Apolipoprotein E and Alzheimer Disease: An Update on Genetic and Functional Analyses

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Abstract. Exceptional advances have been made in understanding the genetics of how common polymorphisms of the apolipoprotein E gene influence the risk and age of onset of Alzheimer disease (AD). The major genetic susceptibility locus for the common forms of AD, there are 3 common alleles, designated e2, e3, and e4. The inheritance of each dose of APOE4 increases the risk of disease and decreases the age of onset; conversely, the APOE2 allele appears to be protective, by lowering the risk of disease and increasing the age of onset. Testing for the APOE4 allele can be a clinically useful tool in the early diagnosis of cognitively impaired patients suspected of having AD. The APOE4 allele also negatively influences functional recovery following a variety of brain insults. What remains in the study of apolipoprotein E is an explanation of how minor changes in a protein can produce such striking differences in risk and age of onset. In vitro and animal model studies strongly suggest that brain apolipoprotein E is a multifunctional molecule, with potential roles in amyloid deposition and clearance, microtubule stability, intracellular signaling, immune modulation, glucose metabolism, oxidative stress, and other cellular processes. While the relevance of these proposed functions to the etiology of AD remains a mystery, these and other hypotheses will be tested as the field of apoE neurobiology grows, adding relevant new data to the functions of apoE in health and in the pathogenic mechanisms leading to AD.

Key Words: Alzheimer disease; Apolipoprotein E; Genetics; Polymorphisms.

INTRODUCTION

Epidemiological and molecular studies suggest that Alzheimer disease (AD) has multiple etiologies, including genetic mutations, susceptibility genes, and environmental factors. Mutations in 3 known genes, the amyloid precursor protein (APP) and presenilin (PS) 1 and 2 genes, nearly always cause the disease (1). These mutations are extremely important for basic neurobiological research because they identify genes that, when mutated, cause the AD phenotype. Mechanisms involving these protein mutations can provide valuable information for further research hypotheses concerning mechanisms of disease. However, from the perspective of the common forms of AD seen in clinical practice, the autosomal dominant forms represent less than 2% of the incidence or prevalence.

Apolipoprotein E (APOE = gene; apoE = protein) is a fourth genetic factor involved in the development of AD. Unlike the 3 deterministic genes, APOE is a susceptibility locus that accounts for approximately half of late-onset AD (2). In addition, the most common etiology in patients with onset between the ages of 50 and 60 yr involves the inheritance of 1 or more APOE4 alleles as susceptibility genes (3, 4). Remarkable progress has been made in understanding the susceptibility genetics of APOE and AD and the influence of a common polymorphism of the gene on recovery from acute brain stresses. While the role of apoE as a plasma lipid-transport molecule has been well documented, the normal functions of apoE in the central nervous system and its role in the etiology of AD have not been identified. The genetic effect of APOE polymorphisms on AD and hypotheses on the role of apoE in AD are reviewed.

DISCUSSION

Biochemical Background

APOE is located on the long arm of human chromosome 19 within an apolipoprotein gene family and has 3 common alleles, designated e2, e3, and e4 (5). These genetic variations result in amino acid substitutions (arginine or cysteine) at positions 112 and 158 of the protein. In the majority of Caucasian populations, APOE3/3 is the most common genotype and APOE3 is the most common allele; APOE4 and APOE2 are considered variants. The apoE protein has several functional domains. Through its lipid-binding domain, plasma apoE is a constituent of very low-density lipoproteins (VLDL) and a subclass of high-density lipoproteins (HDL). VLDL transports triglycerides from the liver to all tissues except brain, and HDL redistributes cholesterol among cells. The protein is also a major constituent of chylomicrons, which transport dietary cholesterol and triglycerides. Through its receptor-binding domain, apoE mediates the cellular uptake of lipid complexes via the low-density lipoprotein (LDL)-receptor and other related receptors. APOE2/2 is the most common genotype associated with type III hyperlipoproteinemia, and the apoE2 protein is defective in LDL-receptor binding. While apoE4 has normal LDL-receptor binding, it is associated with elevated plasma cholesterol and LDL levels.

