Biological Psychiatry: Celebrating 50 Years

Targeting the Interaction Between Apolipoprotein E and Amyloid Precursor Protein: A Novel Alzheimer's Disease Therapy

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The identification of mutations in the amyloid precursor protein (APP) and *PSEN1* and *PSEN2* that cause autosomal dominantly inherited Alzheimer's disease (AD) and result in increased production of aggregation-prone forms of amyloid-β (Aβ) established beyond a doubt that APP processing and the production of Aβ peptides are intimately involved in the disease process and led to the proposal of and support for the amyloid cascade hypothesis for AD (1,2). Despite its strengths, the amyloid cascade hypothesis is incomplete without addressing the essential role of amyloid-associated proteins [for reviews, see (3,4)]. Biochemical and histological studies first showed that in addition to Aβ, amyloid deposits also contain inflammatory/acute phase proteins, such as α1-antichymotrypsin (ACT) and, later, the cholesterol carrier apolipoprotein E (ApoE), both of which were hypothesized and then shown to serve as catalysts or "pathological chaperones" for amyloid formation by binding to the Aβ peptide and promoting its conversion into neurotoxic oligomers/fibrils in vitro. In vivo genetic and immunization experiments also showed that ACT and ApoE are essential for the development of brain amyloid and for the cognitive decline of transgenic animal models of AD. ApoE has additionally been postulated and shown to modulate the clearance of Aβ from the brain. These apparently dichotomous models for the role of ApoE in AD can be rectified by the realization that Aβ oligomers/filaments induced by ApoE binding will not be cleared easily from the brain (4).

Several small fragments of Aβ have been designed as decoy peptides that antagonize the binding of ACT or ApoE to Aβ (Aβ2-9 and Aβ12-28, respectively) and effectively reduce the catalyzed polymerization of Aβ into oligomers and filaments that are neurotoxic in vitro (5). In animal models of AD, treatment with a variant decoy peptide (Aβ12-28P) reduced amyloid load and improved cognition (6).

The significance of these biochemical studies was reinforced by parallel genetic discoveries that implicated ApoE as a key contributing factor in AD. In particular, the inheritance of the *APOE* ε4 allele was found to be the strongest risk factor for AD besides age, with one copy of the *APOE* ε4 allele leading to a three- to fivefold increased risk of AD and with two copies of the *APOE* ε4 allele leading to a more than 10-fold increased risk of AD (7).

Because of the essential genetic and presumably biochemical contributions of ApoE to AD pathology and cognitive decline, it is critical that its role in the AD pathogenic pathway/amyloid cascade be further elucidated in order to develop therapeutics that effectively target ApoE, especially ApoE4, and block its ability to promote amyloid formation.

In addition to binding Aβ peptides, ApoE (residues 1–191) binds to an N-terminal region of the APP protein (8) and effectively increases the amyloidogenic processing of APP into Aβ by enhancing APP endocytosis, which leads to reduced soluble APP production and increased Aβ production, with a rank order of potency of ApoE4 > ApoE3 > ApoE2 (9).

In this issue, Sawmiller *et al.* (10) have built on this research and determined that a fragment of ApoE corresponding to the site that binds to the low-density lipoprotein receptor (residues 133–152) and is essential for binding to APP (called ApoEp) serves as a functional ApoE mimetic that, like ApoE, increases Aβ production in CHO/APPwt and other cells in culture. Adding an N-terminal flag tag to the ApoEp peptide enhanced its ability to increase Aβ production. In contrast, the addition of three lysine residues to the N-terminus of ApoEp eliminated its amyloidogenic effects on cultured cells, and the addition of six lysine residues to the N-terminus of ApoEp resulted in the most effective ApoE antagonist peptide (called 6KApoEp). That is, 6KApoEp serves as a decoy that blocks ApoE (or ApoEp) from binding to APP, and thus inhibits the Aβ-promoting effect of ApoE in a dose-dependent manner (IC50 of approximately 0.32–0.63 μM). Similar to the cell culture experiments, treatment with ApoEp resulted in enhanced Aβ levels and amyloid plaque production together with increased levels of tau pathology in the 3XTgAD mouse model of AD. In contrast, in a different mouse model of AD (5XFAD), treatment with 6KApoEp resulted in reduced amyloid load, decreased levels of phosphorylated and acetylated tau, enhanced synaptogenesis, and decreased levels of neuronal apoptosis, together with increased hippocampal learning and memory functions and decreased hyperactivity.

The implication of these studies is that ApoE and ApoEp appear to stimulate both APP trafficking to the plasma membrane and APP endocytosis, thus promoting its amyloidogenic processing and resulting in a shift toward increased Aβ production and decreased soluble APPα production. In contrast, 6KApoEp appears to inhibit both APP trafficking to the plasma membrane, thus reducing soluble APPα production, and APP endocytosis, thereby inhibiting Aβ production. Importantly, 6KApoEp inhibits both basal and ApoE-induced Aβ production without affecting overall APP expression levels. It is unclear exactly how ApoE binding promotes APP trafficking to the plasma membrane and its subsequent endocytic processing.

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https://doi.org/10.1016/j.biopsych.2019.06.005
ISSN: 0006-3223

For example, both ApoE and ApoEp induce canonical p38 mitogen-activated protein kinase (MAPK) phosphorylation and noncanonical p44/42 MAPK phosphorylation, which may affect APP processing. In contrast, 6KApoEp induced p38 MAPK phosphorylation but inhibited p44/42 MAPK phosphorylation. Thus, 6KApoEp might not block (and might even replicate) some normal effects of ApoE binding to the low-density lipoprotein receptor in addition to its inhibition of ApoE–APP binding. Sawmiller *et al.* (10) suggest that the different effects of ApoE/ApoEp and 6KApoEp on APP processing may be mediated by their differential activation of these MAPK pathways.

Together, these data show that the interaction between ApoE and APP has physiological and pathophysiological consequences, some of which can be ameliorated or blocked by the novel ApoE-derived decoy/antagonist peptide 6KApoEp, which appears to have no detrimental effects of its own (unless, of course, the ApoE–APP interaction has important physiological functions that have not yet been determined). Because 6KApoEp reduces the natural ability of ApoE to promote Aβ production, it may serve as the basis for the development of a human AD therapy. With the failure of so many AD treatments directed at removing already-formed amyloid, this novel approach targeting Aβ production shows promise either as a stand-alone therapy or as part of a combination therapy.

Acknowledgments and Disclosures

This work was supported by National Institutes of Health Grant Nos. R01NS076291, R01AG037942, the State of Colorado, and private philanthropy (to HP).

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Jun 7, 2019; accepted Jun 7, 2019.

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