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Review

APOE and neuroenergetics: an emerging paradigm in Alzheimer's disease

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ABSTRACT

APOE is the major known genetic risk factor for late-onset Alzheimer's disease. Though relationships between *APOE*-encoded apolipoprotein E and β-amyloid are increasingly well described, mounting evidence supports wide-ranging effects of *APOE* on the brain. Specifically, *APOE* appears to affect brain network activity and closely related neuroenergetic functions that might be involved in vulnerability to neurodegenerative pathophysiology. These effects highlight the salience of further investigation into the diverse influences of *APOE*. Therefore, this article reviews the interplay between *APOE* and neuroenergetics and proposes areas for further investigation. This research might lead to the identification of novel therapeutic targets for the treatment and/or prevention of Alzheimer's disease.

1. Introduction

Despite decades of intense research, the causes of Alzheimer's disease (AD) remain poorly understood and truly effective therapies remain out of reach. AD is expected to become markedly more prevalent over the next half century (Ferri et al., 2005), which further intensifies the need to develop therapies as soon as possible. Since the initial reports linking *APOE* to AD in the early 1990s (Corder et al., 1993; Strittmatter et al., 1993), considerable research has focused on elucidating the mechanisms by which the gene contributes to risk for the disease. Current evidence supports *APOE*-encoded apolipoprotein E (apoE) isoforms differentially modulating β-amyloid aggregation and clearance (Bu, 2009; Holtzman et al., 2012; Kim et al., 2009). Genetically, *APOE* ε4 is associated with dramatically increased risk, *APOE* ε3 is associated with neutral risk, and *APOE* ε2 is associated with decreased risk (Bertram and Tanzi, 2008; Gomez-Isla et al., 1996). *APOE*-related risk is gene–dose dependent: in the United States, when compared with persons homozygous for risk-neutral *APOE* ε3, *APOE* ε4 homozygotes have up to 15 times and *APOE* ε4 heterozygotes up to 4 times the risk for developing AD (Ashford and Mortimer, 2002; Raber et al., 2004). Therefore, ameliorating *APOE* ε4's powerful effects might be a viable strategy to decrease AD incidence—delaying the average age of onset by 5 years could reduce the number of cases by more than 50% and save nearly $300 billion in Medicare spending in coming years (Sperling et al., 2011).

Though findings regarding apoE and its interactions with β-amyloid are essential to the current understanding of AD pathophysiology, it is important to further develop knowledge of the potential for *APOE* to affect brain function in a manner that might precede or be independent of β-amyloid pathology. Notably, apoE has known effects on cholesterol transport, inflammation, neurodevelopment, and synaptic plasticity, and study in these contexts

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clearly represents vital avenues of research. Mitochondrial energy metabolism and cellular bioenergetics in the brain (i.e., neuroenergetics) have also begun to be linked to the genetic risk conferred by *APOE*. Therefore, the intent of this article is to review the brain imaging background and potential cellular and molecular mechanisms for this emerging avenue of approach, with the hope that this rapidly evolving knowledge might stimulate innovative research approaches and the identification of tractable therapeutic targets for treatment and/or prevention of disease.

2. Metabolic brain imaging in Alzheimer's disease

Long-standing efforts have focused on the relevance of neuroenergetics in AD both as a mediator of β-amyloid-induced changes and as an independent driver (Reddy and Beal, 2008; Smith et al., 2002; Swerdlow et al., 2010; Yao et al., 2011). The energetic needs of the human brain are remarkable; despite comprising only 2% of gross body mass, the brain accounts for 20% of the body's glucose and oxygen consumption (Jolivet et al., 2009). The provision of energy to the synapse is vital for the signaling function of neurons. Adenosine triphosphate (ATP) can be generated to meet this need primarily via the metabolism of glucose by glycolysis followed by the tricarboxylic acid cycle and oxidative phosphorylation, which is the most efficient method ($\geq$36 net ATP/glucose), or by glycolysis without subsequent oxidative phosphorylation which is faster yet relatively inefficient (2 net ATP/glucose). Despite the limited ATP yield of glycolysis without subsequent oxidative phosphorylation, the temporal dynamics of synaptic signaling make it an important source of energy because of its relative speed. Functional brain imaging has provided a wealth of information on the alterations in neuroenergetics and brain network activity that exist in AD. Brain energy metabolism is most often studied in human subjects by fluorodeoxyglucose (^{18}F) positron emission tomography (FDG PET), which results in the calculation of the cerebral metabolic rate for glucose (CMRgl) for each region of interest. Early FDG PET studies of AD patients found progressive reductions in measurements of CMRgl in the parietal, temporal, and frontal association cortices (Friedland et al., 1985). FDG PET studies of subjects with mild cognitive impairment demonstrate similar reductions (Boyle et al., 2006), and subjects who ultimately convert to AD show specific reductions in the prefrontal cortex and progressive decrements in posterior cingulate cortex (PCC; Drzezga et al., 2003, 2005). The PCC has been consistently noted as a region of particular significance in the metabolic alterations in AD, because it shows very early and comparatively large reductions in CMRgl (Minoshima et al., 1994) and sits at the convergence point of multiple metabolic covariance networks (Salmon et al., 2009). PCC CMRgl reductions in AD patients are thought to represent true changes in glucose metabolism and are not simply the result of local disease-related atrophy (Chételat et al., 2008; Ibáñez et al., 1998). In this context, CMRgl reductions have been interpreted as an indicator of altered synaptic function and energy metabolism, possibly as a consequence of deafferentiation (Chételat et al., 2009; Villain et al., 2008), although another local process (e.g., a primary energy metabolism defect) has not been ruled out. Via its functional neuroanatomy, the PCC is a key integration node between the medial temporal lobe and medial prefrontal subsystems in the default mode network (DMN), a brain system that is active when subjects are engaged in internal cognition and unengaged with the external world (Buckner et al., 2008; Raichle et al., 2001). Certain regions involved in the DMN are key sites of β-amyloid deposition and AD-related atrophy (Buckner et al., 2005), possibly because of conducive metabolic conditions and the linkages between synaptic activity and β-amyloid metabolism (Bero et al., 2011; Cirrito et al., 2005, 2008). Therefore, the PCC might have a particular and unique vulnerability to perturbations of energy metabolism in AD and AD risk.

