HHS Public Access

Author manuscript

JAMA Neurol. Author manuscript; available in PMC 2015 March 10.

Published in final edited form as:

JAMA Neurol. 2014 October ; 71(10): 1213–1215. doi:10.1001/jamaneurol.2014.2013.

Is Apolipoprotein E Required for Cognitive Function in Humans?: Implications for Alzheimer's Drug Development

Courtney Lane-Donovan, S.B.[1] and **Joachim Herz, M.D.**[1]

[1]Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX

More than twenty years ago, a polymorphism in the Apolipoprotein E (apoE) gene was identified as the primary risk factor for late-onset Alzheimer disease (AD).[1] Individuals carrying the ε4 isoform of apoE (apoE4) are at significantly greater risk for AD compared to apoE3 carriers, whereas the apoE2 allele is associated with reduced AD risk.[2] Despite two decades of research into the mechanisms by which apoE4 contributes to disease pathogenesis, a seemingly simple question remains unresolved: Is apoE good or bad for brain health? The answer to this question is essential for the future development of apoE-directed therapeutics.

In *JAMA Neurology*, Mak et al. describe a patient who has undetectable levels of apoE in plasma and cerebrospinal fluid.[3] The patient, a 40-year-old African American man, is homozygous for a rare loss-of-function mutation in apoE. Despite severe dysbetalipoproteinemia and xanthomatosis, the patient is cognitively normal and shows no signs of neurodegeneration. In light of apoE as the primary risk factor for AD, the lack of neurological findings in this patient would appear to answer the question of whether apoE is necessary for brain function with a resounding no.

In the plasma, apoE is a carrier of chylomicron remnants and very-low-density lipoprotein particles and binds to members of the low-density lipoprotein receptor family for uptake into cells. These lipoprotein particles cannot cross the blood-brain barrier; thus, apoE-containing particles released by astrocytes are the main source of brain apoE.[4,5] The importance of circulating apoE is highlighted by the greatly elevated total cholesterol levels, contained mostly in the very low-density lipoprotein fraction, in the apoE-deficient patient described by Mak and colleagues, leading to prominent xanthomatosis[3] and, as had been reported in other rare cases of apoE deficiency, a concomitant increase in cardiovascular disease risk.[6] However, the previous case studies did not investigate potential neurological sequelae of apoE deficiency.

Several mouse apoE knockouts have been generated to investigate the effect of apoE loss on atherosclerosis and cognition, sometimes with conflicting results. Consistently, apoE

Corresponding Author: Joachim Herz, joachim.herz@utsouthwestern.edu, Departments of Molecular Genetics, Neuroscience, Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9046.

Conflicts of Interest: None

COI Statement: The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

knockout mice have elevated cholesterol levels, similar to apoE-deficient patients.[7] Neurological findings in these mice have been less clear, however. Some groups have reported that while apoE knockout mice develop normally, they begin to lose neurons around 5 months of age accompanied by a reduction in working memory,[8,9] which is ameliorated by infusion with recombinant apoE3 or apoE4.[10] These findings have been challenged by other studies that found no age-related neurodegeneration in apoE knockout mice.[11,12]

Alzheimer disease is characterized by the progressive buildup of neuritic plaques comprising fibrillar amyloid beta (Aβ; a cleavage product of the amyloid precursor protein), followed by the appearance of neurofibrillary tangles of hyperphosphorylated tau. These toxic particles affect a variety of processes, including inflammation, synaptic plasticity, and cell viability.[13,14] Apolipoprotein E4 promotes disease pathogenesis through both Aβ-dependent and Aβ-independent pathways. Carriers of apoE4 have earlier and more rapid deposition of plaques, which is thought to stem from impaired clearance of Aβ from the interstitial fluid[15,16] and from fibrillogenesis-promoting properties of apoE4.[17] Also, apoE4 modifies brain function independent of Aβ, as apoE4 carriers show altered connectivity patterns by magnetic resonance imaging in AD-related brain regions as early as infancy.[18]

