thematic review series

Thematic Review Series: ApoE and Lipid Homeostasis in Alzheimer's Disease

The role of APOE on lipid homeostasis and inflammation in normal brains

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Abstract The role of APOE in the risk of Alzheimer's disease (AD) has largely focused on its effects on AD pathological processes. However, there are increasing data that *APOE* genotype affects processes in normal brains. Studies of young cognitively normal humans show effects of *APOE* genotype on brain structure and activity. Studies of normal *APOE* knock-in mice show effects of *APOE* genotype on brain structure, neuronal markers, and behavior. APOE interactions with molecules important for lipid efflux and lipid endocytosis underlie effects of *APOE* genotype on neuroinflammation and lipoprotein composition. These effects provide important targets for new therapies for reduction of the risk of AD before any signs of pathogenesis.—Rebeck, G. W. **The role of APOE on lipid homeostasis and inflammation in normal brains. *J. Lipid Res.* 2017.** 58: **1493–1499.**

Supplementary key words apolipoprotein E • Alzheimer's disease • apolipoproteins • inflammation • lipids/efflux • ATP binding cassette transporter A1

APOE genotype has the most profound genetic risk on late onset Alzheimer's disease (AD) (1). *APOE4* promotes earlier amyloid deposition and clinical symptoms of AD by about 15 years per allele (2). With an allele frequency of 0.14, APOE4 is present in approximately 25% of the US population (3). Thus, there are nearly 80 million people in the US who carry this risk, without any risk-altering treatments. *APOE2*, in contrast, lowers the AD risk in about 35 million US individuals. The main questions that these observations raise are: how does *APOE* genotype affect the risk of AD, and what can be done to decrease that risk in individuals? In this review, we will be examining whether the roles of APOE in neuroinflammation or lipid homeostasis before AD pathogenesis may predispose the brain to damage that occurs later in aging with the accumulation of the Aβ peptide.

THE EFFECTS OF *APOE* GENOTYPE ON INFLAMMATION

Inflammation is a potential early indicator of AD risk or AD onset in humans because genetic factors related to immune functions and inflammation have been identified in genome-wide association studies of AD (4). *APOE* is one of these AD risk genes related to neuroinflammation, as evidenced by several in vitro and in vivo systems. In vivo studies rely largely on mice with the coding sequence of the human *APOE* alleles replacing the mouse *APOE* gene as the best animal model for normal *APOE* regulation and function (5). The *APOE4* knock-in mice are more susceptible to inflammation induced by lipopolysaccharide (6) or by Aβ deposition (7) compared with *APOE2* and *APOE3* mice. *APOE4* mice are also more susceptible to brain damage that has strong inflammatory components, such as traumatic brain injury (8) and experimental autoimmune encephalomyelitis (9). In *APOE* mouse models, peptides based on the APOE receptor binding domain prevent or alleviate effects of inflammation-related insults, such as lipopolysaccharide-induced inflammation (10), traumatic brain injury (11), intracerebral hemorrhage (12), and focal ischemia (13). Similar effects are seen in vitro. APOE isoforms affect inflammatory processes in microglia and astrocytes, with APOE4 promoting the strongest inflammatory effects (10, 14, 15). An APOE peptide inhibits inflammatory processes in isolated microglia (16) through the APOE receptor, LRP1 (17). APOE similarly induces an anti-inflammatory phenotype in isolated macrophages through the APOE receptors, ApoER2 and VLDLR (18). Interestingly, blocking inflammatory signaling increases APOE expression in microglia (19), suggesting that APOE levels and inflammation are in a negative feedback loop, with APOE inhibiting inflammation and inflammation inhibiting APOE levels. These data indicate that *APOE* is

This work was supported by a gift in honor of Rolland "Pap" McCracken for the prevention and treatment of Alzheimer's disease.

Manuscript received 30 January 2017 and in revised form 2 March 2017.

Published, JLR Papers in Press, March 2, 2017
DOI https://doi.org/10.1194/jlr.R075408

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; MTL, medial temporal lobe; NSAID, nonsteroidal anti-inflammatory drug.

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associated with increased inflammatory responses before and after the onset of AD pathogenesis.

THE EFFECTS OF *APOE* GENOTYPE ON LIPID HOMEOSTASIS

APOE is one of the primary apolipoproteins in CNS lipid metabolism (20). Thus, an effect of *APOE* genotype on brain lipid homeostasis may underlie the AD risk associated with *APOE*. As with inflammation, this possibility is supported by the identification of lipid-related genetic risk factors for AD (21), particularly *APOJ* (or clusterin) (22, 23). Although APOJ is not as strong of a genetic risk factor as APOE [the polymorphic site in APOJ has an odds ratio of about 0.9 for the minor allele, compared with an odds ratio of about 5 for the APOE-ε4 allele (24)], both APOE and APOJ are components of CNS lipoproteins (25) and are associated with the functions of CNS lipoproteins: lipid efflux and lipid delivery (26).