The brain has the second largest concentration of APOE mRNA, at levels approximately one third the amount found in liver. Brain apoE is synthesized locally, as shown in liver transplant patients (6), and is the major
apolipoprotein in cerebrospinal fluid (7). ApoE, secreted by astrocytes and microglia, may enter neurons by binding to the LDL-receptor related protein (LRP) or the LDL- and related VLDL-receptor mechanisms (8). An intraneuronal source of apoE was recently demonstrated using in situ hybridization (9). These experiments showed low levels of human APOE mRNA in select cortical neurons. It is not known whether nascent apoE in the CNS preferentially associates with lipids and lipoprotein particles or if complexes with other proteins. Biochemical analysis of apoE-containing lipoproteins in human cerebrospinal fluid have demonstrated that these very large lipoproteins have a unique composition; in contrast, nascent apoE-containing lipoproteins secreted by cultured rat astrocytes contain little core lipid and are smaller (10).

**APOE as a Susceptibility Gene for AD**

Polymorphic variations at the apoE locus, acting as inherited risk factors, affect genetic susceptibility to AD (11, 12). Despite seemingly slight variations, different genotypes have a major effect on the risk and age-at-onset distribution of AD. The APOE4 allele is associated with an earlier age at onset of the common form of AD (13); the APOE2 allele confers a decreased risk and older age at onset (14). Since each individual inherits 2 alleles, the association of risk and onset distribution of AD varies with the different genotypes. APOE4/4 homozygotes, constituting approximately 2% of the general population, have the greatest risk. Statistically, AD will begin in 50% of them before they reach 70 yr of age. APOE2/3 heterozygotes, represented in 12% to 14% of the population, have a median age at onset well over 90 yr. The age-at-onset distribution of the population with the most common genotype, APOE3/3, falls in between. Therefore, on the basis of APOE genotype alone, there is more than a 2-decade difference in the median age-at-onset distribution.

There are, however, differences in the prevalence of each genotype in various ethnic and racial groups (15). In Japan, where the allele frequency of APOE4 is about half that in the US, most of the APOE4-bearing AD patients have the APOE3/4 genotype. Consequently, there are fewer Japanese patients with disease onset before 70 yr of age, and more patients with onset between 76 and 78 yr of age. A second example comes from Finland, where the APOE4 allele frequency in the general population is quite high at 22%. However, age-matched controls for the AD cases in the population had an allele frequency of only 16.5%. It was suggested that the high incidence of fatal myocardial infarction in Finland, which the APOE4 allele also serves as a risk factor, contributed to the attrition of many APOE4-bearers before the age of risk for AD. The association of APOE4 and AD in African-Americans and Hispanics remains controversial and may be absent in a sample of Nigerian AD cases and controls.

Disease duration appears to be influenced by the age of onset rather than the APOE genotype (16). Because the APOE4/4 genotype is associated with earlier ages at onset, these patients generally have a longer disease course. If, however, one compares patients with onsets in the same age range (e.g. APOE4/4 and APOE3/3 patients with onsets between 65 and 69 yr of age), the disease duration is similar and independent of the APOE risk factors. A recent longitudinal study that followed newly diagnosed AD patients over the course of 1 to 6 yr found that APOE4/4 patients have a faster rate of cognitive decline, whereas the APOE2 allele slows disease progression (17).

The APOE4 allele is also associated with sporadic early-onset AD (3) and with familial early-onset AD in pedigrees without presenilin or APP mutations (18). In addition, there appears to be an interaction of APOE genotypes with the age of onset in families with early-onset AD due to mutations in APP (19). Patients with an APP mutation and an APOE4 allele have earlier ages of onset. In contrast, there are asymptomatic individuals with an APP mutation and an APOE2/3 genotype who are at least 1 standard deviation older than the mean age of onset in the pedigree. A similar interaction may exist with the PS II gene mutations (20).

