenals. Furthermore, apoE is unique among apolipoproteins in that it has a special relevance to the central and peripheral nervous systems. It is a key determinant in the cellular recognition and internalization of cholesterol- and phospholipid-rich lipoproteins in the developing brain and in the response to neuronal injury (Boyles et al., 1989, Poirier et al., 1991, 1991a, 1993). It was shown to play a fundamental role in the CNS during hippocampal synaptic plasticity induced by entorhinal cortex lesions in the rat (Poirier et al., 1991, 1991a and 1993).

ApoE is synthesized and secreted by astrocytes in the deafferented zone of the hippocampus following lesions of the entorhinal cortex (Poirier et al., 1991). Experimental evidences suggest that apoE and its main receptor, the so-called LDL receptor, are directly involved in cholinergic synaptic remodelling caused by the loss of entorhinal cortex neurons; a pathophysiological process also observed in AD (Hyman et al., 1984).

The human apoE gene on chromosome 19 has three common alleles (E2, E3, E4), which encode three major apoE isoforms. Recently, the frequency of
the apoE4 allele was shown to be markedly increased in sporadic (Poirier et al., 1993a, Saunders et al., 1993, Noguchi et al., 1993) and late onset familial AD (Corder et al., 1993, Payami et al., 1993). Most interestingly, a gene dosage effect was observed in both familial (Corder et al., 1993) and sporadic (Poirier et al. 1993a) cases (i.e. as age of onset increases, E4 allele copy number decreases). The discovery that the apoE4 allele is strongly linked to both sporadic and familial late onset AD raises the possibility that a dysfunction of the lipid transport system associated with compensatory plasticity and synaptic remodelling could be central to the pathophysiology of AD.

The role of apoE in the CNS is particularly important in relation to the function of the cholinergic system which relies heavily on the integrity of lipid homeostasis to synthesize acetylcholine in neurons. Brain membrane phospholipids, especially phosphatidylcholine (PC) and phosphatidylethanolamine (PE), have been shown to be involved in the availability of choline, a rate-limiting precursor of acetylcholine (ACh) (Blusztajn et al., 1987). The release from PC of free choline precursor for ACh synthesis is accomplished in a one step process through a phospholipase-D type enzyme in cholinergic neurons. Brain levels of choline are decreased by up to 40-50% in frontal and parietal cortices (Nitsch et al., 1992) of AD patients whereas cholesterol, which is required for the proper functioning of nicotinic receptor sub-type (Jones and McNamee, 1988), was shown to be markedly reduced in AD versus control subjects (Svennerholm and Gottfries, 1994). It was recently proposed that the low levels of apoE reported in the brain and CSF of apoE4 AD subjects may compromise cholesterol and phospholipid transport in the CNS and selectively damage the cholinergic system which relies heavily on lipid homeostasis (Poirier, 1994). The relationship between the apoE4 genotype and cholinergic deficits is highly relevant to investigate in genetically distinct individuals. Preliminary studies indicated that ChAT activity is markedly reduced in the hippocampus and cortex of apoE4-AD subjects (Poirier, 1994, Sioninen et al., 1995, Poirier et al., 1995). The major aims of the present study were thus a) to investigate the apparent status and integrity of the cholinergic system in the brain of AD and control subjects with different apoE genotypes; and b) to examine the effect of apoE genotype on the therapeutic response to cholinomimetic treatments.

RESULTS

Pathological Studies
On the basis of its well-recognized post-mortem stability, ChAT activity was examined in relation to apoE genotype in control and AD post-mortem subjects. Figure 1A illustrates that the loss in ChAT activity (Poirier et al., 1995) in the hippocampus of control and AD cases as a function of apoE4 allele copy number (i.e. as apoE4 allele copy number increased, ChAT activity