APOE and APOJ interact with lipid debris in the brain (27) and APOE is necessary for the removal of degenerating membrane after injury (28). APOE lipoproteins also accumulate lipid from a cellular efflux mechanism with the ABCA1 transporter (29). Deletion of the *ABCA1* gene decreases levels of APOE (30, 31) and increases the deposition of Aβ (31) in the brain. APOE isoforms differ in their ability to promote cholesterol efflux from cells, with APOE2 having the greatest efficiency and APOE4 the least (32, 33). This efflux is the first step in the generation of APOE-lipid complexes. APOE4 was found to be part of smaller complexes in normal mouse brains (34, 35), and in mouse brain expressing different APOE isoforms from virus (36, 37). In contrast, APOE2 was associated with larger complexes (36). The relevance of these findings to humans was demonstrated through analysis of human cerebrospinal fluid (CSF), with APOE complexes largest in *APOE2.3* individuals and smallest in *APOE4.4* individuals (38). Consistent with the hypothesis that APOE4 is associated with smaller lipoproteins, APOE4 lipoproteins promoted less cholesterol efflux than APOE3 lipoproteins (39), and *APOE4*-positive individuals had more lipid-depleted APOE in their CSF than *APOE4*-negative individuals (40).

Lipid delivery to cells occurs as APOE and APOJ are endocytosed via members of the LDL receptor family (41); endocytosis promotes neurite outgrowth (42), neuronal sprouting (43), and synapse formation (44). APOE and APOJ also promote endocytosis through TREM2 (45, 46), another prominent genetic risk factor for AD (47). These processes involve clearance into neurons as well as glia (48, 49) or across the blood brain barrier (50). The need for clearance of lipids from the brain may increase with age as membrane damage accumulates and neuronal loss occurs.

The effects of the reduced lipidation capacity of APOE4 may result in reduced neuronal protection or repair. Neuronal injury increases brain APOE levels (51), although the increase is not immediate (52). The presence of an *APOE4* allele decreases the brain's neuronal reparative capacity in AD patients (53). We hypothesize that reduced lipidation of CNS lipoproteins may be an important risk factor of AD; biomarker-based APOE lipidation may be useful in measuring levels of neuroprotection in the brain environment (38). The effects of *APOE* genotype on lipidation may be causally related to some effects of inflammation, due to direct effects on high levels of cholesterol on inflammation (54) or to the connections of regulatory systems controlling brain lipid homeostasis and inflammation (55).

THE EFFECTS OF *APOE* GENOTYPE ON APOE LEVELS AND POSTTRANSLATIONAL MODIFICATION

Humans with the *APOE4* allele have smaller APOE lipoproteins and lower APOE levels in the CSF and plasma, whereas those with the *APOE2* allele have larger APOE lipoproteins and higher APOE levels (56, 57). *APOE4* knock-in mice also have lower levels of APOE in the brain, CSF, plasma, and interstitial fluid compared with *APOE3* or *APOE2* mice (15, 58, 59). The lower levels of APOE may be due to increased degradation of APOE4 compared with the other isoforms (59). If *APOE4* individuals have both smaller lipoproteins and less APOE, then there could be a twofold impact on lipid clearance and delivery processes that contributes to the increased risk for AD.

There are also important posttranslational modifications to the APOE protein. Most notably, APOE4 lacks cysteine residues for the formation of APOE-APOE homodimers and APOE-APOAII heterodimers (26), whereas APOE3 contains one cysteine and APOE2 contains two cysteines for dimer formation. APOE4 is associated with enhanced cleavage of the C terminus of APOE (60), which exacerbates the effects of Aβ on inflammation and behavioral deficits in mice (61). This cleaved APOE4 is neuron specific and induced by neuronal stress (62), with the APOE4 fragments inducing neuronal dysfunction (63). Finally, the APOE protein is modified by O-glycosylation (64), and to a greater extent in the CNS than in the periphery (26). We have identified biochemical differences in modified versions of brain APOE: unmodified APOE is solubilized only in the presence of detergent and modified APOE is solubilized in saline (65). The ratio of these different forms is altered by *APOE* genotypes in mouse and human brains (65). The APOE isoform effects on APOE levels and on dimer formation support loss-of-function explanations for the effects of APOE4, with APOE4 less able to clear debris and deliver lipids than APOE2 or APOE3. In contrast, effects of APOE cleavage fragments on neurotoxicity (66) or the inhibitory effects of APOE4 toward neuronal sprouting (67) support a gain-of-function explanation. Understanding of APOE functions requires a better understanding of the different forms of APOE present in the CNS, particularly because treatment approaches could involve the increase or the decrease of APOE4 levels.