Because murine apoE differs from the 3 human apoE isoforms at numerous amino acid residues, human apoE knock-in mice have been developed to study the roles of the isoforms in vivo in the mouse. These apoE knock-in mice have been crossed with mouse models of AD that carry familial AD mutations in *APP* or *PSEN1*, which cause high levels of Aβ and age-related plaque deposition and cognitive decline. Consistent with findings in human populations, the presence of apoE4 accelerates the development of plaques and cognitive dysfunction in AD mice over apoE3 and apoE2.[19] Intriguingly, gene transfer by adeno-associated virus of the 3 human apoE isoforms into AD mice on a normal mouse apoE background showed that while apoE4 increased plaques, apoE2 actually decelerated plaque growth. However, adeno-associated virus transfer of human apoE also reduced endogenous murine apoE levels by approximately 15%.[20] It is important to point out in this context that the reduction of endogenous mouse apoE alone – or its replacement with any human apoE allele – by itself reduces plaque deposition and ameliorates cognitive deficits in the animals.[21,22]

Several apoE-directed AD therapeutics are currently in development. Some seek to increase apoE levels and lipidation by upregulating expression of adenosince triphosphate-binding cassette transporter A1 protein (ABCA1), eg, through liver X receptor and retinoid X receptor agonists.[23,24] Conversely, other approaches aim at lowering apoE levels. Specifically, passive immunotherapy with anti-apoE antibodies is currently being tested in animal models and has been shown to reduce Aβ deposition in mouse models of AD.[25]

One caveat for the development of systemic apoE-directed therapeutics is the effect of apoE loss on plasma lipoproteins. Both the patient described by Mak and colleagues and apoE knockout mice have impaired clearance of lipoproteins, resulting in massively elevated cholesterol levels in the circulation that could lead to accelerated atherosclerosis[3]. To prevent the disruption of lipid metabolism in AD patients, apoE-directed drugs will need to

be brain-specific. This could take the form of specifically targeting the drug to the central nervous system or targeting apoE-specific interactions in the central nervous system (eg, Aβ binding). Promisingly, systemic administration of anti-apoE antibodies does not alter cholesterol levels in a mouse model of AD, while still modestly reducing levels of Aβ and improving cognition.[25]

The grossly normal cognitive status of the apoE-deficient patient described by Mak and colleagues suggests that therapeutics that reduce cerebral apoE levels will likely not adversely affect cognition in at-risk patients. Because the described patient is only 40 years old, close clinical follow-up is needed to determine if he is at increased risk for age-dependent cognitive decline; however, his grossly elevated lipid profile may confound this because increased plasma cholesterol is independently associated with increased AD risk.[26] Overall, the patient's normal cognitive function together with the earlier mouse work suggest that interventions that reduce cerebral apoE levels may hold promise as a potential therapeutic approach to AD.

Acknowledgments

This study was supported by grants from the National Institutes of Health (HL63762), Consortium for Frontotemporal Dementia Research (A108400), BrightFocus Foundation (A2013524S), Ted Nash Long Life Foundation and Lupe Murchison Foundation.

References

1. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. Aug 13; 1993 261(5123):921–923. [PubMed: 8346443]
2. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nature genetics. Jun; 1994 7(2):180–184. [PubMed: 7920638]
3. Mak ACY, Pullinger CR, Tang LF, et al. Absence of apolipoprotein E: Effects on lipoproteins, neurocognitive and retinal function. JAMA neurology.
4. Bjorkhem I, Lutjohann D, Diczfalusy U, Stahle L, Ahlborg G, Wahren J. Cholesterol homeostasis in human brain: turnover of 24S-hydroxycholesterol and evidence for a cerebral origin of most of this oxysterol in the circulation. Journal of lipid research. Aug; 1998 39(8):1594–1600. [PubMed: 9717719]
5. Pitas RE, Boyles JK, Lee SH, Foss D, Mahley RW. Astrocytes synthesize apolipoprotein E and metabolize apolipoprotein E-containing lipoproteins. Biochimica et biophysica acta. Jan 13; 1987 917(1):148–161. [PubMed: 3539206]
6. Schaefer EJ, Gregg RE, Ghiselli G, et al. Familial apolipoprotein E deficiency. The Journal of clinical investigation. Nov; 1986 78(5):1206–1219. [PubMed: 3771793]
7. Zhang SH, Reddick RL, Piedrahita JA, Maeda N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science. Oct 16; 1992 258(5081):468–471. [PubMed: 1411543]
8. Gordon I, Grauer E, Genis I, Sehayek E, Michaelson DM. Memory deficits and cholinergic impairments in apolipoprotein E-deficient mice. Neuroscience letters. Oct 13; 1995 199(1):1–4. [PubMed: 8584214]
9. Masliah E, Mallory M, Ge N, Alford M, Veinbergs I, Roses AD. Neurodegeneration in the central nervous system of apoE-deficient mice. Experimental neurology. 1995; 136(2):107–122. [PubMed: 7498401]
10. Masliah E, Samuel W, Veinbergs I, Mallory M, Mante M, Saitoh T. Neurodegeneration and cognitive impairment in apoE-deficient mice is ameliorated by infusion of recombinant apoE. Brain research. Mar 21; 1997 751(2):307–314. [PubMed: 9099820]