3. Metabolic brain imaging and *APOE* in older populations

The use of brain imaging to investigate *APOE*'s effects is rooted in the idea of using *APOE*-related changes in CMRgl as an endophenotype—a quantitative, genetically-based biomarker associated with disease risk (Reiman, 2007). Thus, we have proposed CMRgl as an end point in the evaluation of AD treatments and/or preventive therapies, with the underlying assertion being that region-specific CMRgl alterations correlate with disease risk (Reiman et al., 2001), perhaps as a measure of cognitive reserve (Cohen et al., 2009), such that elevated basal energy metabolism might enhance ability to resist pathologic insult (Stranahan and Mattson, 2012), and/or represent an early manifestation of a related parallel pathogenic process. While not all *APOE* ε4 carriers will develop AD (likely reflecting additional covariates underlying disease processes) *APOE* genotype strongly correlates with overall AD risk as well as age of symptomatic onset. We and others have used *APOE* ε4 gene dose to detect and track the brain and cognitive changes associated with the 3 levels of genetic risk for AD. Shortly after the initial reports linking *APOE* to AD, we used FDG PET to compare CMRgl in cognitively normal late-middle age (50–65 years old) *APOE* ε4 homozygotes and noncarrier controls. *APOE* ε4 homozygotes displayed significant reductions in CMRgl in the same parietal, temporal, and prefrontal regions demonstrating CMRgl reductions in probable AD patients (Reiman et al., 1996). Notably, PCC displayed the largest and most significant deficit in CMRgl. In follow-up studies, cognitively normal middle-aged *APOE* ε4 heterozygotes showed similar regional CMRgl reductions and also exhibited longitudinal (2-year) declines in CMRgl (Reiman et al., 2001). Further FDG PET study of cognitively normal middle-aged subjects identified a gene–dose effect in *APOE* (i.e., *APOE* ε4 homozygotes exhibited the lowest values and noncarriers exhibited the highest values, with ε4 heterozygotes falling between these extremes) on CMRgl in the same AD-related brain regions identified in previous FDG PET studies (Reiman et al., 2005). Additionally, using a genome-wide association study we have identified in *GAB2* a common neutral, less common protective, and rare neutral haplotype associated with AD risk in *APOE* ε4 carriers (Reiman et al., 2007). In cognitively normal late-middle age *APOE* ε4 carriers, the putatively protective *GAB2* haplotype was associated with elevated CMRgl (in comparison with both *APOE* ε4 carriers without the protective haplotype and *APOE* ε4 noncarriers with the protective haplotype), again in regions that overlap those previously found in AD patients and *APOE* ε4 carriers (Liang et al., 2011). Though the cellular physiology underlying this association is not well-established, studies center on the role of the *GAB2*-encoded Gab2 protein as an activator of the phosphatidyl inositol kinase pathway.

4. Brain imaging and *APOE* in young adults

In addition to studies of middle- and late-middle age individuals, we have used FDG PET to study even earlier effects of *APOE* ε4 on brain functional measures. In a study of cognitively normal subjects 20–39 years old, *APOE* ε4 carriers exhibited significantly decreased CMRgl in the PCC and other cortical regions associated with metabolic defects in older *APOE* ε4 carriers and AD patients, in this case several decades before the potential onset of dementia, and also several decades before any apparent pathology (Reiman et al., 2004). Our further studies investigating functional mitochondrial activity via cytochrome oxidase histochemistry, which measures the functional enzymatic activity of Complex IV of the electron transport chain (ETC), in young-adult *APOE* ε4 carriers

discovered a mitochondrial activity deficit in the PCC, specifically localized to the superficial layers (I and II) of the cortical lamina (Valla et al., 2010). This result mirrored our earlier study of AD patients, who showed superficial laminar metabolic deficits across the neocortex, and most significantly in the PCC (Valla et al., 2001, 2007). These superficial layers are rich in the dendritic tufts of deeper neurons (e.g., layer III pyramidal), and these reductions might relate to synaptic declines or localized metabolic dysfunction. These findings indicate that functional mitochondrial changes might be an early indicator of AD-related risk and physiological change that is preferentially manifest in *APOE* ε4 carriers (summarized in Fig. 1).

