Review

Apolipoprotein E: a major piece in the Alzheimer's disease puzzle

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Abstract

Alzheimer's disease (AD) is a complex neurodegenerative disorder with multiple etiologies. The presence of the E4 isoform of apolipoprotein E (apoE) has been shown to increase the risk and to decrease the age of onset for AD and is the major susceptibility factor known for the disease. ApoE4 has been shown to intensify all the biochemical disturbances characteristic of AD, including beta amyloid (A β) deposition, tangle formation, neuronal cell death, oxidative stress, synaptic plasticity and dysfunctions of lipid homeostasis and cholinergic signalling. In contrast, other apoE isoforms are protective. Here we review and discuss these major hypotheses of the apoE4-AD association.

Keywords: Alzheimer's disease • apolipoprotein E • amyloid • cell signalling • oxidative stress • synaptic plasticity

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Introduction

The last decade has seen enormous progress in Alzheimer's disease (AD) research with an increased awareness that multiple genetic and environmental factors likely cause the disorder. A diagnosis of AD is confirmed post-mortem by the accumulation of neuritic plaques (NP) and neurofibrillary tangles (NFT) in brain tissue. NPs are extracellular deposits composed mainly of a small insoluble protein called amyloid β -peptide ($A\beta$) that is derived from the β -amyloid precursor protein (APP). NFTs are found inside neurons and are characterised by structures referred to as paired helical filaments (PHF), whose major component is an abnormally phosphorylated and glycosylated form of the '*tau*' protein [1]

Four different genes have definitely been associated with an inherited susceptibility to AD. Other genetic loci have been implicated and additional genes remain to be identified. Mutations in 3 genes, the presenilin 1 (PS1) on chromosome 14, presenilin 2 (PS2) on chromosome 1 and the amyloid precursor protein (APP) on chromosome 21, are highly penetrant, but represent only about 1% of all AD cases. The apolipoprotein E (apoE) gene on chromosome 19 is a susceptibility factor that accounts for approximately half of late onset AD [2].

The mechanisms by which apoE influences AD are unknown, although over the past few years, a wealth of histological and biochemical data has connected apoE to $A\beta$ generation or clearance, NFT formation, oxidation, neurotoxicity, dysfunction in lipid transport, modulation of intracellular signalling and, indeed, with all the major hypotheses of AD pathogenesis. All these data stress the possibility that apoE plays an important role in the puzzle of AD. This short review summarises and discusses the major current facts and hypotheses of the apoE-AD association.

Biochemical background

ApoE is a constituent of many types of lipoproteins that plays a major role in the distribution and metabolism of cholesterol and triglycerides within many organs and cell types in the human body.

ApoE is a major determinant of the recognition and uptake of these lipoproteins via the low density lipoprotein (LDL) receptor, the LDL receptor related protein (LRP), the apoE receptor 2, the very low density lipoprotein (VLDL) receptor and megalin [3].

The largest production of apoE is found in the liver, followed by the brain. In the central nervous system (CNS), apoE is predominantly synthesised and secreted by astrocytes and microglia and may enter into neurons through LDL, LRP or VLDL receptors. Recent studies have also shown apoE synthesis in neurons [3]. Historically it is known that apoE synthesis in the CNS is increased dramatically after injury [4]. However the mechanisms governing apoE synthesis and secretion in brain are not fully understood, although a number of factors have been described. ApoE secretion from human primary astrocytes can be reduced by the combination of interleukin 1 α and β and interferon γ [5]. Estradiol has been shown to increase apoE mRNA levels in rat brain *in vivo* and in astrocytes and mixed glia cultures *in vitro* [6]. ApoE secretion in rat primary astrocytes can also be modulated by neurotransmitter receptors that regulate intracellular cAMP and PKC activity [7]. The understanding of how apoE production is regulated in the CNS remains an important issue that may provide clues about apoE function in normal and AD brain.

