Evidence that an APOE ε4 'double whammy' increases risk for Alzheimer's disease

Caesar and Gandy
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Ina Caesar1,2,3,4* and Sam Gandy1,2,3,4

Abstract
Temporal lobe epilepsy (TLE) is associated with some of the same neuropathological features as those reported for early stages of typical Alzheimer’s disease (AD). The APOE ε4 allele is associated with a gene-dose-dependent increase in AD risk and in the severity of amyloid-β (Aβ) pathology. In a study published in the current BMC Medicine, Sue Griffin and colleagues studied markers of brain resilience in the amputated temporal lobes of TLE patients. They discovered compelling evidence that the APOE ε3 isoform in TLE patients is apparently more neuroprotective from Aβ toxicity than is the APOE ε4 isoform, as shown by the reduced levels of neuronal damage, glial activation, and expression of IL-1α in the APOE ε3/ε3 brains. This result points to a new property of APOE isoforms: not only are APOE ε4 alleles associated with increased brain amyloid plaque burden, but these alleles are also apparently inferior to APOE ε3 alleles in conveying resistance to Aβ neurotoxicity. This ‘double whammy’ result opens up a new direction for studies aimed at elucidating the relevant neurobiological activities of APOE isoforms in the pathogenesis of AD.

Keywords: Alzheimer’s disease, epilepsy, apolipoprotein, cerebral amyloidosis

Background
Alzheimer’s disease (AD) is a progressive neurological disease and is the most common form of dementia. The prevalence of AD is aging-related: 10% of people over 65 years old and 50% of people over 85 years old are affected. The disease course involves unrelenting decortication, with affected people succumbing in a persistent vegetative state after an approximate 10-year course of illness. AD is characterized by the accumulation of extracellular amyloid plaques and intraneuronal neurofilbrillary tangles as well as profound neuronal loss. This neuronal loss correlates better with clinical cognitive status at the time of death than does the burden of either pathology; therefore, an understanding of the molecular mechanisms of neurotoxicity (and ‘neuroresilience’) in AD is of paramount interest.

Apolipoprotein E ε4 (APOE ε4, gene; apoE4, protein) is the major identified genetic risk factor for common sporadic forms of AD, and understanding the relevant neurobiological activities of APOE isoforms has presented a major challenge over the past 20 years. Temporal lobe epilepsy (TLE) is associated with some of the same neuropathological features as those reported for early stages of typical AD [1]. The changes in neuropathology reported for TLE include accumulation of amyloid-β (Aβ) as senile plaques and increased microglial activation compared to healthy controls. The APOE ε4 allele in TLE is associated with a gene-dose-dependent increase in plaque density when compared with brains of APOE ε3/ε3 genotype [2]. An important distinction is that the TLE brain is assumed not to be as generally compromised as is the AD brain. Therefore, the plaque-loaded TLE brain presents an unusual opportunity to study focal parenchymal cerebral amyloidosis situated in what is believed to be an otherwise healthy brain.

In a research article published in the current issue of BMC Medicine, Sue Griffin and colleagues have investigated the brains of TLE patients with APOE ε3 and APOE ε4 alleles. By focusing on TLE, Griffin avoided the confound of the possible underlying vulnerability to neurotoxicity that might characterize the AD brain.
Further, by studying younger subjects than those generally studied in typical AD, the researchers also avoided the possibility of aging-related confounds. This research uncovered compelling evidence that, after correcting for the differences in plaque density, the apoE3 isoform in TLE patients is apparently more neuroprotective from Aβ toxicity than is the apoE4 isoform. This conclusion is supported by the reduced levels of neuronal damage, glial activation, and interleukin-1α (IL-1α) in the APOE ε3/ε3 brains [3] and is consistent with the predictions of Miyata and Smith, who provided evidence for the differential antioxidant activities of apoE3 vs apoE4 proteins [4]. The differential antioxidant activities of apoE isoforms are due to the Cys- and Arg- substitutions at the polymorphic site [5], which are illustrated in Figure 1.

Tissue levels of IL-1α are dependent on APOE isoform
IL-1α is one of the best characterized inflammatory cytokines, and, in earlier studies, Griffin and colleagues have previously established that elevation of brain IL-1α is an important feature of AD. The elevation of IL-1α in the TLE cases was apparently related to an increase in the number of activated microglia. Neurons in the APOE ε3/ε3 brains had twice as many associated microglia per neuron when compared with the respective data from APOE ε4/ε4 brains. The increased numbers of microglia per neuron in APOE ε3/ε3 TLE patients were associated with an increased level of IL-1α mRNA and protein. The IL-1α mRNA levels were five-fold higher in the TLE patients compared to healthy controls, but those levels were independent of APOE isoform. IL-1α protein levels were four-fold higher in APOE ε3/ε3 patients than that in APOE ε4/ε4 patients. The elevated IL-1α protein levels in the TLE patients apparently resulted in increased amyloid precursor protein (APP) and apoE protein expression as a function of the APOE isoform. This supports the idea that microglia activation and elevated IL-1α expression may contribute to the accumulation of APP and apoE, two key proteins known to be important for increasing the risk of AD pathology (see [6], for review), and that this will primarily take place in the APOE ε4/ε4 brain.