Though studies in older populations display mixed results likely because of methodological differences (Trachtenberg et al., 2012c), fMRI studies of 20–35-year-old *APOE* ε4 carriers have found that the DMN exhibits decreased deactivation during memory retrieval tasks in *APOE* ε4 carriers, but displays increased coactivation at rest (Dennis et al., 2010; Filbey et al., 2006; Filippini et al., 2009). Similarly, $H_2{}^{15}O$ PET studies have indicated alterations in at-rest and task-activated cerebral blood flow in similarly-young *APOE* ε4 carriers (Scarmeas et al., 2003, 2005). Interestingly, diffusion tensor imaging has revealed that *APOE* modulates white matter integrity in the young-adult brain, with *APOE* ε4 carriers displaying reduced fractional anisotropy, which might be considered a marker of pathology/vulnerability (Heise et al., 2011). Additionally, a recent fMRI study identified that *APOE* ε2 carriers and *APOE* ε4 carriers both display increased task-related activation of the DMN in comparison with *APOE* ε3 carriers (Trachtenberg et al., 2012a), in addition to differences in resting functional architecture (Trachtenberg et al., 2012b). Unfortunately, the effects of *APOE* ε2 are not frequently studied; the inherent difficulties in populating cohorts for human subject studies might be exacerbated by the rareness (<10%) of *APOE* ε2 in the population and its association with decreased risk for AD. Thus, how *APOE* ε2 effects carry over to FDG PET studies of metabolic alterations remain unknown.

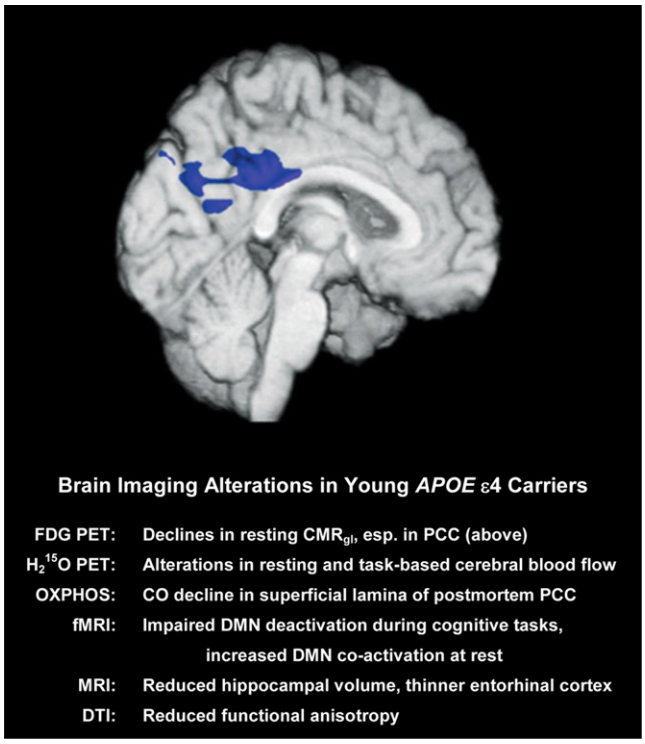

Fig. 1. Medial view localizing abnormally low CMR_{gl} (blue) in the PCC in young adult carriers of the *APOE* ε4 allele, and a summary of brain imaging results thus far reported in similarly-aged young adults and children (citations in text). Widespread changes in neuroenergetics and brain structure point to a neurodevelopmental role for *APOE* and early interference by the *APOE* ε4 allele, but this is yet to be confirmed. Abbreviations: CMR_{gl}, cerebral metabolic rate for glucose; CO, cytochrome oxidase; DMN, default mode network; DTI, diffusion tensor imaging; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; OXPHOS, oxidative phosphorylation; PCC, posterior cingulate cortex; PET, positron emission tomography.

5. Limitations and future directions of metabolic brain imaging

Importantly, both FDG PET and cytochrome oxidase studies have an inherent limitation in not being able to identify with certainty whether neurons or glial cells (particularly astrocytes) are the cellular source of the metabolic signal. Though the brain contains different cell types with different bioenergetic profiles, the compartmentalization of these bioenergetic processes has often been ignored, in part because of the limited resolution of brain imaging. For example, the astrocyte-neuron lactate shuttle hypothesis proposes that astrocytes are largely glycolytic and, under high energy demand, might provide vital energetic support (lactate) to neurons which rely more heavily on oxidative phosphorylation (Pellerin et al., 2007) and can produce ATP from reducing equivalents derived from such provided tricarboxylic acid cycle substrates. The cytochrome oxidase histochemistry signal is thought to be related primarily to neuronal oxidative metabolism (Wong-Riley, 1989); the FDG PET signal is more heavily debated, but it is hypothesized that astrocytes play the key role (Barros et al., 2005). More research is needed to address the relative roles of astrocytes and neurons in neuroenergetic processes, and the respective effects on disease risk. Additionally, metabolic signal alterations might be related to other factors, including the density of cells or synapses. Notably, mice expressing human apoE4 display decreased dendritic arborization and spine density (Dumanis et al., 2009; Ji et al., 2003). Though further research in human tissue is needed to clarify these issues, a magnetic resonance imaging (MRI) study of children shows an interesting association between *APOE* genotype and cortical thickness, with *APOE* ε4 carriers having thinner entorhinal cortices (Shaw et al., 2007). Additional MRI work in young adults demonstrates *APOE* ε4 carriers having smaller hippocampal volumes than *APOE* ε2 carriers (Alexopoulos et al., 2011), but this effect was not found in a study comparing *APOE* ε4 carriers with noncarriers (Richter-Schmidinger et al., 2011).