Dementia with Lewy bodies (DLB) may represent the most common pathologic subgroup of pure AD (21), and data from patient series with the diagnosis of AD with concomitant Parkinson disease pathology show a strong association with APOE4. In a survey of reports on the association of APOE4 and DLB, the levels of association range from very high, paralleling the data with AD, to none. The source of these seemingly discrepant data appears to be the criteria employed to create patient series. In reports clearly stating that the study subjects have AD with concomitant Parkinson disease pathology, there is a highly statistically significant association of the APOE4 allele with the disease (22, 23). These data support the notion that DLB is a subclass of AD, not of Parkinson disease, with perhaps a second genetic polymorphism influencing the appearance of the Lewy bodies. There is no association between APOE4 and risk for either pure Parkinson disease or Parkinson disease with dementia (not of the AD-type) (24, 25).

**APOE Genotyping as a Diagnostic Tool**

Mutational analysis of Mendelian traits with complete penetrance (i.e. disease mutations that always manifest as disease) are accurate for diagnosing symptomatic patients. For example, a patient with early-onset cognitive impairment can be diagnosed as AD of the PS1 type by performing a mutational analysis of the PS1 gene. Family members who do not exhibit any clinical signs or
symptoms of a disease, but carry a deterministic mutation, are predicted to be at very high risk for the disease. Likewise, family members without the mutation are not at risk for this form of AD.

There has been considerable discussion in the clinical literature with regard to the use of APOE genotyping in the differential diagnosis of patients with mild symptoms and signs of possible or probable AD. Sources of the early controversy over APOE genotyping as a diagnostic adjunct were specificity data from epidemiological clinical evaluations without neuropathological confirmation of the disease (26). In reality, only 70% to 90% of cases in most series of clinically probable AD are eventually confirmed by autopsy, with the remaining 10% to 30% of cases diagnosed as non-AD disorders. Thus, estimations of the accuracy of APOE genotyping in clinical series are limited by the accuracy of the clinical diagnosis and the variability between series. Some of the variability is also the result of differences between ethnic and racial groups with respect to APOE allele frequencies.

To circumvent these widely variable estimates, APOE genotyping has been examined in longitudinal series of possible and probable AD patients whose diagnoses have been confirmed by autopsy. The first studies of cases confirmed by autopsy demonstrate a positive predictive value of the APOE4/4 and APOE3/4 genotypes approaching more than 99% (27–29). These 2 APOE genotypes account for approximately 65% of sporadic AD patients (12). Non-AD patients in these series rarely carry an APOE4 allele. A subsequent study of over 2,000 patients from 26 Alzheimer Disease Centers evaluated clinical diagnoses, postmortem diagnoses, and APOE genotype (30). The study concluded that APOE genotyping, when used as a diagnostic adjunct in combination with clinical criteria, improves the specificity of the diagnosis. APOE genotyping of patients suspected of having AD does not provide sufficient sensitivity or specificity to be used alone as a diagnostic test. Since a significant proportion of patients with autopsy-confirmed AD do not carry an APOE4 allele, the absence of an APOE4 allele does not rule out AD, nor is it useful for differentiating AD from other diseases.

Although the relative risk of AD is increased with the presence of 1 or 2 APOE4 alleles, it is not possible to predict whether or when disease will develop in a cognitively intact person (26). It is quite possible for someone with the APOE3/4 genotype to live more than 100 yr without the disease and for a significant proportion of people with the APOE2/3 genotype to have onset before 90 yr of age. Until proper epidemiological studies are available, calculations quantifying the relative risk of AD for a given APOE genotype cannot be accurate. Thus, it is widely agreed that APOE genotyping should not be used for prediction in the general population. However, as additional susceptibility genes are confirmed and epidemiological studies are published, prediction of earlier or later disease onset within each APOE genotype group will probably become more accurate. Once there are safe and effective preventive therapies for AD, the value of predictive testing, with all its ethical and social considerations, should change.

