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Summary

ApoE4: Is it the absence of good or the presence of bad?

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1. Is ApoE 2/3 good or is ApoE 4 evil?

It is well established that ApoE genotype is highly associated with the risk of developing Alzheimer's disease (see Ashford & Mortimer discussion in Debate 3, this volume). The establishment of this association has led to an intense search for the role that ApoE plays in brain function, particularly in functions such as neuroplasticity that are most involved with the Alzheimer neuropathological process. In the course of this search, results have tended to show either that the ApoE e-3 protein has some beneficial effect, or the e-4 protein has some harmful effect. The issue in this debate hinges around this point, which perspective is most sound? Whether the e-3 protein helps to protect the brain from Alzheimer pathology (e-3 good) or the e-4 protein directly instigates the pathological process (e-4 evil)?

The debate on the goodness of ApoE e3 or the badness of ApoE e4, in Cincinnati in July, 2001, and in the written summaries both reflect the dichotomous positions of the roles attributed to the different ApoE alleles. The disparity of the two sides and the importance of this issue were most clearly framed at the beginning of the summary statement by Rebeck et al., in relating the issue to treatment decisions:

– if ApoE 2/3 is good, the treatment would be directed to inducing ApoE expression and developing ApoE agonists (assuming there is only a relation with the quantitative action of these proteins that is relevant).
– If ApoE 4 is bad, treatments would aim to inhibit or antagonize ApoE function.

Consequently, this debate addresses an issue whose solution is required prior to developing specific therapies for AD. Both sides make strong cases, one clearly outlining the harmful effects of ApoE 4, the other presenting the benefits of ApoE 2/3. Thus, a broader perspective needs to be taken to recommend a concluding opinion.

To consider "good" and "evil", things must be placed at two ends of a continuum, and a midpoint of the continuum becomes the balance-point between the two sides. As the arguments are made in this debate, ApoE e2/e3 represent "good" and ApoE e4 is "bad". However, neither side considers the position that both points could be correct. Rather, the issue is framed as whether ApoE e4 is good and ApoE e2/e3 are better, or the alternative view, that AooE e2/3 are not good, and ApoE e4 is very bad. Accordingly, do ApoE e2/e3 just represent an extreme of benefit, or does ApoE e4 represent the extreme of detriment. A related question to resolve is whether the differences between the various allelic proteins are only quantitative, or whether there is a clear qualitative difference in their actions.

The critical perspective that is not discussed by either side is the evolutionary context. It is the back-drop of evolution that sheds light on biological function. That light is needed to resolve which debate position is stronger. In evolution, for a protein to survive, it needs

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to make a contribution in the ecological setting of the animal that is producing it. Over time, a new protein may replace an old protein, either because it confers a new advantage in a stable ecological setting, or the ecological setting has changed and the new protein confers an advantage in the context of the next setting, which it may not have had in the original setting. ApoE ε4 is not a new detrimental allele. ApoE ε4, which exists in a similar form throughout mammals, presumably confers some general advantage. The ApoE ε3 allele appeared in humans about 300,000 years ago, and the ApoE ε2 allele appeared about 200,000 years ago. The question then is whether the advantage of ApoE ε4 became a disadvantage as humans enlarged their brains and extended their life-spans, with APOE ε2/ε3 conferring a reduced level of toxicity. The alternative question is whether APOE e4 is a beneficial protein, which was improved in humans to APOE e2/e3 as humans entered a niche with different stressors and different dietary resources, which required or provided increased cerebral complexity and extended longevity.

The team of Teter, Raber, Nathan, and Crutcher develops the concept that ApoE e4 is more toxic than ApoE e3. They divide their arguments into 6 categories, including the following:

1) Neurite sprouting: ApoE e4 protein is inhibitory, has no effect, or is weakly stimulatory, less than ApoE e3. This negative effect of ApoE e4 is dominant over that of ApoE e3.

   The difficulty with this argument is that it is not clear whether an inhibitory effect on sprouting is good or bad. Blockade of sprouting may be necessary, even protective, in some contexts.
2) Cognition: ApoE ε4 is said to be associated with impaired cognition in humans, relative to other ApoE genotypes. ApoE ε4 in mice is said to be detrimental relative to ApoE -/- mice.

   The issue in humans is a relative statement that does not address the question of absolute benefit or detriment. The mouse studies appear to address this issue and show that ApoE ε4 is bad for mouse memory, at least relative to APOE -/-, but there is no reason to think that a protein carefully adapted to the human would have anything but a negative effect in another species.
3) Tau metabolism: ApoE e4 seems to disrupt the neuronal cytoskeleton and predispose to the formation of neurofibrillary tangles.