Adding another potential confound to FDG PET studies, recent reports using a novel brain imaging approach in young adults showed that aerobic glycolysis, in this case defined as glucose utilization in excess of that used for oxidative phosphorylation despite sufficient oxygen, is differentially present in the medial and lateral parietal and prefrontal cortices, which are also preferentially vulnerable to β-amyloid pathology (Vaishnavi et al., 2010; Vlassenko et al., 2010). Glucose that is not fully metabolized via oxidative phosphorylation might be converted to lactate, an important and oft-debated brain fuel (Nehlig and Coles, 2007), or shunted to the pentose phosphate pathway. Previous studies have viewed FDG PET largely as a marker of cell-autonomous energy metabolism and ignored the complication of glycolysis followed (or not followed) by oxidative phosphorylation; detailed examination of the metabolic fate of glucose might provide even greater insight. FDG PET allows for the measurement of only the first step of the metabolism of glucose (phosphorylation to glucose-6-phosphate by hexokinase) and cannot by itself be used to identify the subsequent metabolic fate of glucose. Further research is needed to determine the relative importance of each use of glucose in the brain and how it might be relevant to disease risk, especially considering the

alterations in glucose uptake apparent in both young and aged *APOE* ε4 carriers and the overlap of these regions with increased aerobic glycolysis and β-amyloid pathology.

6. Cellular functions of apoE in the brain

Though brain imaging can provide a great deal of insight to the effects of *APOE*, an understanding of cellular function and mechanisms conferring risk is essential for any effective therapeutic development. The primary function of apoE in the brain is to traffic cholesterol and other lipids. Though it is expressed in several peripheral tissues, apoE is most highly expressed in the liver and brain (Elshourbagy et al., 1985). In the brain, apoE is the primary apolipoprotein that associates with high-density lipoprotein-like lipoproteins (Pitas et al., 1987b), the only lipoprotein assembly, meaning that apoE plays a vital role in maintaining neural functions dependent on cholesterol, in addition to other roles. Indeed, a significant body of work supports apoE involvement in synaptogenesis (Mauch et al., 2001), neurite outgrowth (Bellosta et al., 1995; Holtzman et al., 1995; Nathan et al., 1994, 1995, 2002; Qiu et al., 2004), and dendritic arborization (Dumanis et al., 2009; Ji et al., 2003), modulation of synaptic plasticity (Herz and Chen, 2006; Klein et al., 2010; Korwek et al., 2009), neurogenesis (Li et al., 2009; Yang et al., 2011), and neuroinflammation (Bales et al., 2000), often with isoform-specific efficacy.

Under normal conditions astrocytes are the primary adult brain source of apoE, with apoE comprising up to 3% of the protein secreted from these cells (Pitas et al., 1987a); microglia and neurons produce much smaller amounts of apoE (Boyles et al., 1985; Xu et al., 1999). When synthesized, apoE is secreted by astrocytes and loaded further with cholesterol and other lipids via the ATP-binding cassette transporter to form lipoprotein particles before being endocytosed by neurons, primarily via low-density lipoprotein (LDL) receptor and LDL-related protein 1, both members of the LDL receptor family (Bu, 2009). Though it is produced only in low amounts at baseline, neuronal apoE expression can be significantly increased, particularly as a response to injury or stress (Aoki et al., 2003; Boschert et al., 1999; Xu et al., 2006, 2008). Considering the known differences in neuronal processing of apoE (described below), this response might be of particular relevance to neural pathophysiology. In the peripheral circulation, lipid trafficking and metabolism are differentially affected by the structurally-dependent lipid- and ligand-binding abilities of apoE isoforms, evident in the pathophysiology of multiple diseases (Mahley, 1988; Mahley and Rall, 2000). Unfortunately, isoform-specific knowledge of these processes in the brain remains insufficient to draw conclusions on potential disease relationships.

7. ApoE structure and its relevance to disease

Aspects of apoE structure are thought to be a driving force in its role in AD risk. ApoE is a 34 kDa, 299 amino acid glycoprotein with 2 major functional domains: the N-terminal domain exists as a 4 helix bundle and contains the apoE receptor binding region at residues 136–150; the C-terminal domain is highly α-helical and contains the major lipid binding region at residues 244–272 (Aggerbeck et al., 1988; Dong et al., 1994; Wetterau et al., 1988; Wilson et al., 1991). When unbound by lipid, the N-terminal and C-terminal domains are linked by a flexible hinge region consisting approximately of residues 165–215 (Fig. 2; Wetterau et al., 1988; for comprehensive reviews of apoE structure see Hatters et al., 2006a; Zhong and Weisgraber, 2009).

In humans, *APOE* is located on chromosome 19 and encodes 3 common alleles: *APOE* ε2 (protective; frequency approximately 10%), *APOE* ε3 (neutral; approximately 70%), and *APOE* ε4 (risk-associated; approximately 20%) (Mahley et al., 2006). Though the 3 isoforms differ at only 2 amino acid positions—apoE2 has cysteine at residues 112 and 158, apoE3 has cysteine at residue 112 and arginine at residue 158, and apoE4 has arginine at residues 112 and 158 (Weisgraber et al., 1981)—these amino acid changes have a profound effect on the structure of the protein and are therefore thought to play a fundamental role in the association of apoE with AD risk. In particular, apoE4 is much more likely to exhibit a compacting phenomenon known as domain interaction because of the presence of arginine at residue 112 (Xu et al., 2004). The presence of this arginine residue results in the side chain of the arginine at residue 61 (located in the N-terminal domain) interacting with the glutamate at residue 255 (located in the C-terminal domain) via the formation of a salt bridge (Dong and Weisgraber, 1996). Notably, human apoE is the only form of the protein with arginine at residue 61. The arginine side chain is less available in apoE2 and apoE3, making them much less likely to undergo domain interaction. It is thought that domain interaction is responsible for many of apoE4's neurotoxic effects (discussed in part below) and might partially underlie its association with AD. Additionally, apoE4 has a propensity to exist as a molten globule (Morrow et al., 2002) and form soluble aggregates (Hatters et al., 2006b) under physiological conditions, both of which are potentially neurotoxic. Physiologically, the differential influence of apoE4 on AD risk might manifest as a gain of toxic function or a loss (limitation) of normal function when compared with apoE3.