THE EFFECTS OF *APOE* GENOTYPE ON NORMAL CNS FUNCTIONS

APOE genotype affects a number of CNS phenotypes in young individuals, as demonstrated both in mice and in humans (65). *APOE4* knock-in mice have several differences compared with *APOE3* mice. In measures of behavior, *APOE4* is associated with deficits in spatial learning and memory (68–71). In measures of neuronal complexity, *APOE4* is associated with reduced dendritic arborization (72, 73), neuronal activity (74), the balance of excitatory and inhibitory neurons (75), neurotransmitter release (76–78), and dendritic spine density (68, 72, 79). In measures of immunohistochemistry, *APOE4* is associated with alterations in levels of VGlut1 (34, 80) and in levels of specific APOE receptors (81). Finally, in biochemical measures, *APOE4* is associated with alterations in APOE solubilization (65) and presynaptic metabolic abnormalities (80). Thus, in normal mice, *APOE4* is associated with many different aspects of brain function, effects important for later brain impairments.

In measures of normal human behavior, *APOE4* is associated with reduced verbal memory (82), as well as visual recall and memory retention (83). In measures of human brain activity using functional magnetic resonance imaging, *APOE4* is associated with increased brain activity in the default mode network, and the hippocampus during an encoding task (84). Indeed, medial temporal lobe (MTL) activation is altered by *APOE* genotype during diverse behavioral tasks (85–87) and *APOE4* carriers have reduced grid-cell-like representations in the entorhinal cortex and increased hippocampal activation (88). *APOE* genotype in the absence of AD is also associated with differences in brain structure. *APOE4* is associated with differences in the MTL at birth (89, 90) [the effects of *APOE4* on MTL structure in older individuals is mixed (84, 91–93)]. There are differences in brain connectivity based on *APOE* and *APOJ* genotypes determined by diffusion tensor imaging (94). Differences in brain structure in *APOE4* individuals are also supported by the observation that dendritic spine density in the hippocampus is lower in aged *APOE4* individuals with no evidence of Aβ deposition (79). Some of these differences are consistent with increased brain activity or connectivity in young individuals with *APOE4*. The antagonistic pleiotropy hypothesis posits that *APOE4* has a positive effect on brain activity and behavior at young ages, but is detrimental at older ages (95). In general, the human studies and mouse studies together have supported the hypothesis that *APOE* genotype impacts normal brain structure and function independent of AD pathology.

APOE-DIRECTED PREVENTATIVE TREATMENTS

Understanding of the basic biology of APOE helps to identify mechanism-based therapies that could rescue *APOE4* phenotypes. In normal brains, these phenotypes could predispose to Aβ deposition with aging, which could be prevented by early prophylactic approaches. For example, as mentioned above, APOE mimetic peptides could serve as a therapeutic approach for *APOE4* individuals for AD, as well as other diseases with neuro-inflammatory components (96). The introduction of active APOE peptides could alleviate conditions caused by lower APOE levels in *APOE4* individuals (59).

Another potential AD preventative treatment is the class of nonsteroidal anti-inflammatory drugs (NSAIDs). Epidemiological studies have repeatedly shown that early NSAID use is associated with reduced AD risk in humans (97–101), but NSAIDs have been unsuccessful at treating AD in clinical trials (102), or preventing AD in short-term prevention trials of the elderly (103). Interestingly, the preventative effect of NSAIDs may be most powerful in those with the *APOE4* risk genotype (97, 104–106). These findings suggest that NSAIDs are protective against AD, but only before accumulation of the neuropathological changes associated with AD (103). We have tested this hypothesis by treating *APOE4* mice with the NSAID, ibuprofen. Ibuprofen rescues the effects of *APOE4* genotype on reduced dendritic spine density and on the altered distribution of APOE in brain fractions (65). These effects of ibuprofen support the epidemiological data that NSAIDs may reduce AD risk factors in normal individuals.

Yet another approach is to counteract the effects of *APOE4* genotypes on the deficient APOE levels and reduced APOE4 lipidation. APOE and related molecules are regulated as part of the LXR/RXR transcriptional system, making that an attractive target for drug discovery (107). LXR activation promotes brain lipid efflux through induction of genes, such as APOE and ABCA1, and, in mouse models, leads to a decrease in lipids in synaptosomes (108). As mentioned above, reducing ABCA1 in genetic knockout models decreases APOE and increases Aβ in mouse brain (30, 31). LXR agonists increase APOE and ABCA1, reducing Aβ levels (59, 109), improving behavior (109, 110), and increasing synaptic plasticity (111). An RXR agonist, bexarotene, reduces Aβ accumulation in a mouse model (112), dependent on the presence of both *APOE* and *ABCA1* (113). Bexarotene also rescues the impaired APOE lipidation and reversed behavioral deficits in *APOE4* mice (34). Finally, induction of ABCA1 activity could be a useful AD therapeutic approach: an agonist for ABCA1 reversed the effects of *APOE4* on reduced lipoprotein lipidation, synaptic markers, and behavioral deficits (35). Specifically increasing the function of ABCA1 is a particularly interesting approach to altering APOE lipid metabolism, because it relies only on promoting lipid efflux through ABCA1, and not induction of the other genes of the LXR transcription system (107).