Neuronal damage and size are associated with APOE isoform
There were no differences in the numbers of neurons in cortical layers III-VI of three specific areas of the temporal lobe in TLE patients depending on APOE isoform in the Griffin study. The DNA damage in neurons was also independent of the APOE genotype. However, the level of DNA damage per neuron was greater in patients with APOE ε4/ε4 than in those with the APOE ε3/ε3 genotype. Further, the average size of neurons in patients with APOE ε4/ε4 genotype was unexpectedly smaller than in patients with APOE ε3/ε3 genotype. Neurons from TLE patients with the APOE ε3/ε3 genotype were larger in terms of the size of both the cytoplasm as well as the size of their nuclei, and the APOE ε3/ε3 neurons appeared to have a more normal morphology than did neurons from TLE patients with the APOE ε4/ε4 genotype. Due to these findings, Griffin et al. propose that neurons from individuals with APOE ε3/ε3 isoform are better protected from the damaging hyperexcitability associated with epilepsy than were the neurons from TLE patients with APOE ε4/ε4 isoform. They also noted that this genetic variation of neuronal sparing may result from typical acute phase responses of neurons that result in alternate levels of IL-1α, APP, and apoE expression. These same molecules would be predicted to protect against DNA fragmentation in TLE
patients carrying the APOE ε3 allele. The basic science mechanisms linking APOE ε4 with a reduction in various biomarkers of resilience may, at least in part, underlie the clinical association of the APOE ε4 allele with one or more of the negative outcome factors when human TLE is linked to APOE ε4, such as increased tendency toward earlier age at onset of TLE and/or bilateral-ity of hippocampal damage, although not all of these negative TLE/APOE ε4 associations have been independently confirmed [7-19]. IL-1α is also genetically linked to the risk for developing TLE in at least two independent studies [20].

Density of Aβ plaques in TLE patients was associated with APOE isoform

Senile plaques are reported in about 10% of all TLE cases and are evident at a younger age than that typically associated with senile plaques in AD [1]. Griffin et al. describes the occurrence of Aβ/apoE immunoreactive senile plaques in TLE patients as a function of age, in a distribution similar to that noted in temporal lobes of early stages of typical AD patients. Aβ/apoE immunoreactive senile plaques were even found in a 10-year-old TLE patient, and senile plaques at such early ages suggests that the neuropathology in TLE patients is not likely to be attributable to the coincidental presence of AD. Due to the limited number of patients with the APOE ε4/ε4 genotype, this study does not reveal whether a specific APOE genotype is associated with either a higher probability of having senile plaques in TLE or with a shift in the age of onset for senile plaque formation. Gouras et al. [2] have previously written in this topic, reporting that APOE ε4 alleles were associated with onset of plaque pathology below the age of 50 years. The role of amyloid plaques in the clinical phenomena linked to TLE and APOE ε4 [7-19] have not been systematically studied, although the recent advent of amyloid plaque imaging PET scanning now enables the investigation required to answer this question.

Conclusions

Griffin et al. show for the first time that the APOE ε3/ε3 genotype is apparently more neuroprotective than the APOE ε4/ε4 genotype, as judged by neuronal damage, glial activation, and brain IL-1α level in TLE patients. These findings are consistent with the idea that neurons in TLE patients carrying the APOE ε4 allele are less resistant to the damaging hyperexcitability associated with epilepsy and, therefore, these neurons are more prone to development of DNA damage. In the setting of aging and AD, however, the lower neuroprotection activity of apoE4 may underlie the increased risk for AD in patients carrying the APOE ε4 allele. This finding opens up new avenues for research aimed at elucidating the molecular basis for apoE3-mediated neuroprotection. ApoE3-mimetic drugs are highly sought as potential AD therapeutics as an example of personalized medicine based on individual genic risk. Recent evidence suggests that beaxotene, a retinoic acid RXR ligand, may be a breakthrough lead in this quest [21]: the drug appears to act through apoE to cause rapid (i.e. within 72 hours) clearance of amyloid plaques in a mouse model of AD. The perfection of apoE-mimetic drugs [22-31] for AD may well have a beneficial side effect of yielding compounds that might be also helpful for mitigating temporal lobe and hippocampal damage in patients with TLE.

Acknowledgements

SG would like to acknowledge the support of the US Department of Veteran Affairs and the APOE and Alzheimer’s Consortium of the Cure Alzheimer’s Fund. JBC is the recipient of a postdoctoral fellowship from the Swedish Research Council.

Author details

1Department of Neurology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York NY 10029. 2Department of Psychiatry, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York NY 10029. 3Alzheimer’s Disease Research Center, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York NY 10029. 4James J Peters VA Medical Center, 130 Kingsbridge Road, New York NY 10468, USA.

Authors’ contributions

Drs Caesar and Gandy each contributed drafts of portions of the original text. Dr Gandy edited the final text. Both authors read and approved the final manuscript.

Authors’ information

Drs Caesar and Gandy are at the Departments of Neurology and Psychiatry and Alzheimer’s Disease Research Center, Mount Sinai School of Medicine, and James J Peters VA Medical Center, New York, NY 10029, USA.

Competing interests

Dr Caesar has no competing interests to declare. Dr Gandy has received honoraria or grants from Pfizer, J&J, Amicus, Diagenic, and Baxter.

Received: 8 February 2012 Accepted: 13 April 2012 Published: 13 April 2012

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Yeni SN, Ozkara C, Buyru N, Baykara O, Hano

Caesar and Gandy BMC Medicine 2012, 10:36
http://www.biomedcentral.com/1714-7015/10/36

Cite this article as: Caesar and Gandy: Evidence that an ApoE ε4 ‘double whammy’ increases risk for Alzheimer’s disease. BMC Medicine 2012 10:36.

Pre-publication history
The pre-publication history for this paper can be accessed here: http://www.biomedcentral.com/1714-7015/10/36/prepub

doi:10.1186/1714-7015-10-36

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