Reviewer’s report

Title: ApoE4: an emerging therapeutic target for Alzheimer's disease

Version: 0 Date: 30 Nov 2018

Reviewer: G. William Rebeck

Reviewer’s report:

This review is an interesting examination of possible mechanisms behind the genetic factor ApoE4 increasing the risk of Alzheimer's disease, and possible therapeutic approaches to address these mechanisms. The subject is important and the topics are thorough.

Minor concerns:

In the portion of Section 2 devoted to Aβ interactions, there should be more of the original citations regarding the effects of ApoE genotype and Aβ aggregation, deposition and clearance. It is a large research area.

The portion related to tau phosphorylation could focus more on the relationship between Tau hyperphosphorylation and ApoE genotype (most of this section is directed to more general aspects of tau in AD).

In the neuroinflammation portion, there could be consideration of interactions between ApoE genotype and NSAID treatment in humans.

In this section, there is discussion of ApoE genotype and miRNA146a levels is difficult to follow.

In the vascular integrity/function portion, there could be a reiteration of the effects of ApoE genotype on the integrity of the blood brain barrier. There are mentions of this effect in other parts of the review, but it is logical to include it here.

At the end of Section 2, it would be interesting to include a paragraph on how the information on different mechanisms may integrate. Figure 1 would be more interesting if the upstream or better-supported effects of ApoE were highlighted somehow.

In the ApoE receptor-related approach, the authors conclude that this is not a promising venue for therapeutic target. It would be more useful then to reduce this section and perhaps expand the "ApoE mimetics" section. There is a rich and comprehensive body of literature regarding ApoE mimetics.

The subtitle related to ApoE2 should be changed to reflect the type of therapy that is required to deliver ApoE2, since that is the therapeutic approach proposed here.
ApoE4 is mentioned as a potential transcription factor, but there is no indication of how that could be translated into a potential therapeutic target for AD. This section could be moved or eliminated.

Finally, as a general comment, there are a few places where the sentences went for 5-6 lines, and those sentences are difficult to follow.

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