APOE4 and Recovery from Acute Brain Stresses

Additional data implicate APOE4 in recovery from several types of acute brain stress (31–37). The first suggestion that APOE4 was involved in the recovery of brain injury was published in 1995 (34). Nicoll and colleagues studied the amyloid load in head trauma patients who were comatose and died within a 30-day period after injury. Interestingly, the average age of the amyloid-bearing patients was over 50 yr, more than 2 decades older than the patients with no amyloid. One interpretation of the data is that head trauma patients without an APOE4 allele had more efficient recovery from their injury (35). Similar APOE allele-specific effects on recovery from post-traumatic coma have also been reported (36).

The head trauma data lead to numerous investigations on the influence of APOE4 on recovery from acute brain insults. A consecutive series of intracerebral hemorrhage (ICH) patients demonstrated a statistically significant difference in mortality between the group of patients with an APOE4 allele and those with the APOE2/3 or APOE3/3 genotypes, with APOE4-bearing patients having a much higher mortality (68% vs 19%) (31). If patients with an APOE4 allele survived through their initial hemorrhage, their functional recovery was generally poor compared with the APOE4-negative patients who had an almost normal functional recovery. Mayeux and colleagues examined the association between APOE genotypes and head trauma, basing their study on an earlier suggestion that head injury was a risk factor for AD (33). They reported a 10-fold increase in the risk of AD associated with the combination of an APOE4 allele and history of traumatic brain injury, compared with a 2-fold increase in risk with APOE4 alone. Head injury in the absence of an APOE4 allele did not increase risk for the disease. Their data imply a synergistic relationship between the e4 allele and head trauma that increases the risk of AD (33). A preliminary examination of APOE genotypes and dementia pugilistica suggests that the APOE4 allele is associated with increased severity of neurological deficits in boxers with chronic traumatic brain injury as the result of their profession (32). A recent neuropathological study on young men who suffered mild chronic head injuries reports that repetitive head injury in young adults is initially associated with neocortical neurofibrillary tangle formation in the absence of Aβ deposition (38). The tau pathology was consistently situated around blood vessels in the worst affected regions.
There are also provocative data suggesting that APOE4-bearing cardiopulmonary bypass patients do not recover some neuropsychological parameters as well as patients without an APOE4 allele (37). Patients entering the hospital for elective cardiopulmonary bypass surgery were neuropsychologically tested preoperatively and several time points postoperatively. Nearly all patients exhibited cognitive deficits immediately following surgery; however, recovery of normal cognition was still significantly impaired in APOE4-bearing patients at several months following the procedure.

It is not known whether the same mechanism that leads to an increased risk and an earlier onset of AD is involved in poorer recovery from acute brain stresses. These observations on the negative influence of the APOE4 allele on recovery are aiding investigators in developing animal models of acute brain stress as a tool to study the function of apoE in the CNS. Any information on the normal or abnormal function of the apoE protein isoforms derived from these animal models may give researchers insight to the etiology of AD.

APOE and the Etiology of AD

In the past 7 yr, the genetics of APOE as a major susceptibility gene for AD have been well documented. What remains is elucidation of the protein’s normal functions in the CNS and how the apoE4 protein influences metabolism to increase the risk of AD. Prior to the discovery of APOE4’s association with AD, there were only a few studies of apoE metabolism in the CNS. Today, the neurobiology of apoE is a new and rapidly developing area. The accumulating data strongly suggest that brain apoE has multiple functions. While the relevance of these proposed functions to the etiology of AD remains a mystery, a common pathway may emerge as other susceptibility genes for AD are identified and widely confirmed.