Structure and apoE polymorphism

Human apoE is a 34 kDa, 299 amino acid apolipoprotein. Structural studies revealed that it is comprised of two independent folded domains that are responsible for different functions of the protein (Fig. 1). A 22 kDa N-terminal domain (residues 1-191) that contains the LDL receptor binding region (residues 136-150) and adopts a water soluble conformation resistant to denaturation, and a 10 kDa C-terminal domain (residues 216-299) with a high lipid binding activity and responsible for apoE-self association in the absence of lipid. The X-ray crystal structure of the N-terminal domain in a lipid free state reveals a globular conformation of four antiparallel α -helices connected by short loops. These α -helices are amphipathic and have their

Fig. 1 Schematic representation of ApoE structure. The N-terminal domain (1-191) is based in the X-ray crystal structure in a lipid free state. It reveals a globular conformation of four antiparallel α -helix connected by short loops. The C-terminal domain is represented as helical segments in model based on secondary structure predictions. Both domains are connected by a protease sensitive loop. **Fig. 1A** represents the apoE3 isoform structure. **Fig. 1B** represents the apoE4 structure in which the amino acid substitution results in changes in the structure with the formation of a salt-bridge between an arginine in position 61 and glutamic acid in 255. (We thank Dr. Angel Gutierrez for his help with the apoE structure figure; Dr. Gutierrez adress is Center for Biotechnology, Dept. of Biosciences, Karolinska Institute).

Table. 1 ApoE polymorphism. The human apoE gene shows polymorphism, with three different alleles, termed $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. ApoE3 is the most common isoform in the general population. The aminoacid changes in position 112 or 158 confer different lipid binding properties and are responsible for the association of each isoform to different diseases.

	<i>ApoE2</i>	<i>ApoE3</i>	<i>ApoE4</i>
Position 112	Cys	Cys	<u>Arg</u>
Position 158	<u>Cys</u>	Arg	Arg
Lipid Preference	HDL	HDL	<u>VLDL</u>
Carrier population	7-8%	77-78%	14-15%
Associated disease	type III hyperlipoproteinemia		Alzheimer's Disease Lewy Body Disease Frontal Lobe Dementia

hydrophobic faces orientated to the centre of the bundle. It is proposed that the four-helix bundle possesses a conformational flexibility that allows structural changes to open the hydrophobic core to interact with the lipid [4]. The structure of the C-terminal domain is not yet determined, although has been recently crystallised [8]. Predictions of the C-terminal secondary structure indicate that is mostly α -helical. Interactions between different regions of the two domains play a critical role in apoE activity and structural changes in one domain are known to affect the properties of the other (Fig. 1).

The human apoE gene shows polymorphism, with three different alleles, termed $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, that give rise to six different phenotypes (E2/2, E2/3, E2/4, E3/3, E3/4 and E4/4). ApoE3 is the most common isoform (77-78%) in the general population, while apoE2 is found in 7-8% and apoE4 in 14-16% of individuals. The difference between isoforms is one single amino acid substitution in position 112 or 158, where apoE3 contains cysteine and arginine, respectively, and apoE2 contains cysteine and apoE4 arginine in both positions. These substitutions affect the three-dimensional structure and the lipid binding properties between isoforms (see Fig. 1 and Table 1). In apoE4, the amino acid substitutions result in changed structure with the formation of a salt-bridge between an arginine in position 61 and a glutamic acid in 255 that causes this isoform to bind

preferentially to very low density lipoproteins (VLDL). ApoE3 and apoE2 bind preferentially high-density lipoproteins (HDL) [4]. ApoE2 binds defectively to the LDL receptor and carriers have high risk to develop type III hyperlipoproteinemia. ApoE4 carriers have an increased risk of cardiovascular disease, and of several neuro-degenerative disorders including AD, Lewy Body Disease and frontal lobe dementia [9].

Association of the apolipoprotein E polymorphism and AD

In 1991, family studies demonstrated linkage of AD with markers on chromosome 19 [10]. Two years later, apoE was implicated in late-onset familial and sporadic AD [11]. ApoE4 carriers were found to have a higher risk for AD and also an early onset for the disease. On the other hand, the presence of E2 had a protective effect, by delaying the onset and decreasing the risk for AD. This discovery has been repeatedly confirmed by epidemiological and genetic studies including several recent meta-analyses with a large number of study subjects [12]. The odds ratios for AD were found to be 3.2 for E3/E4 and 14.9 for E4/E4 as compared with E3/3 subjects. ApoE4/4 carriers had AD odds ratios of 11.6 for late-onset cases and 61.4 for early-onset cases. In contrast, E2/2 and E2/3 had odds ratios for

AD of 0.6. Therefore, it is estimated that 60% of late-onset and 92% of early onset AD can be accounted for by the presence of apoE4 [12]. This large incidence is in contrast with that of the rare deterministic APP, PS1 and PS2 mutations which are calculated to represent less than 1% of the total number of AD cases [2].