CONCLUSIONS

The unparalleled effect of *APOE* on AD risk in older individuals and its varied effects on the function of younger brains emphasize the need to study AD prevention strategies related to *APOE*. Studies on APOE in inflammation and lipid homeostasis are providing mechanisms for how brain alterations associated with *APOE4* might be rescued (**Fig. 1**).

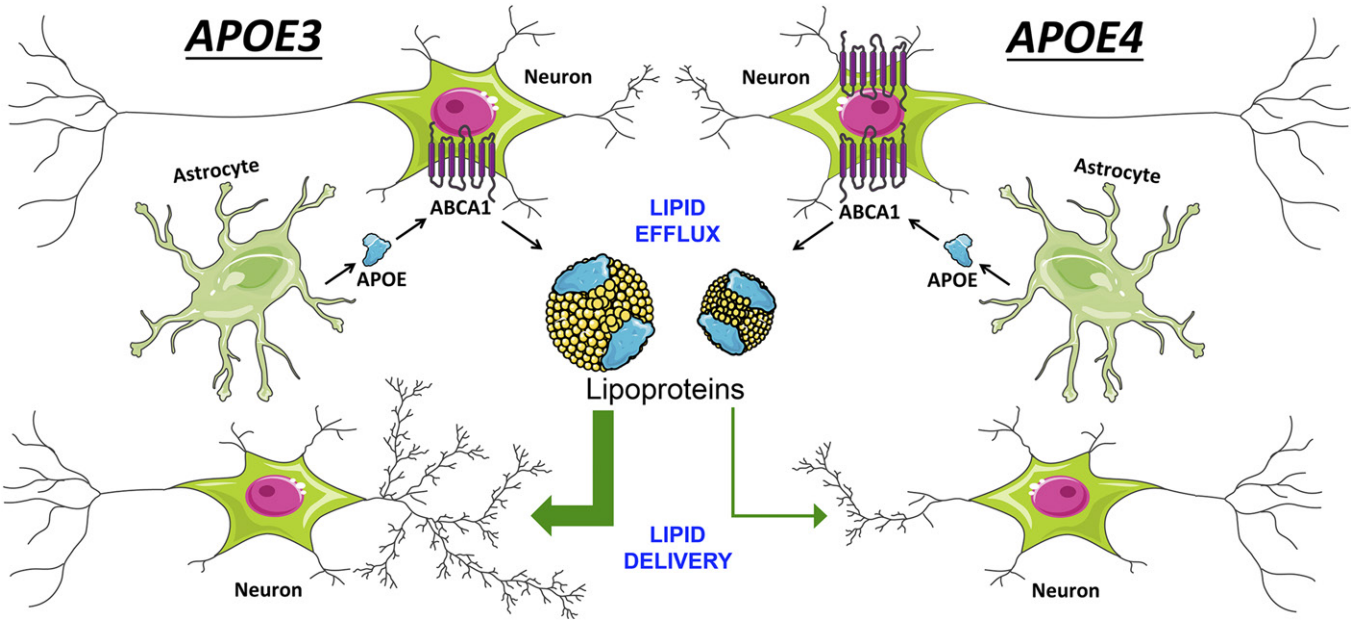

Fig. 1. CNS APOE functions. CNS APOE (in blue) is secreted from glia. It is lipidated through interactions with ABCA1 on neurons and glia, forming high-density CNS lipoproteins (in yellow). These lipoproteins can deliver lipids to neurons to promote neuronal complexity. Compared with APOE3, APOE4 is less able to promote cholesterol efflux, forming smaller CNS lipoproteins, and less able to deliver lipids to neurons for neuroprotective functions. APOE lipoproteins also inhibit glial inflammation, with the smaller and fewer APOE4 lipoproteins less capable of this function. Chronic glial inflammation in the *APOE4* brain contributes to neuronal dysfunction and impaired APOE regulation, but these *APOE4* phenotypes can be mitigated through treatments with anti-inflammatory agents (NSAID).

The many people who have inherited this strong predisposition to AD have no treatments to help them avoid AD and, with increased access to genome sequencing, more of them are recognizing that they are at frighteningly high risk. This population of *APOE4*-positive individuals provides a logical target for in-depth studies of promising AD prevention approaches that are not necessarily related to the neuropathological accumulation of Aβ (114). While prevention approaches to AD are difficult to evaluate, given the need to measure long-term effects, they provide hope if the approaches of treating individuals after the onset of AD pathogenesis are unsuccessful.

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