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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.

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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

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