Beside the classical $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ apoE polymorphism, a number of other polymorphisms in the regulatory region of the apoE gene have been found. Of these, the -491 A/T variant has been reported to increase the risk of late-onset of AD by increasing the level of apoE expression [13]. Lambert et al [14] reported a G→T mutation located within a putative regulatory element of the apoE promoter that modulated the influence of the $\epsilon 4$ allele on AD, presumably by favouring its relative expression. These recent reports suggest that other genetic factors within the apoE locus itself may also modulate the risk for AD.

Current hypotheses

The association of the apoE polymorphism with several neurodegenerative diseases has rapidly stimulated efforts for understanding the neurobiology of apoE. Although there is some information about the normal function of apoE in CNS, this is still not fully understood. Accumulating data suggests that apoE has multiple functions in brain and also that different apoE isoforms possess specific properties. The relevance of these functions and properties for AD pathology has resulted in several hypotheses to explain the association of the apoE polymorphism and disease.

ApoE and A β deposition

The conversion of soluble A β to an aggregated insoluble form with a β -sheet conformation is known to play a central role in NP formation in AD. Mutations in the APP gene or in the PS1 and PS2 genes all give rise to an increased A β production that is thought to underlie the pathogenesis of familial forms of AD [1]. The first evidence indicating a relationship between apoE and A β deposition came from immunoreactivity studies on AD brain [15]. Such data lead to the hypothesis that

apoE could bind A β , and thereby act as a “pathological chaperone”, to reduce the solubility and stabilise the β -pleated structure of amyloid fibrils [16]. Further studies have focused on the influence of the apoE genotype on amyloid deposition. Several groups found that E4 patients have increased numbers of NPs as compared with E3 carriers [1]. The exact reason for this correlation remains unclear. The existence of apoE-A β complexes has been demonstrated *in vitro* [17] and also in AD brain supernatants [18]. However, it remains to be elucidated if apoE4, and not E3 or E2, has an active role in facilitating A β aggregation and/or deposition. In contrast, apoE3 and E2 but not apoE4 may have a protective role by inhibiting A β aggregation or favouring A β clearance.

It has been shown that apoE4, in a lipid free form, has a greater avidity for A β than does apoE3 [19]. Using mice that lack one or both apoE alleles crossed with mice over-expressing the human APP^{V717F} mutant, it was found that apoE dosage determines A β deposition, which was completely abolished in apoE knock-out mice [20]. These data suggest that apoE is an active cofactor in plaque formation. In contrast, it has also been shown that apoE3 and E2 bind more rapidly to A β when associated with lipoproteins [21], and that APP^{V717F} mice bred onto apoE3 and E4 transgenics expressing human apoE in astrocytes, showed markedly reduced A β deposition [22]. These latter data suggest that apoE may be involved in A β clearance.

During the last year a number of new studies performed in transgenic mice have tried to reconcile these apparently contradictory theories. By following the natural levels of A β and apoE in a human APP mutant transgenic mice, Kuo et al [23] reported that brain levels of A β and apoE increased in parallel with age at the expense of a decrease in A β plasma levels. The authors proposed that elevations of brain apoE levels during aging induce a deregulation of A β clearance and signal the start of A β sequestration.

This idea is in agreement with the fact that variant polymorphisms in the apoE gene increase the risk of AD by increasing apoE levels [13, 14], and further support the idea that in addition to type, the amount of apoE is also an important determinant for AD.

ApoE and neurofibrillary tangles

The other major histopathological hallmark of AD is the intraneuronal NFT made up of filamentous aggregates, known as paired helical filaments (PHFs). PHFs are in turn composed of abnormally hyperphosphorylated insoluble forms of the microtubuli-stabilizing protein, *tau* [24]. The formation of PHF-*tau* is accompanied by a gradual loss of microtubules that are otherwise stabilized by *tau*. This results in disorganisation and disintegration of the neuronal cytoskeleton and ultimately leads to cell death [24].