The interaction of apoE with the major microscopic markers of AD, amyloid plaques and tangles, has generated considerable experimental activity. The extracellular role of apoE in amyloidogenesis is by far the most popular hypothesis; however, interest in the function of apoE in microtubular stability appears to be increasing with the recent reports of tau mutations in the chromosome 17 frontotemporal dementias (39). Other experimental avenues indicate that brain apoE is involved in multiple other biological processes. Models involving the storage and redistribution of cholesterol following peripheral and CNS injury were proposed about a decade ago (40). Other functions of apoE in the nervous system, unrelated to lipid transport, have also been suggested. These include the possibility of the protein acting as a neurotrophic factor or modulator of neurotrophin activity, an antioxidant, a mediator of immune responses, a modulator of amyloid deposition, and a stabilizer of microtubules (40). Recent research on apoE and 2 of its receptors in the CNS, the VLDL receptor and the apoER2 receptor, indicates that apoE competitively inhibits the binding of reelin to the receptors (41). Direct binding of reelin to these receptors induces phosphorylation of disabled-1, a cytosolic adaptor protein, and modulates tau phosphorylation (41, 42).

ApoE and Amyloid

Variations in Aβ deposition are commonly observed in different patients and in nondemented individuals meeting the pathological criteria for AD (43). With the genetic association of APOE4 with AD, the amyloid burden was re-examined by comparing patients with defined APOE genotypes. When samples are paired for disease and duration, the amyloid burden can be correlated with APOE genotype, with APOE4/4 patients having the greatest burden (44). It is important to incorporate survival in these analyses because Aβ deposition is a consequence of the disease expressed as a function of APOE genotype and time. Several studies have confirmed the increased amyloid deposition in APOE4-bearing individuals, both with and without AD (45–47). The increased amyloid deposition has been attributed to either selective increases in the amount of Aβ1–40 rather than Aβ1–42 (48) or to nonselective increases in both peptides (47).

A striking piece of evidence that apoE plays a role in amyloid deposition is the observation that a lack of apoE dramatically reduced Aβ deposition in a transgenic model of AD (49). APOE-deficient mice were crossed with transgenic mice over-expressing a human mutant APP gene. In 6-month-old mice homozygous for the APP mutation transgene and the wild-type mouse APOE gene, the cerebral cortex and hippocampus had numerous amyloid deposits. In contrast, 6-month-old mice homozygous for the APP transgene but lacking the wild-type mouse APOE gene had no amyloid deposits. This data was recently confirmed in another laboratory (50). These data support an important role for apoE in facilitating Aβ deposition in vivo. Unexpectedly, APP mutation transgenic mice bearing either human APOE3 or APOE4 showed markedly suppressed Aβ deposition also. In theory, these mice should have a significant amyloid load, possibly with the APOE4-bearing mice having the greatest amounts of amyloid deposition (50). The reason behind this finding is not clear. It may indeed reflect a human apoE-specific role in Aβ clearance or deposition. The human APOE constructs used in this study were under the control of an astrocytic-specific promoter. Since human apoE is expressed by both neurons and glial cells, perhaps neuronal or microglial apoE is more directly involved in the formation of amyloid deposits. A number of laboratories have similar experiments underway using a variety of APOE transgenic and targeted-replacement mice. Comparative analysis of these studies should prove interesting.
In vitro assays have consistently demonstrated apoE binding to the Aβ peptide; however, the isoform specificity is dependent on the source and state of the apoE protein. The nature of apoE in the brain is not yet known, but the discrepancies in data underscore the importance of subtle differences in apoE conformation in its activity. Furthermore, the interaction is greatly influenced by the conformational state of the Aβ peptide used, with apoE preferentially binding to Aβ peptides with a beta-sheet conformation (51). The initial report on the association of APOE with AD included data showing that CSF apoE avidly binds synthetic Aβ in vitro (11). A subsequent study demonstrated both purified delipidated human apoE3 and apoE4 formed complexes with synthetic Aβ peptide (52). ApoE4 and Aβ formed complexes within minutes; whereas Aβ binding to apoE3 required hours. Later studies by other laboratories have different data depending on the molecular nature of the apoE protein. ApoE3 present in conditioned media from transfected cells and in human VLDL isolated from an APOE3 homozygous subject binds Aβ with much greater avidity than apoE4 (53, 54). No isoform-specific differences in Aβ binding were observed when apoE isoforms were produced in E. coli (55). Interestingly, 2 recent reports have suggestive evidence that the apoE found within plaques is different, possibly degraded, when compared with apoE from serum (56, 57).

