Reviewer's report

Title: Atherosclerosis and Alzheimer - diseases with a common cause? Inflammation, oxysterols, vasculature

Version: 1 Date: 11 November 2013

Reviewer: David W Russell

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The hypothesis that Alzheimer’s Disease and atherosclerosis share a common etiology associated with infection is developed. An extensive, comprehensive, and fair review of the literature is used to compare and contrast similarities and differences between the two diseases and to arrive at the conclusion that both appear to be exacerbated by infection.

Specific Comments

1. On page 9, reference is made to the LDL receptor-related receptor; is this the same protein as LRP1, which is referred to later in the manuscript?

2. Is there any evidence that heterozygous carriers of LDL receptor mutations (familial hypercholesterolemia, FH) have an increased incidence of dementia, or do these individuals not live long enough to become susceptible to neurodegeneration?

3. Page 13, line 14: APOE knockout animals

4. Curcumin is often used as an inhibitor of NF-kappaB and relative to this article, has been shown to block induction of cholesterol 25-hydroxylase (ref. 283).

5. T-Y. Chang and colleagues have published papers (PNAS 107:3081 and Mol Ther 21:1497) indicating that knockout of ACAT1 is associated with a marked reduction in amyloid deposition; these should perhaps be added to the section on page 29 in which ACAT inhibitors are discussed.

6. 25-Hydroxycholesterol has been shown (JBC 250:4025 and JLR 40:2264) to drive plasma membrane cholesterol to the ER where it can be esterified by ACAT enzymes; this activity should be mentioned here, either as a complement or competitor to the ACAT allosteric activation theory proposed.

7. The statement is made on page 39, line 6 that sterol oxidation will modulate the formation of 25OHC; the basis for this conclusion is not clear.

8. Page 41, line 17: some infectious agents home…

9. Page 43, line 19: by infection and… (not inflection)

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I am the inventor on a US patent for the cholesterol 25-hydroxylase gene, otherwise I have no competing interests.