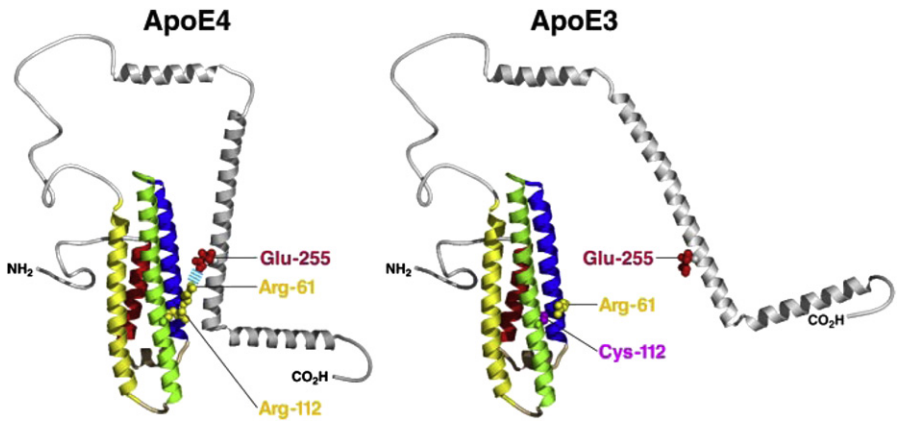

Fig. 2. Structural difference between apolipoprotein E (apoE) 3 and apoE4. Domain interaction prevalent in apoE4 is predicated on the substitution of Arg for Cys at position 112. Abbreviations: Arg, arginine; Cys, cysteine; Glu, glutamate. Reproduced with permission from Zhong and Weisgraber, 2009.

In the case of neural repair, apoE4 likely represents a loss of normal function, because apoE4 is thought to be less effective at these roles (Mahley et al., 2006).

In addition to influences on such functions as synaptic plasticity and neuroinflammation, growing evidence from cell culture, animal model, and pathology studies suggests effects of apoE, most with isoform-specificity, that are linked at the cellular level to dysfunction in neuroenergetics-relevant processes. Therefore, these effects might provide potential mechanisms for the alterations in energy metabolism and synaptic function seen in human brain imaging studies of *APOE* ε4 carriers and might be validated as such given further study in vivo in model systems or in appropriate postmortem tissues. When coupled with the neurodevelopmental effects of *APOE* these processes might serve as "second hits" to alter brain function to increase risk for AD.

8. Mechanisms of apoE cleavage and processing

As previously emphasized, the cellular source of apoE is highly regulated, and neuronal production of apoE appears to be driven by astrocytic signaling mechanisms (Harris et al., 2004b), particularly as a result of neural injury. It has been demonstrated in postmortem human samples that apoE4 undergoes neuron-specific proteolysis (Huang et al., 2001); this dramatic increase in intracellular cleavage of apoE4 compared with apoE3 and apoE2 is thought to be because of apoE4's much greater tendency to exhibit domain interaction. Studies of transgenic mice expressing the human isoform have determined that apoE4 produced in neurons is cleaved by a chymotrypsin-like serine protease termed apoE cleaving enzyme (AECE; Harris et al., 2003). Further, although neurons take up apoE secreted by astrocytes, as demonstrated in transgenic mice, the proteolysis occurs in the neuronal secretory pathway and not in an internalization pathway, indicating cell-source specificity to this potentially toxic event (Brecht et al., 2004). C-terminal segments of apoE4 have been shown to be vital for structural integrity and the protein's ability to alter its conformation (Chroni et al., 2008; Tanaka et al., 2006). Notably, apoE4 cleaved by AECE and missing residues 272–299 (Δ272–299) is capable of translocating into the cytosol to escape the secretory pathway. Reports from Neuro-2a and mouse primary hippocampal neuron cultures show that apoE4 trafficking is impaired throughout the endoplasmic reticulum and Golgi apparatus (Brodbeck et al., 2011). Interestingly, this effect can be eliminated with small-molecule apoE structure correctors that make apoE4's structure more similar to apoE3 and thus decreases domain interaction and subsequent cleavage (Brodbeck et al., 2011). Studies in Neuro-2a mouse neuroblastoma cultures demonstrated that the LDL-receptor binding region (residues 136–150) is required for escape from the secretory pathway, because it is rich in the positively-charged amino acids arginine, lysine, and histidine (Chang et al., 2005).

9. Effects of apoE on cytoskeletal components and intracellular trafficking

ApoE cleavage fragments have been shown to have a number of effects on the cytoskeleton and related intracellular trafficking functions (Fig. 3). In Neuro-2a cells, expressed apoE4 (Δ272–299) has been found to interact with cytoskeletal proteins to form neurofibrillary tangle-like structures containing phosphorylated tau (Huang et al., 2001). Mice expressing high levels of apoE4 (Δ272–299) in neurons display AD-like neurofibrillary tangles and die at 2–4 months. With lower levels of expression the mice display learning and memory deficits at 6–7 months (Harris et al., 2003). Interestingly, neuronal apoE4 (Δ272–299) expression has also been linked to GABAergic interneuron dysfunction and consequential learning and memory deficits mediated by tau (Andrews-Zwilling et al., 2010). Deleterious effects of apoE4 fragments on GABAergic interneurons have also been linked to impaired neurogenesis via tau (Li et al., 2009).

