THE PATHOLOGICAL EFFECTS OF APOE4 FOLLOWING ACTIVATION OF THE AMYLOID CASCADE ARE ASSOCIATED WITH FORMATION OF ANNULAR PROTOFIBRILAR AB OLIGOMERS

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Introduction: Aβ oligomers play a major role in AD. Aβ oligomerization proceeds via two pathways: a fibrillar pathway characterized by soluble fibrillar oligomers and a more toxic pathway in which Aβ forms soluble prefibrillar oligomers (PFO) which further oligomerize to form annular protofibrils (APFs) which permeabilize the membrane. Activation of the amyloid cascade in apoE4 and apoE3 targeted replacement mice revealed that apoE4 stimulates isoform specifically the degeneration of hippocampal CA1 neurons. This is preceded by the accumulation of intracellular Aβ and apoE in the affected neurons.

Aims: To examine the hypothesis that apoE4 stimulates the oligomerization of Aβ via the prefibrillar (PFO) pathway following activation of the amyloid cascade.

Methods: Immunohistochemistry and immunofluorescence stainings utilizing specific conformational Abs were employed to visualize and map distinct Aβ oligomers in the hippocampus of apoE3 and apoE4 targeted replacement mice.

Results: Activation of the amyloid cascade in vivo by inhibition of the Aβ degrading enzyme neprilysin was accompanied by lysosomal and mitochondrial pathology and resulted in accumulation of Aβ and prefibrillar oligomerized Aβ (Ab I-11) within enlarged lysosomes and mitochondria. This was associated with the accumulation of annular protofibrils (Ab α-APF). In contrast, Aβ oligomerization via the fibrillar oligomer pathway (Ab OC) was not stimulated under these conditions.

Conclusion: These findings show that the synergistic pathological effects of apoE4 and the amyloid cascade are specifically associated with activation of the prefibrillar pathway and suggest that annular protofibrillar Aβ oligomers may mediate the resulting neuropathology.