**ApoE and Cytoskeletal Proteins**

ApoE immunoreactivity within neurofibrillary tangles is as striking as the immunoreactivity in amyloid deposits in plaques and blood vessels (44, 58). The staining of tangles implies an intraneuronal role for apoE, and it was proposed that the differential interaction of apoE3 (and apoE2) compared with apoE4 with microtubule-associated proteins was important to the etiology of AD (59). In this hypothesis, apoE2 and apoE3 may sequester or protect tau so that the formation of paired helical filaments and associated hyperphosphorylation of tau near the soma are fractionally slowed during aging. In vitro experiments demonstrated a remarkable difference in the binding of apoE4 and apoE3 to tau. ApoE3 binds to the microtubule-binding domains of tau over a wide range of pH values and concentrations, but does not bind to apoE4. Studies using fragments of apoE and tau have demonstrated which regions of each molecule are critical for complex formation (60). ApoE3, through its LDL-receptor binding domain, binds to the microtubule binding repeat region of tau, the same region that appears to promote self-assembly of tau into paired helical filaments. Like tubulin, neither apoE3 nor apoE4 complexes with tau that has been hyperphosphorylated by incubation with a crude rat brain extract (61). A similar pattern of apoE isoform-specific binding was reported with the dendritic microtubule-associated protein MAP2c, which also affects microtubule assembly and stability (62).

Gel shift and overlay assays have identified several other cytoskeletal proteins that differentially associate with apoE3 and apoE4 (63). In gel shift assays, apoE3 formed SDS-stable complexes with the longest and shortest isoforms of recombinant tau and the 160-kDa neurofilament protein; apoE4 did not bind any cytoskeletal proteins in this assay. Interestingly, the apoE2 isoform did not bind the longest isoform of tau and only weakly associated with the shortest form. The gel shift assay only reveals the strongest protein–protein interactions that remain after electrophoresis in the presence of SDS. Weaker associations can be detected using overlay assays where known amounts of cytoskeletal proteins are slot-blotted onto nitrocellulose and incubated with and apoE isoform. In this assay, both apoE3 and apoE4 complexed with the longest tau isoform and tubulin equally well. In contrast, apoE3 bound actin with a significantly greater affinity than did apoE4. These results indicate that apoE isoforms interact with cytoskeletal proteins with at least 2 different affinities (63).