Full-length apoE4 expressed in Neuro-2a cultures acts along with zinc to phosphorylate tau via the extracellular-signal-regulated kinase pathway (Harris et al., 2004a). Additionally, apoE3 seems to be effective at binding the microtubule-binding repeat region of tau, which is responsible for the formation of the paired helical filaments that compose neurofibrillary tangles; apoE4 does not bind this region and thus might allow more aberrant fibrillization (Strittmater et al., 2000). Proper cytoskeletal structure is required for the appropriate distribution and trafficking of mitochondria, with improper distribution having a number of deleterious effects (Detmer and Chan, 2007), including impaired energy

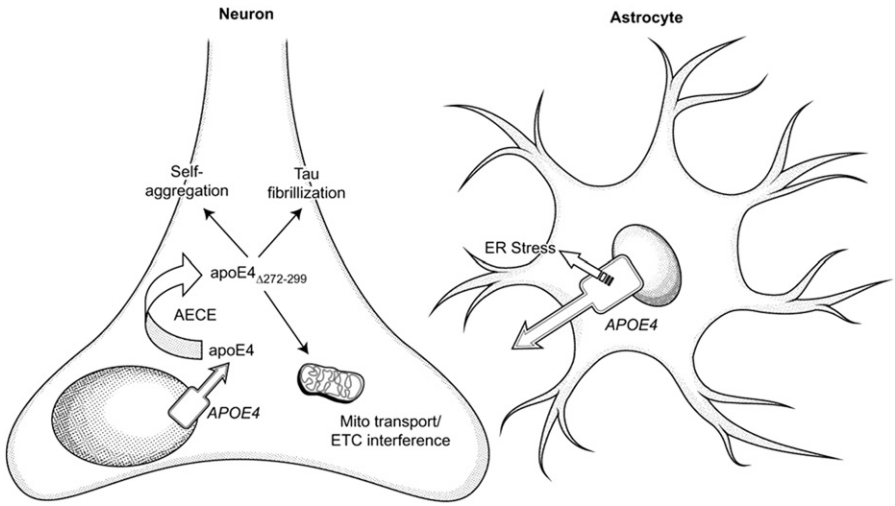

Fig. 3. Summary of the effects of cell type-specific expression and aberrant processing of apolipoprotein E (apoE) 4 in the brain. Astrocyte-expressed apoE is internalized by neurons, but apoE4 expression in astrocytes has been associated with endoplasmic reticulum (ER) stress that might impair astrocyte ability to contribute to brain energy flux. A smaller proportion of brain apoE expression is attributed to neurons: apoE4 expressed in neurons (but not that internalized from astrocytes) is highly susceptible to cleavage by apoE cleaving enzyme (AECE) in the secretory pathway becoming apoE (Δ272–299). ApoE4 cleaved by AECE is capable of escaping the secretory pathway, self-aggregating in the cytosol, increasing the fibrillization of tau, and interfering with mitochondrial (Mito) transport and function. Abbreviation: ETC, electron transport chain.

metabolism. The necessity of effective mitochondrial distribution is intensified in neurons because of their morphology and highly-localized energy use (MacAskill and Kittler, 2010). Therefore, alterations and/or disruptions because of apoE4 fragment interactions with cytoskeletal components might impair the ability to maintain proper energy supply to the synapse, which requires a dynamic population of mitochondria (Li et al., 2004). Overexpression of tau in Neuro-2a cultures has been shown to inhibit mitochondrial transport (Ebneth et al., 1998). Similarly, transgenic mice expressing human apoE4 display impaired axonal transport, with mitochondria accumulating in bulb-like dilations (Tesseur et al., 2000). Interestingly, previous studies of human postmortem tissue and AD mouse models have found axonal swellings containing organelles that appear to precede the formation of AD pathology (Stokin et al., 2005). Additionally, a recent study in differentiated PC12 cells either expressing or incubated with apoE found that apoE4 impairs mitochondrial motility in relation to apoE3 (Chen et al., 2012). This effect was ameliorated by apoE structure correctors. Additionally, microtubule depolymerization is thought to at least partially underlie the deleterious effects of apoE4 on neurite outgrowth (Nathan et al., 1995).