   First, it is possible that some disruption of neural cytoskeleton is important for brain function. For every branch and synapse created, another must be destroyed. As humans have grown larger brains with more connections that must endure for a longer life-span, there is presumably a natural tendency for NFTs to form. NFTs may indeed be considered pathological, but a legitimate counter perspective is that ApoE e4 just is not as efficient at degrading the hyperphosphorylated tau as the more modern ApoE e2/e3.

The team of Rebeck, Kindy, and LaDu takes the position that ApoE performs neuroprotective and neurotrophic functions that are normal brain mechanisms, and the ApoE ε2/ε3 alleles produce proteins that perform these functions more efficiently than the proteins produced by the ApoE ε4 allele. This team reviews the functions of ApoE, including lipid transport and a role in neuroplasticity, as well as possible activities in the metabolism of beta-amyloid and tau. Other possible properties, including anti-oxidant and anti-inflammatory actions, are described. In each case, ApoE ε2/ε3 are shown to be beneficial and more so than ApoE ε4.

One particularly interesting issue that has arisen recently is the role of ApoE in beta-amyloid production, specifically in relationship to neuroplasticity. The Rebeck et al. team reviews some of the literature relating to this concept. There is evidence that the macroglia produce ApoE during times of neuroplastic acitivity. The ApoE then transports cholesterol to the dendrite membranes to form lipid rafts. The entire metabolism of the amyloid-pre-protein (APP) is thought to occur on these rafts. Presumably the APP molecule is transformed by the alpha-secretase into a “nexin” which will promote the formation of new synaptic contacts. Alternatively, the APP molecule may be cleaved sequentially by the beta-secretase to produce a secondary large protein, then by the gamma-secretase to produce beta-amyloid. The proteins produced by the second pathway, which include the apparently neurotoxic beta-amyloid, may be responsible for destroying synapses that are destined to be removed.

Both pathways may be essential for neuroplasticity, one for constructing new connections, and the other for destroying contacts that are no longer required or are under-utilized. The ApoE e4 protein may transport cholesterol to produce lipid rafts which are not as efficient as those produced by ApoE e2/e3 transport, thus allowing accumulation of beta-amyloid, which has longer-term deleterious effects. This concept puts the ApoE allele at the center of the function of neuroplasticity, which is the core function attacked by the Alzheimer process. The role of ApoE would thus be

seen as crucial for learning, but the ApoE $\varepsilon 2/\varepsilon 3$ alleles would clearly represent an advance over the ApoE $\varepsilon 4$ allele, since they are less associated with Alzheimer's disease, and might even be associated with greater levels of education.

The association between ApoE and cholesterol has become more central recently due to epidemiological findings, now widely confirmed [2,3], that the cholesterol reducing "statin" drugs are associated with a decreased incidence of Alzheimer's disease. Specifically, the statin drugs appear to reduce plasma concentrations of brain derived 24S-hydroxycholesterol, indicating that the drugs actually reduce cholesterol turnover in the brain [1]. This data seem to indicate that the role of ApoE in cholesterol modulation could be a critical and modifiable modality for the prevention of Alzheimer's disease.

Given the considerations about ApoE, evolution, and diet, the concern about diet, particularly the role of cholesterol, needs to be clarified. One perspective is that the appearance of the ApoE $\varepsilon 2/\varepsilon 3$ alleles occurred as an "anti-dote" to diets rich in cholesterol that were associated with the eating of animal parts and products. However, an alternative view is that these alleles allowed early humans to live longer lives with less risk of heart disease and neurodegeneration, and this greater success allowed humans to include animal resources in their diet. At this time, there is not sufficient information to recommend a specific diet to prevent Alzheimer's disease. However, there is some data suggesting that reduction of animal fat in the diet is associated with less Alzheimer's disease (for discussion, see Debate 3, this volume). Consequently, a prudent recommendation for the present is to follow the generally recommended guidelines to keep the amount of cholesterol in your diet low. However, in the future, more studies are needed to define the optimal diet for preventing Alzheimer's disease (see www.medafile.com, Top 10 Prevention Suggestions), and this recommendation might also be made with respect to the specific ApoE genotype of the individual.

In sum, the Rebeck team makes strong arguments for several beneficial roles of ApoE, and such positive activities would be expected from the evolutionary perspective that a protein that is widely conserved across many species should have predominantly advantageous effects. The ApoE e4 protein does seem to have a major association with Alzheimer's disease, and the points of the Teter et al., team are well taken. However, the Teter et al. team does not produce a large picture of ApoE e4 serving the role of harmful protein. The issue in life is to combat the stresses associated with time, and it appears after this debate that the ApoE e2/e3 is a good protein that is helping humans to age with less cognitive dysfunction than has the now less common ApoE e4, which was the only allele possessed by our ancestors.

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