Several lines of evidence support the theory that apoE is involved in the stabilization of the microtubule system. One line of evidence has demonstrated that the inhibitory effect of exogenous apoE4 on neurite outgrowth in neuroblastoma cells is associated with microtubule depolymerization (64). Cells treated with apoE4 showed fewer microtubules and a greatly reduced ratio of depolymerized to monomeric tubulin than did cells treated with apoE3. The effect of apoE4 on depolymerization of microtubules was shown by biochemical, immunocytochemical and ultrastructural studies. It was recently reported that both apoE3 and apoE4 equally accelerate tubulin polymerization under conditions of slow microtubule assembly (65). In addition, apoE appears to influence the phosphorylation of tau (66). The authors suggested that this effect may occur through the modulation of several calcium-associated signal transduction pathways that increase the activity of certain protein phosphatases, which in turn dephosphorylate tau. A fourth line of evidence is somewhat more controversial, and perhaps a reflection of how unidentified environmental factors may influence the APOE-deficient mouse’s phenotype. One study has demonstrated dramatic age-dependent disruption of the synaptic and dendritic organization of the neocortex and limbic system of apoE-deficient mice, suggesting that apoE is involved in the stability of the microtubular cytoskeleton (67). A recent study by Anderson and colleagues (68) and our own unpublished observations do not find consistent significant changes in these mice. Interestingly, studies looking at levels of tau phosphorylation (69, 70) or cognitive function (68, 71–73) in the APOE-deficient also vary by laboratory. It is quite possible that relatively minor variances in diet, housing, etc. can have a significant effect on the brain stress response of the APOE-deficient mouse.
The most recent evidence of a potential role of apoE in microtubule stability places the apoE in the extracellular compartment. There are multiple receptors for apoE in the brain. Two of these receptors, the VLDL receptor and the apoER2 receptor (also known as LRP8), are now known to bind reelin, an extracellular matrix protein, and mammalian disabled-1, a cytosolic protein that activates tyrosine kinases (41, 42). Direct binding of reelin to these receptors induces phosphorylation of disabled-1, a cytosolic adaptor protein, and modulates tau phosphorylation kinases. Of great interest are the data demonstrating that apoE competitively inhibits the binding of reelin to the receptors in an isoform-specific manner (apoE3 = apoE4 \(\geq\) apoE2) (41). This intracellular signaling process is active during development. Knockout mice for both of these receptors mimic the disabled-1 and reelin knockout phenotypes, with inversion of cortical layers and absence of cerebellar function. Furthermore, each of these 4 knockout phenotypes exhibits hyperphosphorylation of tau (42). As for the etiology of AD, one speculation could involve a similar intracellular signaling process with one of the other apoE receptors preferentially expressed in the hippocampus and cortex, rather than the cerebellum. Over a long period of time or in response to an acute event, competitive inhibition of reelin binding to this third receptor by apoE3 or apoE4 could result in a bias toward tau hyperphosphorylation and tangle formation, leading to a shorter functional life span of neurons. Individuals expressing the apoE2, which has lower inhibitory activity, would tend towards less tau hyperphosphorylation, depending on the combination of apoE alleles inherited.

APOE4’s Allele-Specific Effect on Glucose Metabolism

A potentially promising avenue of research is the study of how the APOE4 influences glucose metabolism in middle-aged, cognitively normal adults 20 yr before the average age of onset of AD. Positron emission tomography (PET) studies suggest that CNS metabolic disturbances are present decades before the onset of clinical disease. Using PET and \(^{18}\)F-deoxyglucose, cerebral glucose hypo-metabolism was observed in the adult relatives of AD patients 2 decades before the expected mean age of onset for persons with the APOE3/3 genotype (74). A subsequent study identified APOE4/4 volunteers from the general population (75). Each subject with the APOE4/4 genotype was matched with 2 control subjects with the APOE3/3 or APOE2/3 genotypes or both. The APOE4/4 subjects had no evidence of altered cognitive function, yet they had significantly reduced regional glucose metabolism. The average age of the APOE4/4 subjects was approximately 20 yr younger than the expected mean age at onset for the APOE4/4 genotype. Both of these studies support the theory that metabolic changes occur well before the clinical onset of AD. Whether the differences measured in these studies are a direct consequence of altered glucose metabolism or an early sign of neuronal damage remains to be determined.

CONCLUSIONS

The genetic effect of the 3 common APOE alleles on both the risk and the age of onset of AD has been well documented over the past 7 yr. Data emerging from clinical studies indicate that the APOE4 allele also influences a person’s outcome following a variety of acute brain insults. How a single amino acid change in a small protein can lead to such striking differences in disease onset distributions is still not known. Experimental evidence drawn from in vitro studies and animal models has highlighted multiple potential functions of apoE in the brain. Most of these functions are differentially modulated in an apoE isoform-specific manner. Which of these phenomena, if any, are relevant to the expression of AD remains to be determined. Considerable amounts of research on apoE function in the CNS have focused on its role in amyloid plaque deposition or clearance and, to a lesser extent, neurofibrillary tangle formation. Currently less popular, but potentially as pertinent, pathogenic hypotheses involving apoE include subtle modulation of intracellular signaling, cholesterol transport, neurotrophic responses, oxidation, intracellular APP metabolism, and cellular responses to inflammation. These and other hypotheses will be tested as the field of apoE neurobiology grows, adding relevant new data to the functions of apoE in health and in the pathogenic mechanisms leading to AD.

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