10. ApoE and mitochondrial function

In addition to its deleterious effects on intracellular transport, apoE4 has been shown to have direct effects on mitochondria. In an early study, apoE4 was shown to bind the α and β subunits of the F1 portion of ATP synthase in liver (Mahley et al., 1989). Though direct effects on enzyme function were not assessed in that study, neuronal apoE4 fragments have subsequently been shown to perturb mitochondrial function. In Neuro-2a cultures expressing apoE4 (Δ272–299), apoE4 fragments that escape the secretory pathway can cause mitochondrial dysfunction via an unknown mechanism that requires the lipid-binding region (residues 244–272; Chang et al., 2005). It has since been shown in Neuro-2a cultures that apoE4 (Δ272–299) binds the subunits ubiquinol cytochrome c reductase core protein 2 and cytochrome CI of Complex III (ubiquinol:cytochrome c oxidoreductase) and cytochrome c oxidase subunit 4 isoform 1 of Complex IV (cytochrome c:oxygen oxidoreductase) of the ETC and served to significantly reduce respiratory function of both Complex III and Complex IV (Nakamura et al., 2009). This is the precise pattern of ETC dysfunction we observed in peripheral tissue (platelet) mitochondria isolated from AD patients (Valla et al., 2006). Analysis of ETC protein expression in apoE4-expressing Neuro-2a and mouse primary neuron cultures demonstrated reduction in expression of subunits for all ETC complexes, and notably, in a bigenomic manner (Chen et al., 2011)—ETC protein expression is a highly-regulated process with subunits encoded from genes on both the nuclear and mitochondrial genomes (Hock and Kralli, 2009). Complex IV functional activity was also significantly decreased (Chen et al., 2011). As with the previously mentioned studies on intracellular trafficking, small-molecule structure correctors that make apoE4's structure more similar to that of apoE3 were able to alleviate these deficits. Considering the fact that cytoplasmic toxicity of neuronal apoE is apparent after its cleavage by AECE, further knowledge of the enzyme would be useful to enable the design of pharmaceutical agents to modulate AECE activity as a complementary mechanism to altering apoE4's structure (Huang, 2010).

Identification of protein signatures in *APOE* mice found that mitochondrially-enriched fractions prepared from hippocampal tissue of apoE4- and apoE3-expressing mice differed in levels of several proteins involved in such capacities as mitochondrial function, oxidative stress response, and organelle transport (James et al., 2011). Our previous multi-region gene expression study using laser capture microdissection to select only neurons in AD patients found reductions in ETC gene expression, with PCC displaying the most prominent effects (Liang et al., 2008). Further, a recent study using postmortem tissue from the middle temporal gyrus to compare gene expression profiles in middle-aged *APOE* ε4 carriers with noncarrier control subjects found significant differential expression in 70 transcripts, 30 of which are involved in oxidative mitochondrial function (Conejero-Goldberg et al., 2011). Unfortunately, this study lacked the ability to resolve cell type-specific alterations in gene expression, which might be important considering the respective roles of astrocytes and neurons in neuroenergetic processes (Allaman et al., 2011). Future study along these lines, especially in young adults and including analysis of astrocytes (see next section), might prove valuable in elucidating cell type-specific roles in ε4-related functional changes.

ApoE isoforms expressed in b12 cells display differing antioxidant ability in a manner correlated with disease risk (apoE2 > apoE3 > apoE4; Miyata and Smith, 1996). It is possible therefore, that detrimental or beneficial effects of different apoE isoforms are at least in part because of their relative ability to control the levels of reactive oxygen species, of which mitochondria are a primary endogenous source (Lin and Beal, 2006), including AD, in which oxidative stress is thought to be a very early hallmark of pathophysiology (Hirai et al., 2001; Nunomura et al., 2001).

11. ApoE effects on astrocytes

Beyond the effects shown in neurons, apoE4 also appears to alter function in astrocytes. ApoE4 induces endoplasmic reticulum stress in astrocytes (Zhong et al., 2009) that does not occur in neurons (Brodbeck et al., 2011). However, again pointing to the cell type-specific importance of apoE expression, mouse primary astrocyte cultures expressing apoE4 do not show significant changes in ETC gene expression (Chen et al., 2011). Additionally, transgenic mice that express apoE4 under the control of a glial fibrillary acidic protein promoter (astrocyte-specific) display severe deficits in working memory without any evident β-amyloid pathology (Hartman et al., 2001). Recent reports have demonstrated that deleterious effects of β-amyloid internalization by astrocytes in turn affects neuronal viability through effects on astrocytic energy metabolism (Allaman et al., 2010). It is possible that apoE4 acts in a similar manner to this astrocytic β-amyloid, serving as a double hit to impair neuronal function both directly, through escape from the secretory pathway and subsequent toxic effects on the mitochondria, and indirectly, through deleterious effects on astrocytes, serving to attenuate their ability to provide essential metabolic support (Zhong et al., 2009). Notably, based on current understanding of apoE production, loss of expression because of astrocyte endoplasmic reticulum stress might lead to an increase in potentially pathogenic (and nonfunctional if truncated) neuronal apoE (Zhong et al., 2009), in addition to the consequences of loss of functional astrocytic apoE. Interestingly, apoE4 has been shown recently to contribute to breakdown of the blood brain barrier via effects on cyclophilin A, which could further affect energetics because of disruption of nutrient transport (Bell et al., 2012).

12. Potential roles for *TOMM40*

APOE is located in a region of linkage disequilibrium on chromosome 19 that also encompasses *TOMM40* and *APOC1*. *TOMM40*, which encodes Tom40, the pore-forming subunit of the translocase of the outer mitochondrial membrane, has now been proposed as a potential genetic risk factor for AD (Roses et al., 2010). However, the exact nature of the relationship, at least partly, but perhaps not entirely attributable, to linkage disequilibrium, is not yet

understood as the initial findings have not been consistently replicated (Chu et al., 2011; Cruchaga et al., 2011). Functionally, the translocase is responsible for the import of proteins into the mitochondria—99% of mitochondrial proteins must be imported (Bolender et al., 2008). Deep sequencing and phylogenetic analysis of this chromosome 19 linkage disequilibrium region identified a variable-length poly-T polymorphism at the rs10524523 ('523) locus in intron 6 of *TOMM40* that might be able to further refine the age of onset distribution for AD. The mechanism of how *TOMM40* intronic polymorphisms might potentially influence age of onset is unclear, but considering the extent of neuroenergetic defects both in AD and in at-risk ε4 carriers, the possibility of involvement is of great interest.