The hypothesis that apoE isoforms may influence differently *tau* pathology derives from *in vitro* studies demonstrating that the apoE2 and E3 isoforms bind more readily to *tau*, as compared to apoE4, and thereby prevent abnormal *tau* hyperphosphorylation and destabilisation of the neuronal cytoskeleton [25]. Several neuropathology studies have found either a correlation or lack of correlation between apoE4 and NFT. Differences in the subjects studied (such as diagnosis criteria, severity of the disease, etc) could account for these inconsistent observations. In support of the hypothesis that the apoE genotype may influence NFT formation, it has been shown that apoE4 decreases neuronal extension and branching and induces microtubule collapse *in vitro* [26]. In addition, transgenic mice studies have shown that both apoE deficiency [27] and human apoE4 expression in neurons [28] results in *tau* hyperphosphorylation. However, such direct molecular interactions between the apoE and *tau* molecules would require that both meet in the same cytosolic compartment. The question of how apoE accesses the neuronal cytoskeleton has been a major criticism against this hypothesis. Although low levels of neuronal expression of apoE have been shown, it remains puzzling as to how the apoE protein should reach the cytosol, since the normal signal peptide within the apoE gene would direct newly synthesised protein to secretory pathways. In cells expressing the LDL-receptor, it was found that apoE from CSF was taken up and then remained in a vesicular compartment unless *tau* was also expressed. In this case, apoE3 appeared to redistribute while apoE4 did not [29]. In addition, a recent study in neuro-2a cells has shown that apoE does not escape from the

secretory pathway to the cytosol and also that direct expression of apoE in the cytosol is neurotoxic [30]. An alternative mechanism for apoE effects on *tau* phosphorylation is that the molecule modulates cellular signalling pathways involving *tau* kinases and phosphatases. ApoE effects on signal transduction pathways and their importance in AD neuropathology modulation are reviewed below.

ApoE and signalling

There is growing evidence that apoE might be a ligand that activates signal transduction mechanisms some of which are relevant to AD (Fig. 2). For example, apoE was shown to mediate changes in neuronal calcium flux [31] and thereby alter *tau* phosphorylation [32]. In neurons, apoE isoforms differentially influence a P-type like calcium channel causing different increases in free intracellular calcium (Fig. 2). These effects were amplified in the presence of A β but not when using its reversed sequence [31]. More direct evidence that apoE affects signalling cascades involved in *tau* phosphorylation is suggested by a study showing site-specific dephosphorylation of the N-terminus of *tau* in apoE-knockout mice following muscarinic receptor stimulation [27]. This N-terminus region of *tau* is considered to play a major role in the formation of PHF [33].

Signalling events transduced by apoE also involve protein kinase C (PKC). There is a strong consensus from post-mortem studies that PKC regulation is disrupted in AD brain. Moreover, cell culture studies showing that PKC activation results in an enhanced production of non-amyloidogenic N-terminal soluble APP (APPs) derivatives and in some cases a concomitant decrease in A β production have led to the idea that PKC deregulation may contribute to aberrant APP metabolism in AD. We recently demonstrated that apoE3 and apoE4, as well as A β and complexes of A β / apoE3 or E4, can stimulate the translocation of PKC- α thereby affecting APP processing [34]. Interestingly, PKC is known to phosphorylate and inactivate glycogen synthase kinase-3 β (GSK-3 β) (Fig. 2), a proline directed kinase that has been implicated in the abnormal phosphorylation of AD *tau* [29]. GSK-3 β has also been shown to co-

Fig. 2 A model of ApoE effects on signalling pathways relevant for AD.

localise with hyperphosphorylated *tau* in AD degenerating neurones [35]. Recently, Gibb *et al.* [36] reported differential effects of apoE variants on the GSK-3 β mediated phosphorylation of *tau*, as identified by phosphopeptide mapping. Besides its

role in *tau* hyperphosphorylation, a number of other mechanisms have been suggested to explain the role for GSK-3 β in AD. GSK-3 β can bind PS1 [37], whereas the GSK-3 β substrate, β -catenin, also has been found to interact with PS1. Inhibition of GSK-

β activity leads to the accumulation of b-catenin and its translocation into the nucleus to promote transcription [38] (Fig. 2). PS1 mutations can affect β -catenin stability and subcellular localisation [39]. Therefore differential effects of variant apoE isoforms on GSK-3 β may be of great relevance for AD pathogenesis.