11. Anderson R, Barnes JC, Bliss TV, et al. Behavioural, physiological and morphological analysis of a line of apolipoprotein E knockout mouse. Neuroscience. Jul; 1998 85(1):93–110. [PubMed: 9607706]
12. Moghadasian MH, McManus BM, Nguyen LB, et al. Pathophysiology of apolipoprotein E deficiency in mice: relevance to apo E-related disorders in humans. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. Dec; 2001 15(14): 2623–2630. [PubMed: 11726538]
13. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. Nature reviews. Immunology. Dec; 2013 13(12):875–887.
14. Spires-Jones TL, Hyman BT. The Intersection of Amyloid Beta and Tau at Synapses in Alzheimer's Disease. Neuron. May 21; 2014 82(4):756–771. [PubMed: 24853936]
15. Mawuenyega KG, Sigurdson W, Ovod V, et al. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science. Dec 24.2010 330(6012):1774. [PubMed: 21148344]
16. Castellano JM, Kim J, Stewart FR, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. Science translational medicine. Jun 29.2011 3(89):89ra57.
17. Sanan DA, Weisgraber KH, Russell SJ, et al. Apolipoprotein E associates with beta amyloid peptide of Alzheimer's disease to form novel monofibrils. Isoform apoE4 associates more efficiently than apoE3. The Journal of clinical investigation. Aug; 1994 94(2):860–869. [PubMed: 8040342]
18. Dean DC 3rd, Jerskey BA, Chen K, et al. Brain differences in infants at differential genetic risk for late-onset Alzheimer disease: a cross-sectional imaging study. JAMA neurology. Jan; 2014 71(1): 11–22. [PubMed: 24276092]
19. Bales KR, Liu F, Wu S, et al. Human APOE isoform-dependent effects on brain beta-amyloid levels in PDAPP transgenic mice. The Journal of neuroscience : the official journal of the Society for Neuroscience. May 27; 2009 29(21):6771–6779. [PubMed: 19474305]
20. Hudry E, Dashkoff J, Roe AD, et al. Gene transfer of human Apoe isoforms results in differential modulation of amyloid deposition and neurotoxicity in mouse brain. Science translational medicine. Nov 20.2013 5(212):212ra161.
21. Bales KR, Verina T, Dodel RC, et al. Lack of apolipoprotein E dramatically reduces amyloid beta-peptide deposition. Nature genetics. Nov; 1997 17(3):263–264. [PubMed: 9354781]
22. Kim J, Jiang H, Park S, et al. Haploinsufficiency of human APOE reduces amyloid deposition in a mouse model of amyloid-beta amyloidosis. The Journal of neuroscience : the official journal of the Society for Neuroscience. Dec 7; 2011 31(49):18007–18012. [PubMed: 22159114]
23. Cramer PE, Cirrito JR, Wesson DW, et al. ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. Science. Mar 23; 2012 335(6075):1503–1506. [PubMed: 22323736]
24. Donkin JJ, Stukas S, Hirsch-Reinshagen V, et al. ATP-binding cassette transporter A1 mediates the beneficial effects of the liver X receptor agonist GW3965 on object recognition memory and amyloid burden in amyloid precursor protein/presenilin 1 mice. The Journal of biological chemistry. Oct 29; 2010 285(44):34144–34154. [PubMed: 20739291]
25. Liao F, Hori Y, Hudry E, et al. Anti-ApoE Antibody Given after Plaque Onset Decreases Abeta Accumulation and Improves Brain Function in a Mouse Model of Abeta Amyloidosis. The Journal of neuroscience : the official journal of the Society for Neuroscience. May 21; 2014 34(21):7281–7292. [PubMed: 24849360]
26. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. May; 2008 16(5):343–354. [PubMed: 18448847]