Suggested hypotheses with a direct effect on mitochondrial function include effects of the polymorphism on splicing of Tom40 transcripts resulting in isoforms (Roses et al., 2010) with differential functionality or even propensity to bind apoE. In the latter case the pathologic action would be synergistic between Tom40 and apoE, and correspondingly *TOMM40* and *APOE*. Additionally, genome-wide pathway analysis has implicated genes involved in intracellular protein transport, particularly *TOMM40*, in AD (Hong et al., 2010). Other hypotheses include effects on apoE transcription; a previous AD genome-wide association study has shown that *TOMM40* single nucleotide polymorphisms influence apoE levels in the cerebrospinal fluid (Bekris et al., 2010), yet the '523 poly-T repeat does not appear to alter cerebrospinal fluid levels of β-amyloid in aged control subjects, indicating that the mechanism influencing age of onset might not exert itself via a β-amyloid-linked process (Pomara et al., 2011). A recent study using fibroblast cultures found no apparent effects of the '523 poly-T repeats on expression levels of Tom40 protein and mRNA, Tom40 mRNA splicing, or mitochondrial function and morphology (Hedskog et al., 2012). Structural MRI and neuropsychological data shows that cognitively normal late-middle aged *APOE* ε3 homozygotes who are also homozygous for longer '523 poly-T repeats have significant declines in learning and memory function and gray matter volume in the ventral PCC and medial ventral precuneus when compared with other *APOE* ε3 homozygotes (Johnson et al., 2011). The detection of presymptomatic changes in the PCC serves again to highlight the apparent differential vulnerability of the region to processes linked to vulnerability to neurologic disease. Additional investigation to clarify the possible effects of *TOMM40* genotype might help to explain disease onset variation in at-risk populations and might also provide an impetus to further examine neuroenergetic dysfunction.

13. Conclusions

The strong association between *APOE* and AD has been known for nearly 2 decades, during which time significant advances have been made in understanding how *APOE* might contribute to disease risk. Though considerably more research is needed to establish the mechanistic effects of *APOE* on disease processes, mounting evidence linking *APOE* to alterations in neuroenergetics has illuminated exciting new areas for research. Because of the apparently early nature of these functional changes (i.e., often apparent in young adults), modulation of related cellular and molecular processes might provide viable targets for therapies aiming to prevent and/or treat AD, and potentially a number of other neurological disorders with possible links to *APOE* (Verghese et al., 2011). Though no apoE-directed therapies (e.g., small molecule structure correctors) have yet been used in humans, bioenergetically-relevant therapies have undergone clinical trials. Most prominent have been efforts using intranasal insulin (Craft et al., 2012; Reger et al., 2006, 2008a, 2008b), ketogenic medium chain triglycerides (Henderson et al., 2009), and peroxisome proliferator-activated receptor-γ agonists (Geldmacher et al., 2011; Gold et al., 2010; Risner et al., 2006; Sato et al., 2011; Watson et al., 2005). It remains to be clarified whether clinically affected *APOE* ε4 carriers and noncarriers might respond differently to amyloid-targeting therapies. A recent Phase II trial of the amyloid antibody therapy bapineuzumab found less benefit in carriers than in noncarriers with AD dementia (Salloway et al., 2009), but the subsequent Phase III studies failed to demonstrate a clear benefit in AD dementia patients whether they were carriers or noncarriers (not yet published). It has also been suggested that these treatments might be associated with a greater risk of vasogenic edema and cerebral microhemorrhage in clinically affected carriers than noncarriers (Salloway et al., 2009), perhaps related to blood-brain barrier breakdown in *APOE* ε4 carriers (Bell et al., 2012). If a differential response to these and other treatments are confirmed in *APOE* ε4 carriers and noncarriers, it could be attributable to the apoE4 protein or, perhaps more likely, underlying disease severity (because each copy of the ε4 allele in a person's *APOE* genotype is associated with a younger average age at onset, it is possible that the treated AD dementia patients who carry the *APOE* ε4 allele have greater disease severity than the treated noncarriers of the same age).

An alternative, or perhaps synergistic, interpretation of the *APOE* ε4-associated deficits in AD, considering the early functional (Reiman et al., 2004; Valla et al., 2010) and morphologic changes (Alexopoulos et al., 2011; Shaw et al., 2007) reported in *APOE* ε4 carriers, is that these alterations do not reflect progressive disease-related changes in the brain but rather *APOE*-related neurodevelopmental alterations. As such, *APOE* ε4 might convey a developmental limitation that provides a foothold for the regional vulnerability that contributes to an earlier age of clinical onset decades later. Such a model would fit well with the concept of cognitive reserve in that *APOE* ε4 carriers might not demonstrate equivalent synaptic number or dendritic complexity, as in apoE-expressing mice (Dumanis et al., 2009; Ji et al., 2003), and thus far reported to manifest as reduced entorhinal cortical thickness in young human subjects (Shaw et al., 2007).

Additionally, further understanding of the role of *TOMM40* polymorphisms might provide insight. Hopefully, the extension of current knowledge can lead to continued improvement in elucidating the causes of disease and correspondingly the development of critically needed therapies.

Disclosure statement

All authors report no conflicts of interest.

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