Another recent study showed that apoE4 but not apoE3 has the ability to stimulate transcriptional activity of the cAMP response element binding protein (CREB) in primary neurons as a consequence of activating the extracellular signal-regulated kinase (ERK) pathway [40]. CREB modulates the activity of a wide range of transcription factors and apoE4 has indeed been shown to upregulate expression of both c-fos and the anti-apoptotic factor Bcl-2 [40] (Fig. 2). Therefore it is strongly indicated that apoE isoforms differently induce the expression of genes for signalling intermediates involved in maintenance of cell survival.

Toxic / Antioxidant duality of apoE

Another line of investigation proposes that the mechanism of apoE isoform association to AD includes differential effects on neurotoxicity. ApoE toxicity was first shown using synthetic peptides of apoE and chick sympathetic neurons in culture [41]. Subsequently, it was described that apoE toxicity in rat hippocampal neurons occurs through a member of the LDL receptor family and a proteoglycan complex [42]. Post-mortem studies have shown that protein modification by 4-hydroxynonenal [43] and higher oxidative insults [44] in AD are associated with inheritance of the apoE4 allele. In contrast, it has been reported that full-length apoE has isoform specific effects on promoting cell survival and neurite outgrowth [26].

This controversy is also extended to the apoE contribution to A β induced neurotoxicity, with apoE having been shown to both decrease and to increase the toxic effects of A β [45, 46]. Miyata and Smith [47] reported that physiological concentrations of apoE purified from human apoE transfected cells have isoform-specific antioxidant activities and protect against A β induced toxicity in rat neuronal B12 cells. Higher apoE concentrations resulted in enhanced cell death. Recent studies are in agreement with the idea that apoE3 has a better antioxidant

ability than E4 [48].

In vivo studies using transgenic mice that express human apoE3, apoE4 or both, demonstrated that apoE3/E3 animals were more protected than apoE3/4 against age-induced and excitotoxin-induced neurodegeneration and that apoE4/4 showed no protection [49]. These data confirm the idea that apoE4 is not only less neuroprotective than apoE3 but also acts as a dominant negative factor that interferes with the beneficial function of apoE3.

The mechanisms behind this toxic / antioxidant duality of apoE remain unknown. ApoE4 may induce neuronal death by an apoptotic mechanism mediated via the LDL-receptor [50] but other mechanisms distinct from classical necrosis or apoptosis and independent of LDL receptors have been also described [51]. We recently demonstrated that recombinant apoE isoforms at physiological concentrations are toxic to human neuroblastoma cells and also potentiate the deleterious effects of A β . Both these toxicities were reversed in the presence of exogenous lipid in the form of rabbit β -VLDL [52]. These data suggest that apoE status or the conformation of apoE-containing lipoproteins might be an important determinant of apoE neurotoxicity.

One reductionist model has lead to the hypothesis that the 22 KDa apoE proteolytic fragment is responsible for apoE toxicity [51]. In this context, it is possible that apoE will be more resistant to proteolysis when associated with other lipoproteins or that compositional and/or structural differences of lipoprotein containing apoE particles may be important for neurodegeneration. When taking into account the fact that each apoE isoform possesses structurally defined abilities in lipid binding, it has to be also considered that the composition of lipoprotein particles may differ with apoE genotype.

Understanding the factors that govern the neurotoxic effects of apoE and its survival-promoting effects, as well as the positive or negative modulation of A β toxicity by apoE remains crucial for elucidating the role of apoE in neurodegenerative processes.

ApoE, lipid metabolism and synaptic repair

The major function of apoE is to redistribute lipids and participate in cholesterol homeostasis [4]. The structural differences between different apoE isoforms have major consequences for the ability of

