Yes, apoE4 is really toxic in Alzheimer disease

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ApoE4 is associated with a spectrum of phenotypes which range from decreased age of disease onset to brain pathologies such as increased Aβ deposition and synaptic impairments. In view of this, the question of apoE4 toxicity is first addressed at the level of the different apoE4 phenotypes. It is difficult to resolve this issue based on human studies. However animal model studies revealed that most of the apoE4 phenotypes (eg the accumulation of Aβ and phosphorylated tau decreased levels of brain apoE receptors) are more pronounced in apoE4 expressing mice then in mice which are apoE deficient and have no apoE. This suggests that having apoE4 is more pathological than not having apoE at all and that apoE4 is thus toxic.What does this teach us about therapy, not much. It can be shown that both loss of a structural feature of apoE4 and the gain of a structural feature both can result in either gain or loss of function. Accordingly apoE4 therapy should be directed not at the gain vs loss of apoE4 driven phenotypic features, but rather at structural difference between apoE4 and apoE3 as the guide for development of therapeutic strategies. Examples will be discussed showing that approached based on either converting apoE4 to an apoE3 – like structure (loss of function) or removal of apoE4 (based on gain of structure) are both effective.