variant apoE isoforms to carry lipids. ApoE mediated effluxes of cholesterol and phosphatidylcholine from both neurons and astrocytes have been shown to be isoform dependent. ApoE2 was the most and apoE4 the less efficient at inducing cholesterol secretion in a number of cellular models [53]. These quantitative and qualitative differences may have special relevance for some diseases, including hypercholesterolemia for E2 carriers and AD for E4 carriers. Cholesterol levels are reduced in AD brains and growing evidence indicates that cholesterol itself is involved in AD pathogenesis. Recent epidemiological studies show a strong reduction in the incidence of Alzheimer's disease in patients treated with cholesterol-lowering statins [54]. Cholesterol modulates the cleavage of the APP protein and production of A β and treatment with the cholesterol-lowering drug simvastatin reduces A β levels both *in vivo* and *in vitro* [55]. On the other hand, A β modulates the synthesis and the distribution of cholesterol in neurons [56]. In addition, a recent report has demonstrated that cholesterol deficiency induced by inhibition of cholesterol biosynthesis in cultured neurons results in *tau* hyperphosphorylation [57]. Lipid redistribution and cholesterol homeostasis have also special relevance in the nervous system during development and aging, where apoE has been shown to participate in processes of growth, remodelling and regeneration. Although neuronal regeneration in brain is very limited, some synaptogenesis has been shown in pre-synaptic axons as a compensatory mechanism of input loss [58]. In AD there is extensive synaptic and neuronal loss in the limbic system and neocortex. Data from *in vitro* experiments suggests a different participation of variant apoE isoforms in repair processes. Treatment of neuronal cultures with reconstituted apoE3 enhances neurite outgrowth, whereas apoE4 treatment decreases synaptic plasticity [59]. In addition, apoE knockout and apoE4, but not E3, transgenic mice show an age-dependent disruption of synaptic organization [60, 61]. These apoE isoform differences have been also reported in post-mortem studies. ApoE4 carriers show a poor compensation of neuronal loss in different brain regions, whereas non-E4 carriers exhibit marked regenerative changes in the same areas [58]. Such data suggest that apoE4 may

Fig. 3 ApoE4 negatively influences many aspects of AD.

compromise the synaptic plasticity mechanisms provided by other apoE isoforms.

ApoE and cholinergic dysfunction

Cholinergic signal transduction is well known to be impaired in AD. Acetylcholine (ACh) muscarinic agonist stimulation of phosphoinositide (PI) hydrolysis is reported to be approximately 50% lower in the prefrontal cortex of AD brains as compared to controls [62]. Also, AD brain regions with extensive neuritic plaque accumulation show a disrupted muscarinic M1 receptor-G-protein coupling [63]. It has also been reported that there is an association between inheritance of apoE4 and the extent of cholinergic dysfunction in AD. ApoE4 carriers with AD show a greater deficit in cholinesterase activity in the hippocampus and cortex, whereas the total number of cholinergic neurons is reduced to a greater extent in apoE4-AD subjects [64, 65].

The association between cholinergic dysfunction and apoE4 was also found to have an impact on responses to therapies based on the enhancement of cholinergic function. ApoE4

carriers are reported to have poorer responses to acetylcholinesterase inhibitors, as compared to non-apoE4 subjects [65]. An impaired lipid delivery, especially of phosphatidylcholine and cholesterol, to the cholinergic system has been proposed as one mechanism for this association [64, 65]. However, apoE knockout and apoE4 mice don't show cholinergic deficits [66]. Also there are no significant differences in muscarinic receptor levels between AD patients with different apoE genotypes [65]. In a recent report, we demonstrated that variant apoE isoforms have different effects on ACh muscarinic receptor stimulated signalling *in vitro*. ApoE4 impaired carbachol stimulated PI hydrolysis, whereas apoE3 alone was without effect and could also protect against A β (1-42)-mediated disruption. Both apoE4- and A β (1-42)- induced impairments were prevented by estrogen by a mechanism likely to involve antioxidant effects and phosphatidylinositol-3-kinase activation [67]. A direct negative influence of apoE4 on cholinergic signalling may participate in the lower effectiveness of cholinergic replacement treatments reported for apoE4-AD patients.

Conclusions

Genetic and epidemiological studies demonstrate that apoE4 is the most important known risk factor for AD. In addition, apoE is the only molecule that has been associated with all the biochemical disturbances characteristic of the disease: A β deposition, tangle formation, oxidative stress, neurodegeneration, lipid dysfunction, synaptic plasticity loss and cholinergic dysfunction. In all cases, the presence of apoE4 has been shown to exacerbate these disturbances, in contrast to the protection seen with others apoE isoforms (Fig. 3). Considering that a fully accepted hypothesis has not yet been proposed to explain the temporal sequence of molecular and cellular events responsible for AD then understanding the omnipresence of apoE in this complex pathology may be the key for finding shared common pathways that integrate different hypotheses. This may offer new perspectives and strategies for intervention in the natural course of Alzheimer's disease or, at least, help slow its progression.

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